CLINICAL STUDY PROTOCOL

NCT Number: NCT03571516

Study Title: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age With Short Bowel Syndrome Who Are Dependent on Parenteral Support

Study Number: SHP633-301

Protocol Version and Date:

Original Protocol:	03 Oct 2017
Amendment 1:	18 Jan 2018
Amendment 2:	04 Dec 2018
Amendment 3:	24 May 2019
Amendment 4:	17 Dec 2019

PROTOCOL: SHP633-301

TITLE:	A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support
NUMBER	SHP633-301
PHASE	3
DRUG:	Teduglutide
INDICATION:	Short bowel syndrome
EUDRACT NO.:	2017-003606-40
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA
PROTOCOL HISTORY:	Original Protocol: 03 Oct 2017

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** [redacted]
[redacted], MD PhD [redacted] [redacted], Global Clinical Development	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-301.

Title: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	_____ _____ _____

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the Shire Medical Monitor by fax or e-mail:
Fax: [redacted], Email: [redacted]

For protocol- or safety-related issues, the investigator must contact Quintiles Medical Support:

Primary Contact

[redacted], MD

[redacted]

Mobile: [redacted]

US Toll Free Number: [redacted]

Phone: [redacted]
(medical emergencies)

Email: [redacted]

Backup Contact

[redacted], MD

[redacted]

Mobile: [redacted]

Phone: [redacted]

Phone: [redacted]
(medical emergencies)

Email: [redacted]

In addition, the investigator may also contact Shire:

[redacted], PharmD, MSc

[redacted]

Phone: [redacted]

Mobile: [redacted]

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (e.g., inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (e.g., wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	E-mail Address
North and South America	[redacted]
European Union and Rest of World	[redacted]

Telephone numbers (provided for reference, if needed):

Shire (USA)
[redacted]

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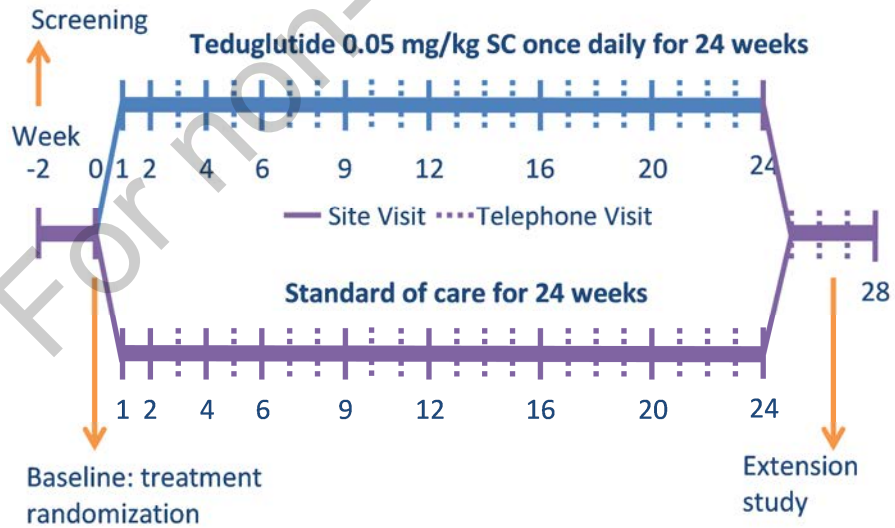
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
$AUC_{tau,ss}$	area under the concentration-time curve at steady-state over the dosing interval
CL/F	apparent clearance
$C_{max,ss}$	maximum plasma concentration at steady state
CRO	contract research organization
eCRF	electronic case report form
DMC	data monitoring committee
EDC	electronic data capture
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
EQ-5D-5L	5-level EuroQol five dimensions questionnaire
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	glucagon-like peptide
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medicinal Journal Editors
I/O	oral fluid intake and urine output
IP	Investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PN	parenteral nutrition
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
SD	standard deviation
SOC	standard of care
ULN	upper limit of normal
US	United States

STUDY SYNOPSIS

Protocol number: SHP633-301	**Drug:** Teduglutide
Title of the study: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support	
Number of subjects (total and for each treatment arm): At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in a standard of care (SOC) comparator arm	
Investigator(s): Multicenter study	
Site(s) and Region(s): This study is planned to be conducted in approximately 5 to 10 sites globally.	
Study period (planned): 2017-2020	**Clinical phase:** 3
Objectives: The objectives of this clinical study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with short bowel syndrome (SBS) dependent on parenteral support.	
Investigational product, dose, and mode of administration: Teduglutide 0.05 mg/kg by subcutaneous (SC) injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm.	
Methodology: This is a randomized, multicenter, open-label study, consisting of a minimum 2-week screening period, a 24-week treatment period, and a 4-week follow-up period.  	

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum 4 weeks). At the baseline visit (Week 0), subjects will randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for parenteral nutrition (PN) reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (t=0, 1, and 4 hours) and at Week 6 or 12 (t= 2 hours) .

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS the subject may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period may be interrupted and the subject may consent to the extension study immediately if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

Inclusion and Exclusion Criteria:

Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age.
3. Weight at least 5 kg and weight-for-length *Z*-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. Lack of terminal ileum and ileocecal valve
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.
8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.
9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µl due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2-week period
13. More than 3 serious complications of intestinal failure (e.g., catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

Maximum Duration of Subject Involvement in the Study:

The study consists of a 2-week screening period, a 24- week treatment period, and a 4-week follow-up period.

Endpoints:

Efficacy

Efficacy endpoints consist of the following:

Primary

- Reduction in weight-normalized parenteral nutrition (PN) fluid volume by at least 20% from baseline at Week 24/EOT

Secondary

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by week 24
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to Week 24/EOT

Pharmacokinetics

Pharmacokinetic endpoints include but are not limited to the following:

- Area under the plasma concentration–time curve at steady state over the dosing internal ($AUC_{tau, ss}$)
- Maximum plasma concentration at steady state ($C_{max,ss}$)
- Apparent clearance (CL/F)

Safety

Safety endpoints consist of the following:

- Adverse events (AEs)
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

Health Economics and Outcomes Research

Health economics and outcomes research (HEOR) endpoints include the following:

- The 5-level EuroQol five dimensions questionnaire (EQ5D-5L) quality of life questionnaire to be completed by the subjects' caregivers at baseline and Week 24
- Cumulative number of hospitalization days during the study

Statistical Methods:

Efficacy

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and there is no use of PN recorded in the subject diary during the week prior to that visit. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

Pharmacokinetics

Plasma concentrations will be summarized using descriptive statistics (number, mean, and standard deviation) at nominal time points. Pharmacokinetic parameters will be derived using a population PK modeling approach and summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum).

Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (e.g., number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, serious adverse events will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores; and descriptive statistics (e.g., n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

Health Economics and Outcomes Research

The HEOR endpoints will be summarized descriptively.

STUDY SCHEDULES

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X													
Eligibility	X	X												
Randomization		X												
Demographics	X													
SBS history	X													
Medical and surgical history	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L		X												
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight	X	X	X	X		X		X			X			X
Length and head circumference	X	X				X								X
UGI/SBFT	X													
Safety labs and urinalysis[b, c]	X	X[b]	X	X	(X)	X	(X)	X	(X)	(X)	X	(X)	(X)	X
PK sampling[a]		X						[X][d]						[X][d]
Antibodies to teduglutide[a,e]		X												X[e]
Native GLP-2[f]	X													
Provide intake and output diaries[g]	X	X	X	X		X		X			X			X
Review diaries and nutritional support		X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support as needed[h]		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Dispense IP[a, i]		X	X	X		X		X			X			X

EN=enteral nutrition;EQ-5D-5L=five-level EuroQol five dimensions questionnaire; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PK=pharmacokinetics; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with short bowel follow-through

[a] Applicable to the teduglutide treatment arm only.

[b] At baseline, safety labs (Table 4) and PK can be separated by 1 day if blood volumes are limiting. Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline, and repeated if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity. Urine collection should be attempted, but inability to obtain urinalysis is not a protocol deviation.

[d] Subjects will have blood samples taken for teduglutide PK analysis predose and 1 and 4 hours post dose at baseline (Visit 0). Subjects also will have blood samples taken for teduglutide PK analysis 2 hours post dose at Week 6 (Visit 6) or Week 12 (Visit 12) of the treatment period.

[e] Samples for antibody analysis will be drawn at the baseline and Week 12 visits. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.

[f] Blood samples for native GLP-2 should be collected postprandial. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

[i] The initial dose will be calculated based on body weight measured at baseline (Visit 0), and adjusted as needed, based on body weight measured at each in-clinic study visit.

Note: (X) denotes optional assessments; [X] denotes possible PK sampling time point (Refer to footnote "e".)

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Visit type	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**
Study day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**175**	**182**	**189**	**196**
±window (days)	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
EQ-5D-5L												X				
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight				X				X				X				X
Length and head circumference				X				X				X				X
Safety labs and urinalysis[b,c]	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X
Antibodies to teduglutide[d,e]																X
Native GLP-2[f]												X				

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Visit type	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**
Study day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**175**	**182**	**189**	**196**
±window (days)	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**
Provide intake and output diaries				X				X				X				
Review diaries and nutritional support[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support as needed[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess follow-up period escape criteria													X	X	X	X
Dispense IP[d, i]				X				X								

EN=enteral nutrition; EOS=end of study; EOT=end of treatment; EQ-5D-5L=five-level EuroQol five dimensions questionnaire; ET=early termination; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with short bowel follow-through

[a] At EOS subjects may enroll in an extension study, if subjects require treatment before the end of the 4-week follow-up they may enter the extension study immediately.

[b] Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR are tested if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity.

[d] Applicable to the teduglutide treatment arm only.

[e] Samples for antibody analysis will be drawn at the EOS (Week 28) visit.

[f] Blood samples for native GLP-2 should be collected postprandial. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.
Note: (X) denotes optional assessments.

[i] The dose will be adjusted as needed, based on body weight measured at each in-clinic study visit.

1. BACKGROUND INFORMATION

1.1 Short Bowel Syndrome

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal diseases that result in major surgical resections of the small intestine (O'Keefe et al., 2006). Unlike the adult population, the majority of cases of SBS in pediatric subjects are due to congenital anomalies or catastrophic events that occur during infancy such as necrotizing enterocolitis, gastroschisis, intestinal atresia, midgut volvulus, or long-segment Hirschsprung disease (Beattie et al., 2010; Goulet and Ruemmele, 2006). A Canadian population-based study in neonates estimates an overall incidence of SBS to be 24.5 cases per 100,000 live births (Wales et al., 2004).

The small intestine is capable of remarkable adaptation, but excessive loss of absorptive surface area or specialized functions can lead to dependence on parenteral nutrition (PN) fluids (O'Keefe et al., 2006). Although PN is life-sustaining in intestinal failure, it is associated with serious complications, including liver disease, life-threatening catheter-related blood stream infections, and central venous thrombosis (Beattie et al., 2010; Goulet and Ruemmele, 2006). Dependence on PN is also associated with reduced quality of life in both patients and caregivers and has an extremely high cost of care (Huisman-de Waal et al., 2007). About 30% of infants with SBS become independent of PN requirements within 12 months of the initial insult, and an additional 10% wean off PN within 24 months. After this time, linear intestinal growth slows. It is estimated that 42% to 86% of pediatric patients with SBS are able to become independent of PN within 1 to 3 years (Gonzalez-Hernandez et al., 2017; Khan et al., 2015; Squires et al., 2012). Nevertheless, despite optimal medical management, some children remain dependent on PN for many years (Squires et al., 2012). Infants who have less than 10% of expected small intestinal length for their gestational age have a low likelihood of ever achieving enteral autonomy (i.e., independence from parenteral support). Providing the maximum tolerated amount of enteral nutrition (EN) has been the primary strategy to promote enteral adaptation (Spencer et al., 2005).

Accelerating the adaptive process and achieving enteral autonomy is an urgent goal for all patients with SBS who are dependent on PN (Khan et al., 2015; Squires et al., 2012). The adaptive process is in part controlled by glucagon-like peptide 2 (GLP-2), a 33 amino acid peptide hormone secreted from L-type enteroendocrine cells in the terminal ileum and colon in response to luminal nutrients and bile acids (Martin et al., 2006). The post-prandial plasma concentration of GLP-2 in infants with SBS correlates with length of the remaining small intestine (Sigalet et al., 2004). Infants who lack terminal ileum may have impaired adaptation due to inadequate production of GLP-2.

1.2 Teduglutide

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$), approximately 2 hours in healthy adult subjects, 1.3 hours in adult SBS subjects, and 0.22 hours in pediatric SBS subjects, compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines (Tappenden et al., 2013; Thymann et al., 2014).

A Phase 3 study, TED-C13-003, has been completed in pediatric SBS subjects. In this study, teduglutide was administered to 3 cohorts of pediatric subjects from ages 1-17 years. Thirty-seven pediatric subjects received teduglutide at doses of 0.0125, 0.025, or 0.05 mg/kg/day for 12 weeks. Five additional pediatric subjects were enrolled in an observational standard of care (SOC) cohort. There were clear dose-dependent effects of teduglutide seen at the 0.025 and 0.05 mg/kg/day doses compared to SOC and the 0.0125 mg/kg/day dose. In the 0.025 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 37%, including complete independence from PN support in 1 subject, and a reduction of 3.94 hours per day infusion time. In the 0.05 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 39%, including complete independence from PN support in 3 subjects, and a reduction of 4.18 hours per day infusion time. Teduglutide was generally safe and well tolerated by pediatric subjects in all dosing cohorts. There were no deaths during the study and no treatment-emergent serious adverse events (SAEs) related to teduglutide were reported. No discontinuations from study were due to adverse events (AEs). Additional studies in pediatric patients with SBS are ongoing.

Teduglutide (0.05 mg/kg/day) is currently approved for the treatment of adult patients with SBS in >30 countries. On 29 Jun 2016, the European Commission granted an extension of the Market Authorization for teduglutide for the treatment of patients aged 1 year and above with SBS.

Always refer to the latest version of the investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy and safety of teduglutide (SHP633).

2. OBJECTIVES

2.1 Rationale for the Study

There is no approved pharmacological therapy to improve intestinal adaptation in infants with SBS who are dependent on parenteral support. This study will evaluate whether teduglutide is safe and effective in this patient population.

2.2 Study Objectives

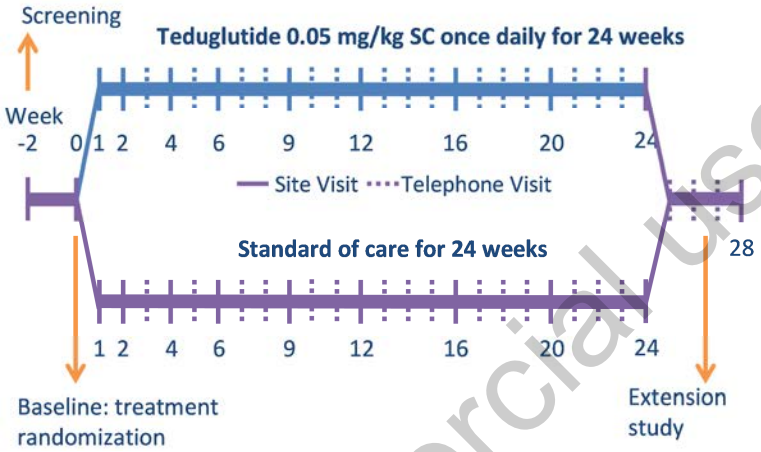
The objectives of this study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with SBS dependent on parenteral support.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a randomized, multicenter, open-label study, consisting of a minimum 2-week screening period, a 24-week treatment period and a 4-week follow-up period. A schematic representation of the study design is presented in Figure 1.

Figure 1: Study Schematic



3.1.1 Screening Period

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum: 4 weeks). The schedule of evaluations to be conducted during the Screening Period can be found in Table 1.

3.1.2 Treatment Period

At the baseline visit (Week 0), subjects will randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS, while those in the teduglutide arm will receive 0.05 mg/kg by subcutaneous (SC) injection once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for PN reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability (Appendix 2). Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm, will occur at baseline (t=0, 1, and 4 hours) and at Week 6 or 12 (t=2 hours).

The schedule of evaluations for the Treatment Period can be found in Table 1 (Visits -1 to 12) and Table 2 (Visits 13 to 28).

3.1.3 Follow-up Period

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product (IP) will be administered. At EOS the subject may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period may be interrupted and the subject may consent to the extension study immediately if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

The schedule of evaluations for the Follow-up Period can be found in Table 2 (Visits 13 to 28).

3.2 Study Duration

The study consists of a minimum 2-week screening period, a 24-week treatment period and a 4-week follow-up period.

3.3 Sites and Regions

This study is planned to be conducted at approximately 5 to 10 sites globally.

4. STUDY POPULATION

At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in an SOC comparator arm.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. Lack of terminal ileum and ileocecal valve.
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.
8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.

9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/μL due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 μmol/L) over a 2 week period.
13. More than 3 serious complications of intestinal failure (e.g., catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

4.3 Reproductive Potential

Not applicable; this study will enroll infants.

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (e.g., in the interest of subject safety). The investigator should discuss withdrawal of a subject from investigational product with the medical monitor as soon as possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT/early termination are to be performed as completely as possible. Whenever

possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period. Comments (spontaneous or elicited) or complaints pertaining to IP discontinuation made by the subject must be recorded in the source documents. The reason for discontinuation, the date and the total amount of investigational product administered must be recorded in the electronic case report form (eCRF) and source documents.

Subjects who discontinue will not be replaced.

4.4.1 Reasons for Discontinuation

The reason(s) for permanent discontinuation of treatment and/or withdrawal from the study must be determined by the investigator, and recorded in the subject's medical record and in the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document, and the most clinically relevant reason should be entered in the eCRF.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by parent/guardian
- Lack of efficacy
- Other

4.4.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact the parent(s)/guardian(s) of any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Medications and Procedures

Prior treatment includes all treatment and procedures (including but not limited to prescription treatments, herbal treatments, vitamins, non-pharmacological treatment, as appropriate) received within 14 days prior to the screening visit (Visit -1) (or pharmacokinetic equivalent of 5 half lives, whichever is longer, must be recorded on the appropriate eCRF page.

5.2 Concomitant Medications and Procedures

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins) and PN must be recorded from the first dose of investigational product and for the duration of the study in the appropriate sections of the eCRF. Any diagnostic, surgical or other therapeutic treatments received by a subject during the course of the study will also be recorded on the eCRF.

The mechanism of action of teduglutide may increase enteral absorption of oral drugs (e.g., drugs used for management of SBS such as motility medication, opioids, psychotropics, metronidazole), so consideration should be given to modifying concomitant enteral medication regimens. Titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic index (e.g., warfarin, digoxin, psychotropics) are given.

5.3 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.4 Prohibited Treatment

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the pretreatment visit (Table 3):

Table 3: Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pretreatment Visit
Teduglutide	Any
GLP-2, human growth hormone, or analogs of these hormones	6 months
Octreotide, GLP-1 analogs, and enteral glutamine	30 days

GLP=glucagon-like peptide

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

Teduglutide will be provided in sterile, single-use 3 mL vials containing 5 mg or 1.25 mg teduglutide as a white lyophilized powder to be reconstituted before use with 0.5 mL sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the current investigator's brochure.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

All investigative study sites will be initially provided with sufficient investigational product to randomly assign a subject into the study (for either of the proposed treatment groups). Randomization will occur through an interactive response system. Random assignment of a subject will trigger replacement supplies for that investigative study site.

6.2.2 Allocation of Subjects to Treatment

Subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. The actual treatment given to individual subjects is determined by a randomization schedule.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined.

6.2.3 Dosing

The initial dose will be calculated based on body weight measured at baseline (Visit 0), and adjusted as needed, based on body weight measured at each in-clinic study visit. No other adjustments to dose will be made during the teduglutide treatment period, unless discussed with the sponsor's medical monitor.

Following reconstitution, teduglutide will be administered by SC injection once daily (QD) into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used. Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later.

The subject should be dosed at approximately the same time each day. Consecutive doses should be separated by at least 12 hours. Each day, the injection site should be alternated.

Any subject who achieves complete independence from PN support at any time during the treatment period will continue to receive teduglutide treatment.

The first SC injection in teduglutide-naïve subjects should be administered under the supervision of the investigator or designee and the subject observed for hypersensitivity reactions for at least 4 hours during their initial dosing visit. The site of administration (arm, thigh, and abdomen) of the first teduglutide dose must be specified and recorded in the eCRF.

Detailed instructions for reconstitution and injection of the investigational product can be found in the Instructions for Use.

Following the 24-week Treatment Period, subjects will enter a 4-week follow-up period. During the follow-up, the investigator will assess the subject via weekly telephone visits. The follow-up period may be interrupted and the subject may consent to the extension study immediately if at least one of the following criteria is met:

1. Increasing PN requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.2.5 Dose Selection Rationale

Teduglutide is approved for adult and pediatric use in the EU at a dose of 0.05 mg/kg SC once daily. A completed 12-week dose finding study (TED-C13-003) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit-risk profile most meaningful at the 0.05 mg/kg/day dose (Carter et al., 2017).

Population pharmacokinetic modeling and simulations were conducted to determine the optimal dose to be used in pediatric subjects using data from 8 adult clinical studies including adult Phase 1 studies and Phases 2/3 studies as well as TED-C13-003 and suggested the same adult dose (0.05mg/kg) in pediatric subjects (aged between 1.67-14.7 years) (Marier et al., 2017).

To support dosing in the current age group, further PK simulation was conducted based on the population PK model previously established and a virtual population of 1000 pediatric patients created based on Centers for Disease Control (CDC) growth charts in the target age group (4 to 12 months) and taking into consideration body weights of pediatric patients with SBS enrolled in study TED-C13-003 (approximately 15% lower than healthy subjects in the same age group).

Monte Carlo simulations for all age groups were performed according to the SC dosing regimens of 0.0125, 0.025 and 0.05 mg/kg every 24 hours. Rich concentration-time profiles were simulated with the customized population PK model to derive the exposure metrics area under the concentration curve at steady state (AUC_{ss}) and maximum concentration at steady state ($C_{max,ss}$). Following 0.05 mg/kg daily SC administration, the median $C_{max,ss}$ of teduglutide in neonate patients (24.9 ng/mL) was within 20% of that observed in the 2 to 4 and 4 to 6 years age groups (26.9 and 29.4 ng/mL, respectively); and approximately ~28% lower than that in adult patients with SBS. The clinical package in conjunction with C_{max} was considered to support teduglutide dose selection since AUC_{ss} was previously shown not to correlate with efficacy. Thus, the 0.05 mg/kg dose is proposed for testing in this age group.

6.3 Labeling, Packaging, and Storage

6.3.1 Labeling

The investigational product will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of investigational product will be provided for this study. The vials will be labeled in accordance with applicable regulatory requirements.

Ancillary kits, containing supplies needed for the reconstitution and administration of the investigational product will also be provided and labeled in accordance with the applicable regulatory requirements.

All investigational product used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice.

6.3.2 Storage and Handling

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2-8°C (35.6-46.4°F) until dispensed to a subject. Once dispensed to a subject, the IP can be stored refrigerated or up to a controlled room temperature (acceptable range of 2-25°C, or 35.6-77°F). Parent/legal guardian will be instructed to keep the subject's IP and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the IP may be refrigerated. The IP is for single use only, and should be used within 3 hours following reconstitution.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual

means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (i.e., certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), e.g., fumigation of a storage room.

Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels, as they are distributed.

6.4 Drug Accountability

Investigational product will not be dispatched to the study site until the sponsor or designee has received all required documents from the study site in accordance with applicable regulatory requirements and relevant standard operating procedures. Upon receipt, the study site's pharmacist or delegate is responsible for ensuring that all investigational product received at the site is inventoried and accounted for throughout the study. A copy of the shipping documents must be maintained for the investigator's records. Kits will be shipped to the site once the subject is screened.

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Investigational product kits will be dispensed at each of the applicable study visits at which the subject is required to be at the clinic. Each investigational product kit is sufficient for a treatment period of 1 week and enough kits will be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

Each subject will be given the investigational product according to the protocol. The investigator is to keep a current record of the inventory and dispensing of all clinical supplies.

All dispensed medication will be documented on the eCRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, subject returned investigational product, and empty/used investigational product packaging are to be sent to the sponsor or designee. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

Returned investigational product must be counted and verified by clinical site personnel and the sponsor (or study monitor). Shipment return forms, when used, must be signed prior to shipment from the site. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

The parent(s)/guardian(s) of subjects must be instructed to bring unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed and recorded at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (e.g., bottles, trays, vials) or at the individual count level for opened containers/packaging.

Subjects who have received 80% of the planned doses administered will be assessed as being compliant with the study protocol.

7. STUDY PROCEDURES

7.1 Study Schedule

Detailed study procedures and assessments to be performed for subjects throughout the study are outlined in the study schedules (Table 1and Table 2) and must be referred to in conjunction with the instructions provided in this section.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period.

7.1.1 Screening

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent/assent from the parent(s)/guardian(s) of the subject. The screening visit assessments and procedures, beginning with informed consent/assent, will be performed as outlined in Table 1.

7.1.2 Treatment Period

The randomized Treatment Period will comprise Weeks 1 to 24, during which all assessments will be performed as outlined in Table 1 and Table 2.

7.1.3 Follow-up Period

The Follow-up Period will comprise Weeks 25 to 28, during which all assessments will be performed as outlined in Table 2.

7.2 Study Evaluations and Procedures

7.2.1 Demographics and Other Baseline Characteristics

Demographics and Medical History

Demographic and/or other baseline variables obtained at the screening and/or baseline visits are listed below. Abnormal findings of clinical significance (if any) will be recorded as past medical history.

- Demography (including age, gestational age, sex, and race)
- Medical history (including surgical history)
- SBS history, including remnant anatomy

Upper Gastrointestinal Series with Short Bowel Follow-through

An upper GI contrast series with small bowel follow-through will be performed on all subjects during the screening period if one has not been done since the subject's last GI surgery.

7.2.2 Efficacy Assessments

Subject Diaries

All available diary data will be reviewed by the investigator or their designee at each clinic and telephone visit to assess clinical status and opportunity for PN reduction and advance in feeds. Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

Intake Diary

Intake diaries will be used to collect and evaluate each subject's nutritional support. The parent/legally authorized representative/study site staff will complete the appropriate fields of the PN and EN sections of the intake diary daily throughout the study.

The following data will be captured in the intake diaries:

- Parenteral support volume and infusion duration
- Enteral nutrition (formula) including volume and calories

Site personnel will determine the actual PN and EN daily calories based on diary entries.

Output Diary

Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit; in addition, output should be recorded for subjects within 1 week of implementing a change in the PN prescription.

Urine data:

- Measure and record the weight of all urine-only diapers. Urine volume will be calculated using the following formula: 1 g (scale weight) = 1 mL or 1 cc
- At the discretion of the investigator, the parent or legal guardian/study site staff may be asked to collect the first void after the daily PN infusion to measure specific gravity

Stool data (includes diapers with mixed urine and stool):

- Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency (see Output diary). Stool volume will be calculated using the formula: 1 g (scale weight)=1 mL or 1 cc

All ostomy output volume should be recorded.

Native GLP-2

Blood samples for native GLP-2 should be collected postprandial. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

7.2.3 Safety Assessments

Laboratory Evaluations

Safety laboratory tests to be performed at site visits consist of clinical chemistry, hematology, and urinalysis and will be performed as outlined in the study plan (Table 1 and Table 2). Scheduled laboratory testing will be processed by a central lab. All laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the laboratory. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

During the Treatment Period, subjects will also have safety labs within approximately 5 to7 days after a PN adjustment. Safety labs performed after PN adjustment and between site visits will consist of clinical chemistry and urinalysis and may be processed by the central laboratory or a local laboratory. Local lab results are not required to be entered in the eCRFs; however, if the local lab results indicate any new clinically significant changes, they must be reported as an adverse event (see Section 8). Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

At baseline, blood samples for safety labs and PK can be separated by 1 day if blood volumes are limiting.

Safety labs at telephone visits will be collected at the discretion of the investigator.

For all subjects in the teduglutide treatment arm, prothrombin time (PT) and international normalized ratio (INR), tested at baseline, will be repeated if clinically indicated.

New clinically significant labs should be reported as AEs.

Close monitoring criteria related to liver test abnormalities: The investigator should contact the medical monitor within 24 hours of their awareness if the subject develops any of the following changes in laboratory parameters:

- ALT or AST >5x ULN and >2x baseline value
- Total or direct bilirubin that is >2x baseline value or an absolute increase of ≥3 mg/dL (51.3 µmol/L)

If such changes are observed, the labs should be repeated along with an INR, and an inquiry should be made as to the presence of clinical symptoms consistent with new liver injury. The subject should be followed closely to determine the trajectory of the laboratory abnormalities and appropriate evaluations should be made, such as abdominal ultrasound with Doppler imaging to exclude vascular causes and biliary obstruction, consideration of sepsis, liver hypoperfusion, acute viral hepatitis (such as hepatitis A, EBV, or HSV), exposure to hepatotoxic medications, mitochondrial hepatopathy, or metabolic liver disease (such as hereditary fructose intolerance or arginosuccinate synthetase deficiency). Further evaluations can be performed at the discretion of the investigator in consultation with the Shire medical monitor.

The following clinical laboratory assessments will be performed according to the study schedules:

Table 4: List of Laboratory Tests

Biochemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bicarbonate
- Bilirubin (total and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- C-reactive protein
- Creatinine
- Estimated Glomerular Filtration Rate (Schwartz formula)
- Gamma-glutamyl transferase
- Glucose
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Triglycerides

Hematology[a]:
- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- Red blood cell morphology, if needed
- White blood cell count with differential

Coagulation[b]:
- Prothrombin time
- International normalized ratio

Urinalysis:
- Specific gravity
- Urine Sodium

[a] Hematology is not collected at Week 1 or at telephone visits.
[b] For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline and repeated only if clinically indicated.

Antibodies to Teduglutide

Blood samples will be drawn to test for antibodies to teduglutide. Samples will be taken before teduglutide administration at the screening visit (Visit -1) and at least 14 hours after the previous dose at Week 12 (Visit 12); samples may be drawn from a central line or peripheral access. One additional sample will be collected at the EOS 4 weeks after the EOT (i.e., Week 28 or EOS).

Volume of Blood

Efforts will be made to minimize the amount of blood drawn from all pediatric subjects participating in this study. The volumes of blood to be drawn from each subject will vary depending on clinical status. Approximate volumes of blood to be drawn from each subject are shown in Table 5.

Table 5: Approximate Volume of Blood to be Drawn from Each Subject

Assessment	Sample Volume (mL)	No. Samples	Total Volume (mL)	Notes
Subjects Receiving Teduglutide Treatment				
Biochemistry	0.6	12	7.2	
Hematology	0.6	11	6.6	
Coagulation Parameters	0.6	1	0.6	PT and INR tested at baseline only, repeat while on study only if clinically indicated.
Antibodies	1.5	5	7.5	
Pharmacokinetics	1.5	4	6	Baseline: 3 timepoints Week 6: 1 timepoint OR Week 12: 1 timepoint
Native GLP-2	0.1	3	0.3	
Total mL:	**4.9**	**36**	**28.2**	
Subjects Receiving Standard of Care				
Biochemistry	0.6	12	7.2	
Hematology	0.6	11	6.6	
Native GLP-2	0.1	3	0.3	
Total mL:	**1.3**	**26**	**14.1**	

GLP=glucagon-like peptide; INR=international normalized ratio; PT=prothrombin time

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments should be combined. Blood volume estimates do not include safety labs performed after PN adjustment, and anti-teduglutide antibody testing during no-teduglutide treatment.

Physical Examinations, Vital Signs, Weight, Length, and Head Circumference

Physical examinations will be performed according to the study schedules (Table 1, and Table 2). Any new clinically significant findings noted during physical examinations should be recorded on the appropriate AE page of the eCRF.

Vital signs will be measured according to the study schedules. Measurements will include systolic and diastolic blood pressure (mmHg), pulse (beats per minute), and body temperature (°C/°F). Blood pressure should be determined by the appropriate size cuff (using the same method, the same leg, and in the supine position throughout the study, when possible). Blood pressure measurements should be attempted as part of the vital signs, but lack of blood pressure results will not constitute a protocol deviation. New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Length and head circumference will be measured at selected visits. A height z-score, weight Z-score, and weight/length ratio will be calculated by the sponsor using the site-provided height and weight data collected at each site visit.

7.2.4 Pharmacokinetic Assessments

Subjects will have blood samples taken for teduglutide PK analysis predose and 1 and 4 hours post dose at baseline (Visit 0). Subjects also will have blood samples taken for teduglutide PK analysis 2 hours post dose at Week 6 (Visit 6) or Week 12 (Visit 12) of the treatment period. Blood for PK sampling should be collected via peripheral IV or venipuncture, not from a central line. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified.

7.2.5 Health Economics and Outcomes Research

Five-level EuroQol Five-dimensions Questionnaire

To assess caregiver burden, parents/legally authorized representatives will be asked to complete the 5-level EuroQol five dimensions questionnaire (EQ-5D-5L) at the visits specified in Table 1, and Table 2. The EQ-5D-5L is a generic, multi-attribute, health related QOL questionnaire composed of a descriptive system and a visual analog scale (VAS) (Herdman et al., 2011).

The EQ-5D-5L descriptive system has the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, or extreme problems. In addition to showing which levels the subject selected for the 5 dimensions, the information from the 5 dimensions can also be combined to provide a value from 0, representing death, to 1, representing perfect health. The VAS provides results from 0, labeled “worst imaginable health state” to 100, labeled “best imaginable health state.”

Hospitalizations

Each hospitalization that occurs during the study will be recorded, including date of admission, date of discharge, reasons for hospitalization, discharge diagnosis, and discharge status.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

AEs that are related to IP that are not resolved at EOS will be followed until the event resolves or stabilizes, as judged by the investigator.

Laboratory values, vital signs, and clinical findings at the scheduled physical examinations must be reported as AEs if the investigator considers the finding to be a clinically significant change from the baseline.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. It is assumed that some of the infants participating in this study may be hospitalized for planned surgery(ies) that will occur during their participation in the study. Such pre-planned, elective surgeries, do not need to be reported as SAEs for this protocol.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory or vital sign can represent an AE if the change is clinically relevant or if, during the study, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, during the study, there are abnormal clinical laboratory values or vital signs which were not present at the beginning of the study, further investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory or vital sign is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

Not applicable.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.

- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Administration of a dose greater than the allocated dose of the study medication or at a frequency greater than the dosing interval specified by the protocol.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally-authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

All Adverse Events of Special Interest, as defined in Section 8.3, must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event even if the event does not fulfill seriousness criterion.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol, and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested). Fax or e-mail the completed form to the Shire Global Drug Safety Department. A copy of the completed Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the Shire medical monitor or designee using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3, and must be reported to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (i.e., the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (e.g., drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The Sponsor and/or Clinical Contract Research Organization (CRO) is responsible for notifying the relevant regulatory authorities, and US central Institutional Review Boards (IRBs)/EU central ethics committees (ECs), of related, unexpected SAEs.

In addition, the Clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP633 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

8.3 Adverse Events of Special Interest

An AE of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program and for which ongoing monitoring and immediate notification by the investigator to the sponsor is required.

The AEs of special interest that require expedited regulatory reporting include the following:

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the GI tract including the hepatobiliary system
- Tumor-promoting ability (e.g., benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

For AEs of special interest, the sponsor must be informed within 24 hours of first awareness as per the SAE notification instructions described in Section 8.2.2 even if the event does not fulfill the seriousness criteria.

8.4 Dose Interruption Criteria

The investigator is responsible for contacting the sponsor/designee when the subject's teduglutide dosing regimen is interrupted. The length of dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

Investigational product must be interrupted if any of the following events occur:

- An adverse event of special interest (see Section 8.3)
- Intestinal obstruction
- Biliary obstruction
- Pancreatic duct obstruction

Investigational product must be permanently discontinued if any of the following events occur:

- Severe hypersensitivity, such as anaphylaxis, determined by the investigator to be related to IP.
- Any malignancy

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Process

The study will be analyzed by the sponsor or designee. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, US) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the definitions and statistical methods for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

9.4 Planned Interim Analysis, and Data Monitoring Committee

No interim analyses is planned for this the study.

A data monitoring committee (DMC) will be involved in the management of this study. The DMC members will review the data approximately every 3 months according to the DMC Charter. The DMC review will include all cumulative safety data (i.e., AEs, laboratory assessments, physical examinations, etc.) from study assessments through each cutoff period. Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of investigational product.

The DMC for this study will be conducted in accordance with the FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006).

The DMC will be an external, independent board comprised of physicians with relevant training. The DMC will be restricted to individuals free of significant conflicts of interest, including, but not limited to, financial, scientific, or regulatory in nature. The DMC will be governed by a Charter agreed to by members of the Board and the sponsor. Members of the Board may not be study investigators or be employed at the same institution as a study investigator, individuals employed by the sponsor, independent contractors hired by the sponsor, or members of regulatory agencies. The DMC may make recommendations to the sponsor regarding study aspects including stopping, modifying or continuing the study; however, the sponsor will have the final responsibility to determine whether the study should be modified or temporarily or permanently stopped.

9.5 Sample Size Calculation and Power Considerations

The sample size is determined based on enrollment feasibility for this rare condition and the age of the study population.

9.6 Study Population

Intent to treat (ITT) population: All subjects randomized in the study.

Safety analysis population: All subjects who have at least one safety assessment after the baseline visit.

Per-protocol population: All subjects in the ITT population without a major protocol deviation that affects interpretation of efficacy results.

Pharmacokinetic analysis population: All subjects randomized in the teduglutide treatment arm for which the primary PK data are sufficient and interpretable.

9.7 Efficacy Analyses

Efficacy endpoints consist of the following:

Primary Efficacy Endpoint

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

Secondary Efficacy Endpoints

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by Week 24
- Change in weight-normalized parenteral fluid volume from baseline to each visit

- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT

Due to the limited size of the study population, descriptive statistics will be used with a goal of summarizing the sample. As such, no claims of significance will be made for any of the data. Continuous variables will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and there is no use of PN recorded in the subject diary during the week prior to that visit. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

9.8 Safety Analyses

Safety endpoints consist of the following:

- Adverse events
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (e.g., number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, SAEs will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores, and descriptive statistics (e.g., n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

9.9 Health Economics and Outcomes Research Analyses

Health economics and outcomes research endpoints consist of the following:

- EQ5D-5L
- Cumulative number of hospitalization days during the study

Health economics and outcomes research endpoints will be summarized using descriptive statistics (number, mean and standard deviation) at nominal time points.

9.10 Pharmacokinetics Analyses

Pharmacokinetic endpoints include but are not limited to the following:

- Area under the plasma concentration-time curve at steady-state over the dosing interval ($AUC_{tau,ss}$)
- Maximum plasma concentration at steady-state ($C_{max,ss}$)
- Apparent clearance (CL/F)

Plasma concentrations will be summarized using descriptive statistics (number, mean, and standard deviation) at nominal time points. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum).

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (e.g., CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly. The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator will be appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.2.1 Documentation and Retention of Records

10.2.2.2 Electronic Case Report Forms

Electronic case report forms are supplied by the sponsor or designee and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data will be recorded directly onto the eCRF.

All data sent to the sponsor must be endorsed by the investigator.

The study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.2.3 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diaries, and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the parent/guardian agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (e.g., subject's medical file, appointment books, original laboratory reports, X-rays etc). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.2.4 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.2.5 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent and assent, where applicable, from the parent(s)/guardian(s) of all study subjects prior to any study-related procedures including screening assessments. All consent and assent documentation must be in accordance with applicable regulations and GCP. Each subject's legally authorized representative is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent and assent documentation (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject's legally authorized representative, as applicable.

This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form (and assent form where applicable) that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (i.e., sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor/designee has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor/designee.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market teduglutide; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (e.g., to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (e.g., Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2 to 4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

11. REFERENCES

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	03 Oct 2017	Global

Appendix 2 Guidelines for Nutritional Support Management During the Study

The nutritional support adjustment guidelines are designed to standardize management of parenteral and enteral nutritional support in this study. Adjustments to nutritional support should be considered at every scheduled clinic visit. Adjustments at phone visits may also be performed, but nutritional assessments at phone visits serve primarily to confirm that nutritional adjustments at prior clinic visits were tolerated.

All attempts should be made to follow the guidelines, but departure from the guidelines will not constitute a protocol deviation.

Clinical judgment is required within the algorithm. Each decision point requires integrating multiple sources of information into a yes/no decision. When individual data points are conflicting, the investigator must use their best judgment in the assessment.

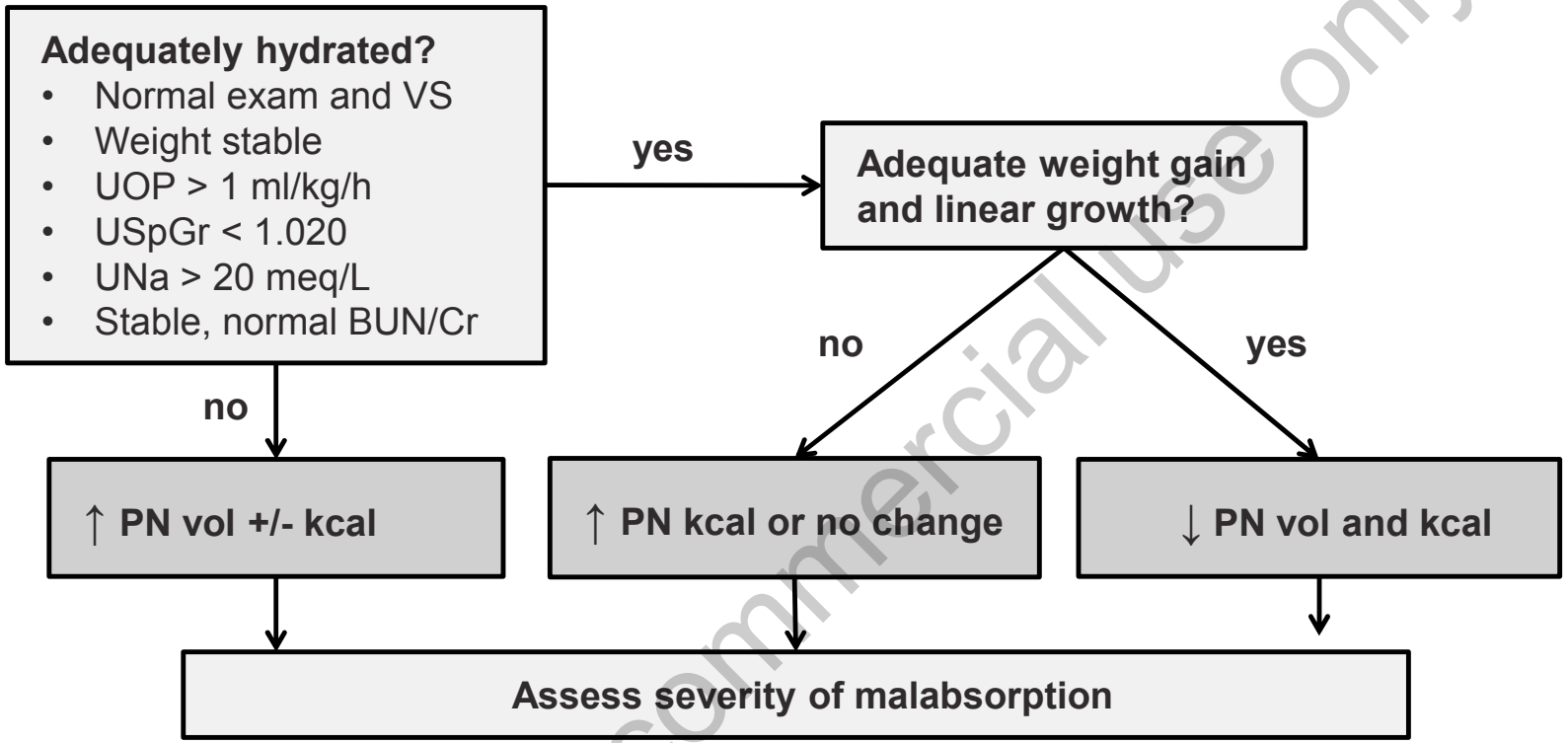
If intestinal adaptation is occurring, reductions in parenteral support volume and calories are expected to be in decrements of 5 to 10% relative to baseline values. Parenteral support components are at the discretion of the investigator, but care should be taken to balance carbohydrate, fat, and protein. Likewise, if intestinal adaptation is occurring, enteral nutrition volume and calories should be increased in increments of approximately 10% relative to baseline values.

Assessment of the severity of malabsorption may require estimation of stool output for children who have mixed stool and urine output.

Adjustments should be based on the actual nutritional support in volume and calories the subject infuses. Subjects should remain compliant with the nutritional support prescription in volume and calories during the study.

During the 48-hour output measurement period prior to the subject's scheduled visit, no further changes to the prescribed nutritional support should be made.

Figure A-1: Parenteral Nutrition/Intravenous Adjustment Algorithm for All Subjects



BUN=blood urea nitrogen; Cr=creatinine; PN=parenteral nutrition; UNa=urine sodium; UOP=urine output; USpGr=Urine specific gravity; VS=vital signs; vol=volume

Protocol Administrative Clarification MEMORANDUM

To: SHP633-301 Trial Master File (TMF), SHP633-301 Study Sites
From: [redacted], MS – [redacted] and [redacted], MBA – [redacted]
Date: 08 Nov 2017
Subject: Protocol Administrative Clarification Memorandum
EUDRACT NO: 2017-003606-40

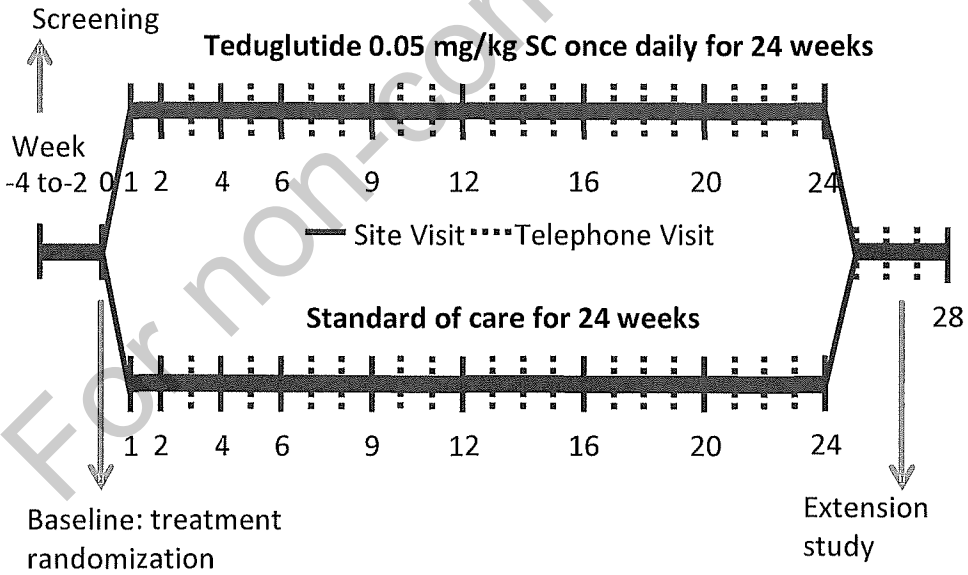
Protocol Title: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support

Protocol Version: Original Protocol 03 Oct 2017

The following Administrative Letter is for Protocol SHP633-301, Original Version dated 03 Oct 2017. These changes are considered administrative in nature and the clarifications do not compromise the scope, design, or integrity of the study. These changes do not compromise subject safety in any way.

The administrative changes include:

1. **To clarify the duration of the screening period and total time on study**: The study consists of a screening period of 2-4 weeks, a 24-week treatment period, and a 4-week follow-up period for a total of up to 30-32 weeks total time on study.
2. **To clarify the study schematic:** The study schematic will be replaced with the following diagram:



cc: SHP633-301 TMF Main Study File

3. **To provide a clear definition of the end of the trial**: The end of trial is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on study (whether during the 24-week treatment period or the 4-week follow-up period).

4. **To clarify the timing of the required pharmacokinetic (PK) draws after investigational product administration**: There are no PK draw windows after the first dose of investigational product identified in the protocol. The sponsor wishes to clarify that all PK draw windows are permitted to be +/- 10 minutes from scheduled time of draw.

5. **To clarify the procedures for assessing subject compliance in Section 6.5**: In addition to counting returned vials, subject compliance will be checked by site personnel at every visit by reviewing the subject diaries and asking the subject or the subject's parent or legally-authorized representative if they have administered the investigational product according to instructions. If any doses have been missed, the reason for missed dose should be documented in the subject's source documentation including, as applicable, the eCRF.

   The sponsor also wishes to clarify that the investigator is responsible for contacting the sponsor or designee when the subject's daily investigational product dosing regimen is interrupted. Attempts should be made to contact the sponsor or designee prior to dose interruption. Reasons for dosage interruption may include but are not limited to hospitalization and AEs, a lapse in investigational product delivery, etc.

The protocol will be updated with these changes during any subsequent amendment.

Copies of this letter shall be distributed to the Principal Investigators of the study and should be forwarded to the site Ethics Committees as necessary.

If you have further questions, please do not hesitate to contact your CRA or Shire directly.

I have reviewed the above Memorandum and am in agreement with the specified administrative clarifications.

Thank you,

[redacted]

[redacted], Pharm.D., MSc.

[redacted]—Teduglutide

SHP633-301 Medical Monitor

[redacted]

Date

cc: SHP633-301 TMF Main Study File

PROTOCOL: SHP633-301

TITLE:	A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support
NUMBER	SHP633-301
PHASE	3
DRUG:	Teduglutide
INDICATION:	Short bowel syndrome
EUDRACT NO.:	2017-003606-40
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA
PROTOCOL HISTORY:	Original Protocol: 03 Oct 2017 Amendment 1: 18 Jan 2018

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted] **Date:** [redacted]

[redacted], MD PhD
[redacted], Global Clinical Development

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-301.

Title: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the Shire Medical Monitor by fax or e-mail:
Fax: [redacted], Email: [redacted]

For protocol- or safety-related issues, the investigator must contact IQVIA Medical Support:

Primary Contact

[redacted], MD

[redacted]

Mobile: [redacted]

US Toll Free Number: [redacted]

Phone: [redacted]
(medical emergencies)

Email: [redacted]

Backup Contact

[redacted], MD

[redacted]

Mobile: [redacted]

Phone: [redacted]

Phone: [redacted]
(medical emergencies)

Email: [redacted]

In addition, the investigator may also contact Shire:

[redacted], PharmD, MSc

[redacted]

Phone: [redacted]

Mobile: [redacted]

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (e.g., inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (e.g., wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	E-mail Address
North and South America	[redacted]
European Union and Rest of World	[redacted]

Telephone numbers (provided for reference, if needed):

Shire (USA)
[redacted]

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 18 Jan 2018	Global
Description of Change		Section(s) Affected by Change
Updated emergency contact information to reflect the change of the Contract Research Organization's name.		Emergency Contact Information
Clarified the duration of the screening period and total time on study. Provided a clear definition of study completion. Updated the study schematic to reflect the study design changes.		Synopsis, Section 3.1, Section 3.2
Revised the telephone and clinic visit schedule to assure laboratory measurement could be collected without exceeding weekly/monthly total blood volume restrictions.		Synopsis, Table 1, Section 3.1.2
Moved the PK sampling from Week 6 to Week 7 so that the samples could be collected without exceeding weekly/monthly total blood volume restrictions. Clarified that blood for pharmacokinetic samples of postdose may be taken within ± 10 minutes of the time pre-specified.		Synopsis, Table 1, Section 3.1.2, Section 7.2.4, Table 5
Clarified that end jejunostomy or ileostomy are examples of small bowel ostomy rather than the stratification factors.		Synopsis, Section 3.1.2, Section 6.2.2
Clarified that all subjects regardless of treatment arm are eligible for the extension study.		Synopsis, Section 3.1.3
Clarified that if a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.		Synopsis, Table 2, Section 3.1.3, Section 6.2.3
Clarified that subjects must be 4 to 12 months corrected		Synopsis, Section 4.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 18 Jan 2018	Global
Description of Change		Section(s) Affected by Change
gestational age at screening.		
Changed dose adjustments to Week 12 rather than at every clinic visit to reduce site burden.		Synopsis, Table 1, Section 6.2.3
Clarified the definition of enteral autonomy.		Synopsis, Section 9.7.2
Updated the pharmacokinetic endpoint and analysis to reflect that only descriptive statistics will be calculated on plasma teduglutide concentration values. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.		Synopsis, Section 9.10
Removed assessment of the 5-level EuroQol five dimensions questionnaire to reduce caregiver burden.		Synopsis, Table 1, Section 7.2.5, Section 9.9
Clarified that native GLP-2 samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.		Table 2, Section 7.2.2
Inserted a footnote to clarify that parenteral support and parenteral nutrition are used interchangeably.		Section 1.1
Removed the 5 mg vial of teduglutide as this size vial will not be supplied for this study.		Section 6.1
Clarified the procedures for assessing subject compliance.		Section 6.5
Specified that it is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow through performed since the subject's most recent surgery.		Section 7.2.1
Corrected the volume of blood to be collected for native GLP-2.		Table 5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 18 Jan 2018	Global
Description of Change		Section(s) Affected by Change
Removed references to subject assent as assent is not possible in a study of infants.		Section 7.1.1, Section 10.3.1
Clarified the definitions of the analysis sets.		Section 9.6
Clarified that an adjustment to enteral nutrition as appropriate is part of the PN/IV adjustment algorithm.		Figure A-1
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout protocol.

See Appendix 1 for protocol history, including all amendments.

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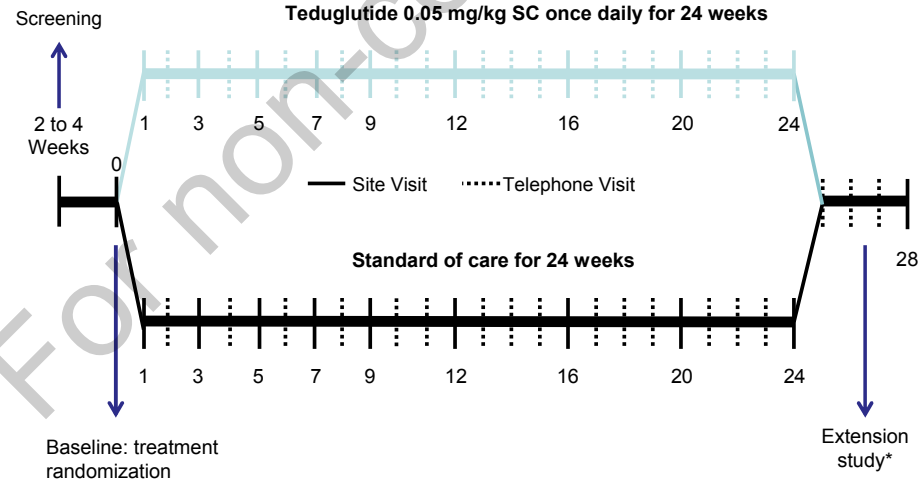
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
AUC_{ss}	area under the concentration-time curve at steady-state
$C_{max,ss}$	maximum plasma concentration at steady state
CRO	contract research organization
eCRF	electronic case report form
DMC	data monitoring committee
EDC	electronic data capture
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	glucagon-like peptide
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medicinal Journal Editors
I/O	oral fluid intake and urine output
IP	Investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PN	parenteral nutrition
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
SD	standard deviation
SOC	standard of care
ULN	upper limit of normal
US	United States

STUDY SYNOPSIS

Protocol number: SHP633-301	**Drug:** Teduglutide
Title of the study: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support	
Number of subjects (total and for each treatment arm): At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in a standard of care (SOC) comparator arm	
Investigator(s): Multicenter study	
Site(s) and Region(s): This study is planned to be conducted in approximately 5 to 10 sites globally.	
Study period (planned): 2017-2020	**Clinical phase:** 3
Objectives: The objectives of this clinical study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with short bowel syndrome (SBS) dependent on parenteral support.	
Investigational product, dose, and mode of administration: Teduglutide 0.05 mg/kg by subcutaneous (SC) injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm.	
Methodology: This is a randomized, multicenter, open-label study, consisting of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period.	



* At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the

subjects may proceed immediately to the EOS if at least one "escape" criteria is met.

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum 4 weeks). At the baseline visit (Week 0), subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for parenteral nutrition (PN) reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 or 12 (2 hours±10 minutes postdose).

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

Inclusion and Exclusion Criteria:

Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length *Z*-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. Lack of terminal ileum and ileocecal valve
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.
8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.
9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µl due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2-week period
13. More than 3 serious complications of intestinal failure (e.g., catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

Maximum Duration of Subject Involvement in the Study:

The study consists of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

Endpoints:

Efficacy

Efficacy endpoints consist of the following:

Primary

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

Secondary

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by week 24
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to Week 24/EOT

Pharmacokinetics

The pharmacokinetic endpoint is plasma teduglutide concentration at nominal time point.

Safety

Safety endpoints consist of the following:

- Adverse events (AEs)
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

Health Economics and Outcomes Research

Health economics and outcomes research (HEOR) endpoints include the following:

- Cumulative number of hospitalization days during the study

Statistical Methods:

Efficacy

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

Pharmacokinetics

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.

Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (e.g., number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, serious adverse events will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores; and descriptive statistics (e.g., n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

Health Economics and Outcomes Research

The HEOR endpoints will be summarized descriptively.

STUDY SCHEDULES

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X													
Eligibility	X	X												
Randomization		X												
Demographics	X													
SBS history	X													
Medical and surgical history	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight	X	X	X		X		X		X		X			X
Length and head circumference	X	X					X							X
UGI/SBFT	X													
Safety labs and urinalysis[b, c]	X	X[b]	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	(X)	X
PK sampling[a]		X							[X][d]					[X][d]
Antibodies to teduglutide[a,e]		X												X[e]
Native GLP-2[f]	X													
Provide intake and output diaries[g]	X	X	X		X		X		X		X			X
Review diaries and nutritional support		X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support as needed[h]		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IP[a, i]		X	X		X		X		X		X			X

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Adjust IP dose[j]														X

EN=enteral nutrition; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PK=pharmacokinetics; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] Applicable to the teduglutide treatment arm only.

[b] At baseline, safety labs (Table 4) and PK can be separated by 1 day if blood volumes are limiting. Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline, and repeated if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity. Urine collection should be attempted, but inability to obtain urinalysis is not a protocol deviation.

[d] Subjects will have blood samples taken for teduglutide PK analysis predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the treatment period.

[e] Samples for antibody analysis will be drawn at the baseline and Week 12 visits. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.

[f] Blood samples for native GLP-2 should be collected postprandial. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

[i] The initial dose will be calculated based on body weight measured at baseline (Visit 0).

[j] The dose will be adjusted as needed, based on body weight measured at Week 12 visit.

Note: (X) denotes optional assessments; [X] denotes possible PK sampling time point (Refer to footnote "e".)

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Visit type	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**
Study day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**175**	**182**	**189**	**196**
±window (days)	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight				X				X				X				X
Length and head circumference				X				X				X				X
Safety labs and urinalysis[b,c]	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X
Antibodies to teduglutide[d,e]																X
Native GLP-2[f]												X				
Provide intake and output diaries				X				X				X				
Review diaries and nutritional support[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support as needed[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess follow-up period escape criteria[d]													X[i]	X[i]	X[i]	X
Dispense IP[d]				X				X								

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Visit type	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site
Study day	91	98	105	112	119	126	133	140	147	154	161	168	175	182	189	196
±window (days)	±3	±3	±3	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4

EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] At EOS subjects may enroll in an extension study, if subjects require treatment before the end of the 4-week follow-up they may enter the extension study immediately.

[b] Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR are tested if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity.

[d] Applicable to the teduglutide treatment arm only.

[e] Samples for antibody analysis will be drawn at the EOS (Week 28) visit.

[f] Blood samples for native GLP-2 should be collected postprandial. Blood samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.
Note: (X) denotes optional assessments.

[i] If a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.

1. BACKGROUND INFORMATION

1.1 Short Bowel Syndrome

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal diseases that result in major surgical resections of the small intestine (O'Keefe et al., 2006). Unlike the adult population, the majority of cases of SBS in pediatric subjects are due to congenital anomalies or catastrophic events that occur during infancy such as necrotizing enterocolitis, gastroschisis, intestinal atresia, midgut volvulus, or long-segment Hirschsprung disease (Beattie et al., 2010; Goulet and Ruemmele, 2006). A Canadian population-based study in neonates estimates an overall incidence of SBS to be 24.5 cases per 100,000 live births (Wales et al., 2004).

The small intestine is capable of remarkable adaptation, but excessive loss of absorptive surface area or specialized functions can lead to dependence on parenteral nutrition (PN)[1] fluids (O'Keefe et al., 2006). Although PN is life-sustaining in intestinal failure, it is associated with serious complications, including liver disease, life-threatening catheter-related blood stream infections, and central venous thrombosis (Beattie et al., 2010; Goulet and Ruemmele, 2006). Dependence on PN is also associated with reduced quality of life in both patients and caregivers and has an extremely high cost of care (Huisman-de Waal et al., 2007). About 30% of infants with SBS become independent of PN requirements within 12 months of the initial insult, and an additional 10% wean off PN within 24 months. After this time, linear intestinal growth slows. It is estimated that 42% to 86% of pediatric patients with SBS are able to become independent of PN within 1 to 3 years (Gonzalez-Hernandez et al., 2017; Khan et al., 2015; Squires et al., 2012). Nevertheless, despite optimal medical management, some children remain dependent on PN for many years (Squires et al., 2012). Infants who have less than 10% of expected small intestinal length for their gestational age have a low likelihood of ever achieving enteral autonomy (i.e., independence from parenteral support). Providing the maximum tolerated amount of enteral nutrition (EN) has been the primary strategy to promote enteral adaptation (Spencer et al., 2005).

Accelerating the adaptive process and achieving enteral autonomy is an urgent goal for all patients with SBS who are dependent on PN (Khan et al., 2015; Squires et al., 2012). The adaptive process is in part controlled by glucagon-like peptide 2 (GLP-2), a 33 amino acid peptide hormone secreted from L-type enteroendocrine cells in the terminal ileum and colon in response to luminal nutrients and bile acids (Martin et al., 2006). The post-prandial plasma concentration of GLP-2 in infants with SBS correlates with length of the remaining small intestine (Sigalet et al., 2004). Infants who lack terminal ileum may have impaired adaptation due to inadequate production of GLP-2.

[1] For the purpose of the study the terms parenteral support (PS) and parenteral nutrition (PN) are used interchangeably.

1.2 Teduglutide

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$), approximately 2 hours in healthy adult subjects, 1.3 hours in adult SBS subjects, and 0.22 hours in pediatric SBS subjects, compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines (Tappenden et al., 2013; Thymann et al., 2014).

A Phase 3 study, TED-C13-003, has been completed in pediatric SBS subjects. In this study, teduglutide was administered to 3 cohorts of pediatric subjects from ages 1-17 years. Thirty-seven pediatric subjects received teduglutide at doses of 0.0125, 0.025, or 0.05 mg/kg/day for 12 weeks. Five additional pediatric subjects were enrolled in an observational standard of care (SOC) cohort. There were clear dose-dependent effects of teduglutide seen at the 0.025 and 0.05 mg/kg/day doses compared to SOC and the 0.0125 mg/kg/day dose. In the 0.025 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 37%, including complete independence from PN support in 1 subject, and a reduction of 3.94 hours per day infusion time. In the 0.05 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 39%, including complete independence from PN support in 3 subjects, and a reduction of 4.18 hours per day infusion time. Teduglutide was generally safe and well tolerated by pediatric subjects in all dosing cohorts. There were no deaths during the study and no treatment-emergent serious adverse events (SAEs) related to teduglutide were reported. No discontinuations from study were due to adverse events (AEs). Additional studies in pediatric patients with SBS are ongoing.

Teduglutide (0.05 mg/kg/day) is currently approved for the treatment of adult patients with SBS in >30 countries. On 29 Jun 2016, the European Commission granted an extension of the Market Authorization for teduglutide for the treatment of patients aged 1 year and above with SBS.

Always refer to the latest version of the investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy and safety of teduglutide (SHP633).

2. OBJECTIVES

2.1 Rationale for the Study

There is no approved pharmacological therapy to improve intestinal adaptation in infants with SBS who are dependent on parenteral support. This study will evaluate whether teduglutide is safe and effective in this patient population.

2.2 Study Objectives

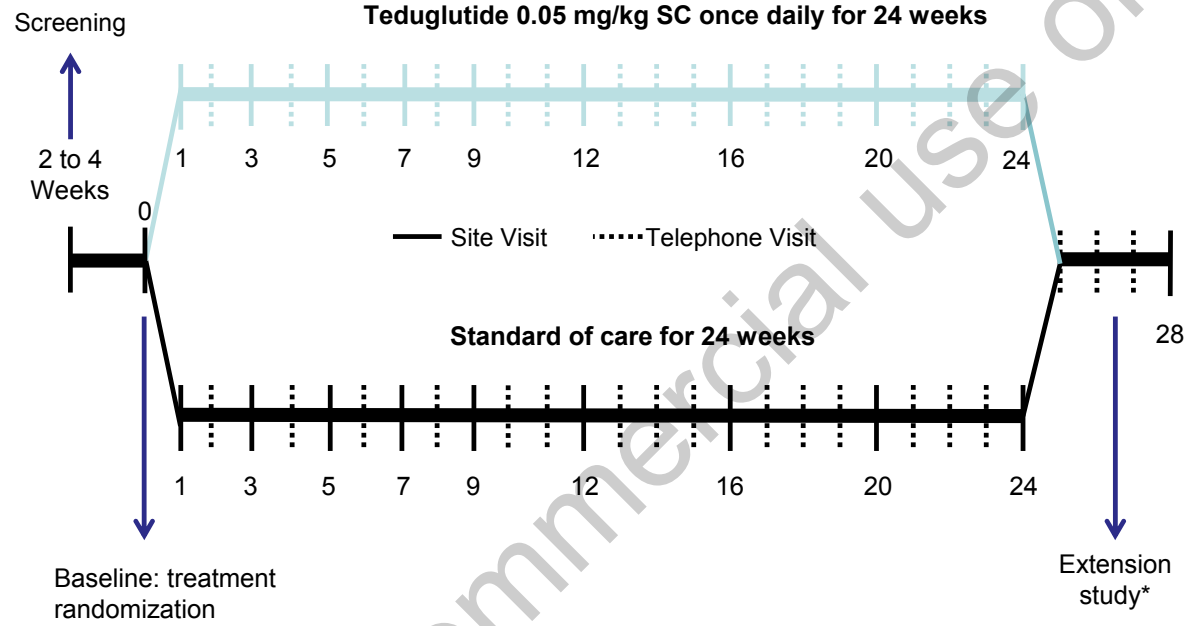
The objectives of this study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with SBS dependent on parenteral support.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a randomized, multicenter, open-label study, consisting of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. A schematic representation of the study design is presented in Figure 1.

Figure 1: Study Schematic



*At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one "escape" criteria is met.

3.1.1 Screening Period

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum: 4 weeks). The schedule of evaluations to be conducted during the Screening Period can be found in Table 1.

3.1.2 Treatment Period

At the baseline visit (Week 0), subjects will randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS, while those in the teduglutide arm will receive 0.05 mg/kg by subcutaneous (SC) injection once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for PN reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability (Appendix 2). Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 or 12 (2 hours±10 minutes postdose).

The schedule of evaluations for the Treatment Period can be found in Table 1 (Visits -1 to 12) and Table 2 (Visits 13 to 28).

3.1.3 Follow-up Period

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product (IP) will be administered. At EOS, all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS visit if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

The schedule of evaluations for the Follow-up Period can be found in Table 2 (Visits 13 to 28).

3.2 Study Duration

The study consists of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

3.3 Sites and Regions

This study is planned to be conducted at approximately 5 to 10 sites globally.

4. STUDY POPULATION

At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in an SOC comparator arm.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. Lack of terminal ileum and ileocecal valve.
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.

8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.
9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µL due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2 week period.
13. More than 3 serious complications of intestinal failure (e.g., catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

4.3 Reproductive Potential

Not applicable; this study will enroll infants.

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (e.g., in the interest of subject safety). The investigator should discuss withdrawal of a subject from investigational product with the medical monitor as soon as possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT/early termination are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period. Comments (spontaneous or elicited) or complaints pertaining to IP discontinuation made by the subject must be recorded in the source documents. The reason for discontinuation, the date and the total amount of investigational product administered must be recorded in the electronic case report form (eCRF) and source documents.

Subjects who discontinue will not be replaced.

4.4.1 Reasons for Discontinuation

The reason(s) for permanent discontinuation of treatment and/or withdrawal from the study must be determined by the investigator, and recorded in the subject's medical record and in the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document, and the most clinically relevant reason should be entered in the eCRF.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by parent/guardian
- Lack of efficacy
- Other

4.4.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact the parent(s)/guardian(s) of any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Medications and Procedures

Prior treatment includes all treatment and procedures (including but not limited to prescription treatments, herbal treatments, vitamins, non-pharmacological treatment, as appropriate) received within 14 days prior to the screening visit (Visit -1) (or pharmacokinetic equivalent of 5 half lives, whichever is longer, must be recorded on the appropriate eCRF page.

5.2 Concomitant Medications and Procedures

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins) and PN must be recorded from the first dose of investigational product and for the duration of the study in the appropriate sections of the eCRF. Any diagnostic, surgical or other therapeutic treatments received by a subject during the course of the study will also be recorded on the eCRF.

The mechanism of action of teduglutide may increase enteral absorption of oral drugs (e.g., drugs used for management of SBS such as motility medication, opioids, psychotropics, metronidazole), so consideration should be given to modifying concomitant enteral medication regimens. Titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic index (e.g., warfarin, digoxin, psychotropics) are given.

5.3 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.4 Prohibited Treatment

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the pretreatment visit (Table 3):

Table 3: Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pretreatment Visit
Teduglutide	Any
GLP-2, human growth hormone, or analogs of these hormones	6 months
Octreotide, GLP-1 analogs, and enteral glutamine	30 days

GLP=glucagon-like peptide

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

Teduglutide will be provided in sterile, single-use 3 mL vials containing 1.25 mg teduglutide as a white lyophilized powder to be reconstituted before use with 0.5 mL sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the current investigator's brochure.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

All investigative study sites will be initially provided with sufficient investigational product to randomly assign a subject into the study (for either of the proposed treatment groups). Randomization will occur through an interactive response system. Random assignment of a subject will trigger replacement supplies for that investigative study site.

6.2.2 Allocation of Subjects to Treatment

Subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy). The actual treatment given to individual subjects is determined by a randomization schedule.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined.

6.2.3 Dosing

The initial dose will be calculated based on body weight measured at baseline (Visit 0), and adjusted as needed, based on body weight measured at Week 12. No other adjustments to dose will be made during the teduglutide treatment period, unless discussed with the sponsor's medical monitor.

Following reconstitution, teduglutide will be administered by SC injection once daily (QD) into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used.

Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later.

The subject should be dosed at approximately the same time each day. Consecutive doses should be separated by at least 12 hours. Each day, the injection site should be alternated.

Any subject who achieves complete independence from PN support at any time during the treatment period will continue to receive teduglutide treatment.

The first SC injection in teduglutide-naïve subjects should be administered under the supervision of the investigator or designee and the subject observed for hypersensitivity reactions for at least 4 hours during their initial dosing visit. The site of administration (arm, thigh, and abdomen) of the first teduglutide dose must be specified and recorded in the eCRF.

Detailed instructions for reconstitution and injection of the investigational product can be found in the Instructions for Use.

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.2.5 Dose Selection Rationale

Teduglutide is approved for adult and pediatric use in the EU at a dose of 0.05 mg/kg SC once daily. A completed 12-week dose finding study (TED-C13-003) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit-risk profile most meaningful at the 0.05 mg/kg/day dose (Carter et al., 2017).

Population pharmacokinetic modeling and simulations were conducted to determine the optimal dose to be used in pediatric subjects using data from 8 adult clinical studies including adult Phase

1 studies and Phases 2/3 studies as well as TED-C13-003 and suggested the same adult dose (0.05mg/kg) in pediatric subjects (aged between 1.67-14.7 years) (Marier et al., 2017).

To support dosing in the current age group, further PK simulation was conducted based on the population PK model previously established and a virtual population of 1000 pediatric patients created based on Centers for Disease Control (CDC) growth charts in the target age group (4 to 12 months) and taking into consideration body weights of pediatric patients with SBS enrolled in study TED-C13-003 (approximately 15% lower than healthy subjects in the same age group). Monte Carlo simulations for all age groups were performed according to the SC dosing regimens of 0.0125, 0.025 and 0.05 mg/kg every 24 hours. Rich concentration-time profiles were simulated with the customized population PK model to derive the exposure metrics area under the concentration curve at steady state (AUC_{ss}) and maximum concentration at steady state ($C_{max,ss}$). Following 0.05 mg/kg daily SC administration, the median $C_{max,ss}$ of teduglutide in neonate patients (24.9 ng/mL) was within 20% of that observed in the 2 to 4 and 4 to 6 years age groups (26.9 and 29.4 ng/mL, respectively); and approximately ~28% lower than that in adult patients with SBS. The clinical package in conjunction with C_{max} was considered to support teduglutide dose selection since AUC_{ss} was previously shown not to correlate with efficacy. Thus, the 0.05 mg/kg dose is proposed for testing in this age group.

6.3 Labeling, Packaging, and Storage

6.3.1 Labeling

The investigational product will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of investigational product will be provided for this study. The vials will be labeled in accordance with applicable regulatory requirements.

Ancillary kits, containing supplies needed for the reconstitution and administration of the investigational product will also be provided and labeled in accordance with the applicable regulatory requirements.

All investigational product used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice.

6.3.2 Storage and Handling

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2-8°C (35.6-46.4°F) until dispensed to a subject. Once dispensed to a subject, the IP can be stored refrigerated or up to a controlled room temperature (acceptable range of 2-25°C, or 35.6-77°F). Parent/legal guardian will be instructed to keep the subject's IP and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot

be maintained, the IP may be refrigerated. The IP is for single use only, and should be used within 3 hours following reconstitution.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (i.e., certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), e.g., fumigation of a storage room.

Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels, as they are distributed.

6.4 Drug Accountability

Investigational product will not be dispatched to the study site until the sponsor or designee has received all required documents from the study site in accordance with applicable regulatory requirements and relevant standard operating procedures. Upon receipt, the study site's pharmacist or delegate is responsible for ensuring that all investigational product received at the site is inventoried and accounted for throughout the study. A copy of the shipping documents must be maintained for the investigator's records. Kits will be shipped to the site once the subject is screened.

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Investigational product kits will be dispensed at each of the applicable study visits at which the subject is required to be at the clinic. Each investigational product kit is sufficient for a treatment period of 1 week and enough kits will be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

Each subject will be given the investigational product according to the protocol. The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. All dispensed medication will be documented on the eCRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, subject returned investigational product, and empty/used investigational product packaging are to be sent to the sponsor or designee. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

Returned investigational product must be counted and verified by clinical site personnel and the sponsor (or study monitor). Shipment return forms, when used, must be signed prior to shipment from the site. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

The parent(s)/guardian(s) of subjects must be instructed to bring unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed and recorded at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (e.g., bottles, trays, vials) or at the individual count level for opened containers/packaging.

Subject compliance will be checked by site personnel at every visit by reviewing the subject diaries and asking the subject or the subject's parent or legally-authorized representative if they have administered the investigational product according to instructions. If any doses have been missed, the reason for missed dose should be documented in the subject's source documentation including, as applicable, the eCRF.

The investigator is responsible for contacting the sponsor or designee when the subject's daily investigational product dosing regimen is interrupted. Attempts should be made to contact the sponsor or designee prior to dose interruption. Reasons for dosage interruption may include but are not limited to hospitalization and AEs, a lapse in investigational product delivery, etc.

Subjects who have received 80% of the planned doses administered will be assessed as being compliant with the study protocol.

7. STUDY PROCEDURES

7.1 Study Schedule

Detailed study procedures and assessments to be performed for subjects throughout the study are outlined in the study schedules (Table 1 and Table 2) and must be referred to in conjunction with the instructions provided in this section.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period.

7.1.1 Screening

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the parent(s)/guardian(s) of the subject. The screening visit assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1.

7.1.2 Treatment Period

The randomized Treatment Period will comprise Weeks 1 to 24, during which all assessments will be performed as outlined in Table 1 and Table 2.

7.1.3 Follow-up Period

The Follow-up Period will comprise Weeks 25 to 28, during which all assessments will be performed as outlined in Table 2.

7.2 Study Evaluations and Procedures

7.2.1 Demographics and Other Baseline Characteristics

Demographics and Medical History

Demographic and/or other baseline variables obtained at the screening and/or baseline visits are listed below. Abnormal findings of clinical significance (if any) will be recorded as past medical history.

- Demography (including age, gestational age, sex, and race)
- Medical history (including surgical history)
- SBS history, including remnant anatomy

Upper Gastrointestinal Series with Small Bowel Follow-through

An upper GI contrast series with small bowel follow-through will be performed on all subjects during the screening period if one has not been done since the subject's last GI surgery.

It is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow-through performed since the subject's most recent surgery.

7.2.2 Efficacy Assessments

Subject Diaries

All available diary data will be reviewed by the investigator or their designee at each clinic and telephone visit to assess clinical status and opportunity for PN reduction and advance in feeds. Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

Intake Diary

Intake diaries will be used to collect and evaluate each subject's nutritional support. The parent/legally authorized representative/study site staff will complete the appropriate fields of the PN and EN sections of the intake diary daily throughout the study.

The following data will be captured in the intake diaries:

- Parenteral support volume and infusion duration
- Enteral nutrition (formula) including volume and calories

Site personnel will determine the actual PN and EN daily calories based on diary entries.

Output Diary

Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit; in addition, output should be recorded for subjects within 1 week of implementing a change in the PN prescription.

Urine data:

- Measure and record the weight of all urine-only diapers. Urine volume will be calculated using the following formula: 1 g (scale weight) = 1 mL or 1 cc
- At the discretion of the investigator, the parent or legal guardian/study site staff may be asked to collect the first void after the daily PN infusion to measure specific gravity

Stool data (includes diapers with mixed urine and stool):

- Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency (see Output diary). Stool volume will be calculated using the formula: 1 g (scale weight)=1 mL or 1 cc

All ostomy output volume should be recorded.

Native GLP-2

Blood samples for native GLP-2 should be collected postprandial. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

7.2.3 Safety Assessments

Laboratory Evaluations

Safety laboratory tests to be performed at site visits consist of clinical chemistry, hematology, and urinalysis and will be performed as outlined in the study plan (Table 1 and Table 2). Scheduled laboratory testing will be processed by a central lab. All laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the laboratory. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

During the Treatment Period, subjects will also have safety labs within approximately 5 to7 days after a PN adjustment. Safety labs performed after PN adjustment and between site visits will consist of clinical chemistry and urinalysis and may be processed by the central laboratory or a local laboratory. Local lab results are not required to be entered in the eCRFs; however, if the local lab results indicate any new clinically significant changes, they must be reported as an adverse event (see Section 8). Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

At baseline, blood samples for safety labs and PK can be separated by 1 day if blood volumes are limiting.

Safety labs at telephone visits will be collected at the discretion of the investigator.

For all subjects in the teduglutide treatment arm, prothrombin time (PT) and international normalized ratio (INR), tested at baseline, will be repeated if clinically indicated.

New clinically significant labs should be reported as AEs.

Close monitoring criteria related to liver test abnormalities:

The investigator should contact the medical monitor within 24 hours of their awareness if the subject develops any of the following changes in laboratory parameters:

- ALT or AST >5x ULN and >2x baseline value

- Total or direct bilirubin that is >2x baseline value or an absolute increase of ≥3 mg/dL (51.3 µmol/L)

If such changes are observed, the labs should be repeated along with an INR, and an inquiry should be made as to the presence of clinical symptoms consistent with new liver injury. The subject should be followed closely to determine the trajectory of the laboratory abnormalities and appropriate evaluations should be made, such as abdominal ultrasound with Doppler imaging to exclude vascular causes and biliary obstruction, consideration of sepsis, liver hypoperfusion, acute viral hepatitis (such as hepatitis A, EBV, or HSV), exposure to hepatotoxic medications, mitochondrial hepatopathy, or metabolic liver disease (such as hereditary fructose intolerance or arginosuccinate synthetase deficiency). Further evaluations can be performed at the discretion of the investigator in consultation with the Shire medical monitor.

The following clinical laboratory assessments will be performed according to the study schedules:

Table 4: List of Laboratory Tests

Biochemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bicarbonate
- Bilirubin (total and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- C-reactive protein
- Creatinine
- Estimated Glomerular Filtration Rate (Schwartz formula)
- Gamma-glutamyl transferase
- Glucose
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Triglycerides

Hematology[a]:
- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- Red blood cell morphology, if needed
- White blood cell count with differential

Coagulation[b]:
- Prothrombin time
- International normalized ratio

Urinalysis:
- Specific gravity
- Urine Sodium

[a] Hematology is not collected at Week 1 or at telephone visits.
[b] For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline and repeated only if clinically indicated.

Antibodies to Teduglutide

Blood samples will be drawn to test for antibodies to teduglutide. Samples will be taken before teduglutide administration at the screening visit (Visit -1) and at least 14 hours after the previous dose at Week 12 (Visit 12); samples may be drawn from a central line or peripheral access. One additional sample will be collected at the EOS 4 weeks after the EOT (i.e., Week 28 or EOS).

Volume of Blood

Efforts will be made to minimize the amount of blood drawn from all pediatric subjects participating in this study. The volumes of blood to be drawn from each subject will vary depending on clinical status. Approximate volumes of blood to be drawn from each subject are shown in Table 5.

Table 5: Approximate Volume of Blood to be Drawn from Each Subject

Assessment	Sample Volume (mL)	No. Samples	Total Volume (mL)	Notes
Subjects Receiving Teduglutide Treatment				
Biochemistry	0.6	12	7.2	
Hematology	0.6	11	6.6	
Coagulation Parameters	0.6	1	0.6	PT and INR tested at baseline only, repeat while on study only if clinically indicated.
Antibodies	1.5	5	7.5	
Pharmacokinetics	1.5	4	6.0	Baseline: 3 timepoints Week 7: 1 timepoint OR Week 12: 1 timepoint
Native GLP-2	1.5	3	4.5	
Total mL:	**6.3**	**36**	**32.4**	
Subjects Receiving Standard of Care				
Biochemistry	0.6	12	7.2	
Hematology	0.6	11	6.6	
Native GLP-2	1.5	3	4.5	
Total mL:	**2.7**	**26**	**18.3**	

GLP=glucagon-like peptide; INR=international normalized ratio; PT=prothrombin time

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments should be combined. Blood volume estimates do not include safety labs performed after PN adjustment, and anti-teduglutide antibody testing during no-teduglutide treatment.

Physical Examinations, Vital Signs, Weight, Length, and Head Circumference

Physical examinations will be performed according to the study schedules (Table 1 and Table 2). Any new clinically significant findings noted during physical examinations should be recorded on the appropriate AE page of the eCRF.

Vital signs will be measured according to the study schedules. Measurements will include systolic and diastolic blood pressure (mmHg), pulse (beats per minute), and body temperature (°C/°F). Blood pressure should be determined by the appropriate size cuff (using the same method, the same leg, and in the supine position throughout the study, when possible). Blood pressure measurements should be attempted as part of the vital signs, but lack of blood pressure results will not constitute a protocol deviation. New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Length and head circumference will be measured at selected visits. A height z-score, weight Z-score, and weight/length ratio will be calculated by the sponsor using the site-provided height and weight data collected at each site visit.

7.2.4 Pharmacokinetic Assessments

Subjects will have blood samples taken for teduglutide PK analysis predose, and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the treatment period. Blood for PK sampling should be collected via peripheral IV or venipuncture, not from a central line. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified.

7.2.5 Health Economics and Outcomes Research

Hospitalizations

Each hospitalization that occurs during the study will be recorded, including date of admission, date of discharge, reasons for hospitalization, discharge diagnosis, and discharge status.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

AEs that are related to IP that are not resolved at EOS will be followed until the event resolves or stabilizes, as judged by the investigator.

Laboratory values, vital signs, and clinical findings at the scheduled physical examinations must be reported as AEs if the investigator considers the finding to be a clinically significant change from the baseline.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. It is assumed that some of the infants participating in this study may be hospitalized for planned surgery(ies) that will occur during their participation in the study. Such pre-planned, elective surgeries, do not need to be reported as SAEs for this protocol.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory or vital sign can represent an AE if the change is clinically relevant or if, during the study, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, during the study, there are abnormal clinical laboratory values or vital signs which were not present at the beginning of the study, further investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory or vital sign is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

Not applicable.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.

- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Administration of a dose greater than the allocated dose of the study medication or at a frequency greater than the dosing interval specified by the protocol.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally-authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

All Adverse Events of Special Interest, as defined in Section 8.3, must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event even if the event does not fulfill seriousness criterion.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol, and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested). Fax or e-mail the completed form to the Shire Global Drug Safety Department. A copy of the completed Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the Shire medical monitor or designee using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3, and must be reported to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (i.e., the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (e.g., drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The Sponsor and/or Clinical Contract Research Organization (CRO) is responsible for notifying the relevant regulatory authorities, and US central Institutional Review Boards (IRBs)/EU central ethics committees (ECs), of related, unexpected SAEs.

In addition, the Clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP633 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

8.3 Adverse Events of Special Interest

An AE of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program and for which ongoing monitoring and immediate notification by the investigator to the sponsor is required.

The AEs of special interest that require expedited regulatory reporting include the following:

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the GI tract including the hepatobiliary system
- Tumor-promoting ability (e.g., benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

For AEs of special interest, the sponsor must be informed within 24 hours of first awareness as per the SAE notification instructions described in Section 8.2.2 even if the event does not fulfill the seriousness criteria.

8.4 Dose Interruption Criteria

The investigator is responsible for contacting the sponsor/designee when the subject's teduglutide dosing regimen is interrupted. The length of dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

Investigational product must be interrupted if any of the following events occur:

- An adverse event of special interest (see Section 8.3)
- Intestinal obstruction
- Biliary obstruction
- Pancreatic duct obstruction

Investigational product must be permanently discontinued if any of the following events occur:

- Severe hypersensitivity, such as anaphylaxis, determined by the investigator to be related to IP.
- Any malignancy

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Process

The study will be analyzed by the sponsor or designee. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, US) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the definitions and statistical methods for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

9.4 Planned Interim Analysis, and Data Monitoring Committee

No interim analyses is planned for this the study.

A data monitoring committee (DMC) will be involved in the management of this study. The DMC members will review the data approximately every 3 months according to the DMC Charter. The DMC review will include all cumulative safety data (i.e., AEs, laboratory assessments, physical examinations, etc.) from study assessments through each cutoff period. Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of investigational product.

The DMC for this study will be conducted in accordance with the FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006).

The DMC will be an external, independent board comprised of physicians with relevant training. The DMC will be restricted to individuals free of significant conflicts of interest, including, but not limited to, financial, scientific, or regulatory in nature. The DMC will be governed by a Charter agreed to by members of the Board and the sponsor. Members of the Board may not be study investigators or be employed at the same institution as a study investigator, individuals employed by the sponsor, independent contractors hired by the sponsor, or members of regulatory agencies. The DMC may make recommendations to the sponsor regarding study aspects including stopping, modifying or continuing the study; however, the sponsor will have the final responsibility to determine whether the study should be modified or temporarily or permanently stopped.

9.5 Sample Size Calculation and Power Considerations

The sample size is determined based on enrollment feasibility for this rare condition and the age of the study population.

9.6 Study Population

Intent to treat (ITT) population: All subjects randomized in the study.

Safety analysis population: The safety analysis set will contain all subjects who meet the following criteria:

- Teduglutide treatment arm: subjects who receive at least 1 dose of teduglutide and have undergone at least 1 post-baseline safety assessment; analyses will be performed according to dose group as appropriate.
- Standard of care treatment arm: subjects who have undergone at least 1 post-baseline safety assessment.

Per-protocol population: All subjects in the ITT population without any major protocol deviation that affects interpretation of efficacy results.

Pharmacokinetic analysis population: All subjects who received at least 1 dose of teduglutide and have at least 1 evaluable postdose PK concentration value.

9.7 Efficacy Analyses

9.7.1 Efficacy Endpoints

Efficacy endpoints consist of the following:

9.7.1.1 Primary Efficacy Endpoint

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

9.7.1.2 Secondary Efficacy Endpoints

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by Week 24
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT

9.7.2 Method of Analysis-Efficacy Endpoints

Due to the limited size of the study population, descriptive statistics will be used with a goal of summarizing the sample. As such, no claims of significance will be made for any of the data. Continuous variables will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

9.8 Safety Analyses

9.8.1 Safety Endpoints

Safety endpoints consist of the following:

- Adverse events
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

9.8.2 Method of Analysis-Safety Endpoints

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (e.g., number and percentage of subjects). Adverse events will

be summarized by severity and relationship to treatment. In addition, SAEs will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores, and descriptive statistics (e.g., n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

9.9 Health Economics and Outcomes Research Analyses

Health economics and outcomes research endpoints consist of the following:

- Cumulative number of hospitalization days during the study

Health economics and outcomes research endpoints will be summarized using descriptive statistics (number, mean and standard deviation) at nominal time points.

9.10 Pharmacokinetics Analyses

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points.

Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (e.g., CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly. The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator will be appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.2.1 Documentation and Retention of Records

10.2.2.2 Electronic Case Report Forms

Electronic case report forms are supplied by the sponsor or designee and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data will be recorded directly onto the eCRF.

All data sent to the sponsor must be endorsed by the investigator.

The study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.2.3 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diaries, and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the parent/guardian agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (e.g., subject's medical file, appointment books, original laboratory reports, X-rays etc). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.2.4 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.2.5 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent, where applicable, from the parent(s)/guardian(s) of all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject's legally authorized representative is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject's parent or guardian has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject's legally authorized representative, as applicable. This document may require translation into the local

language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (i.e., sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor/designee has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor/designee.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market teduglutide; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (e.g., to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (e.g., Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2 to 4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on

medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

11. REFERENCES

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	03 Oct 2017	Global
Amendment 1	18 Jan 2018	Global

Appendix 2 Guidelines for Nutritional Support Management During the Study

The nutritional support adjustment guidelines are designed to standardize management of parenteral and enteral nutritional support in this study. Adjustments to nutritional support should be considered at every scheduled clinic visit. Adjustments at phone visits may also be performed, but nutritional assessments at phone visits serve primarily to confirm that nutritional adjustments at prior clinic visits were tolerated.

All attempts should be made to follow the guidelines, but departure from the guidelines will not constitute a protocol deviation.

Clinical judgment is required within the algorithm. Each decision point requires integrating multiple sources of information into a yes/no decision. When individual data points are conflicting, the investigator must use their best judgment in the assessment.

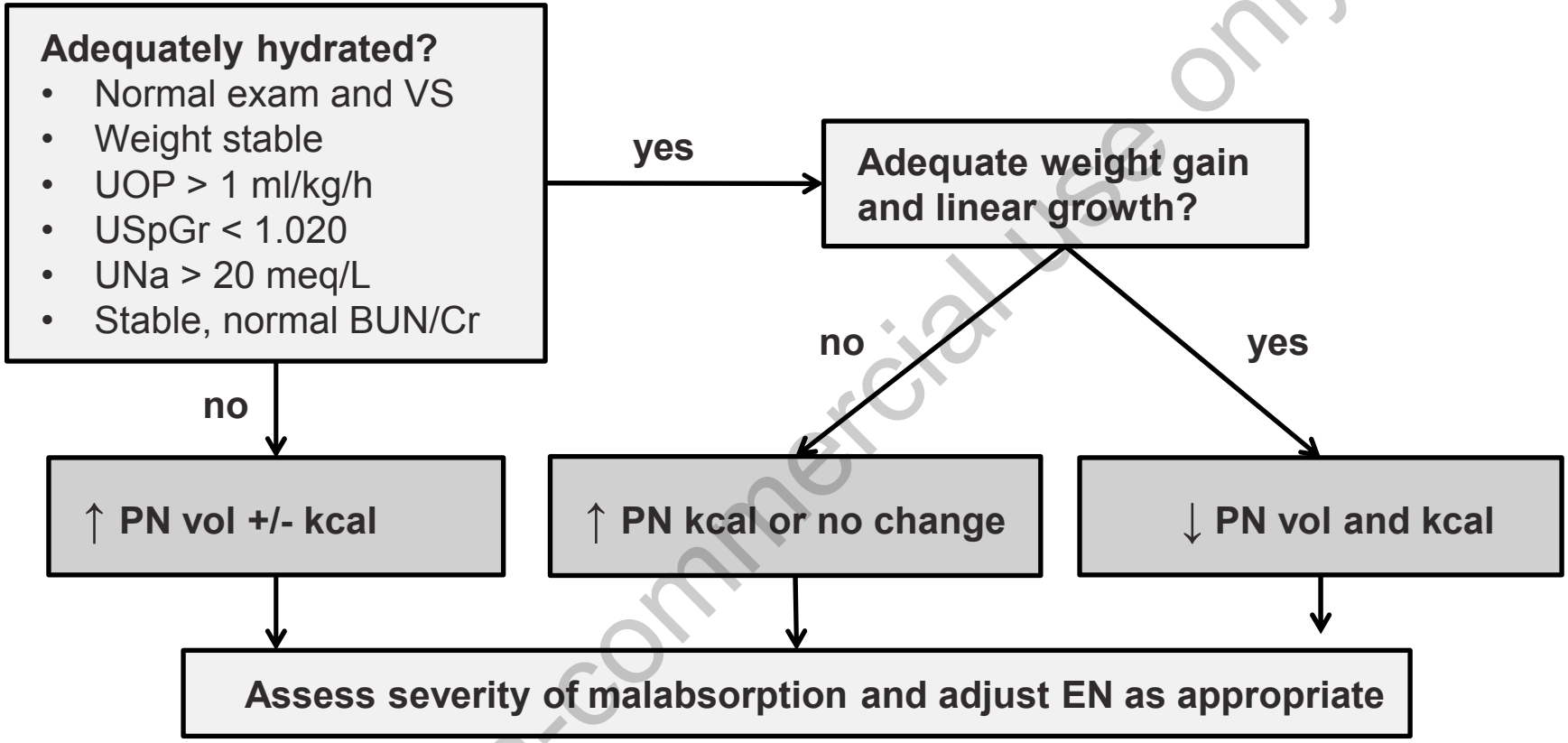
If intestinal adaptation is occurring, reductions in parenteral support volume and calories are expected to be in decrements of 5 to 10% relative to baseline values. Parenteral support components are at the discretion of the investigator, but care should be taken to balance carbohydrate, fat, and protein. Likewise, if intestinal adaptation is occurring, enteral nutrition volume and calories should be increased in increments of approximately 10% relative to baseline values.

Assessment of the severity of malabsorption may require estimation of stool output for children who have mixed stool and urine output.

Adjustments should be based on the actual nutritional support in volume and calories the subject infuses. Subjects should remain compliant with the nutritional support prescription in volume and calories during the study.

During the 48-hour output measurement period prior to the subject's scheduled visit, no further changes to the prescribed nutritional support should be made.

Figure A-1: Parenteral Nutrition/Intravenous Adjustment Algorithm for All Subjects



BUN=blood urea nitrogen; Cr=creatinine; PN=parenteral nutrition; UNa=urine sodium; UOP=urine output; USpGr=Urine specific gravity; VS=vital signs; vol=volume

PROTOCOL: SHP633-301

TITLE:	A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support
NUMBER	SHP633-301
PHASE	3
DRUG:	Teduglutide
INDICATION:	Short bowel syndrome
EUDRACT NO.:	2017-003606-40
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA
PROTOCOL HISTORY:	Original Protocol: 03 Oct 2017 Amendment 1: 18 Jan 2018 Amendment 1.1: 07 Aug 2018 (France-specific)

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	Date: [redacted]
[redacted], MD PhD [redacted], Global Clinical Development	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-301.

Title: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: _____
(please hand print or type) _____
_____

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the Shire Medical Monitor by fax or e-mail:
Fax: [redacted], Email: [redacted]

For protocol- or safety-related issues, the investigator must contact IQVIA Medical Support:

Primary Contact

[redacted], MD

[redacted]

Mobile: [redacted]

US Toll Free Number: [redacted]

Phone: [redacted]
(medical emergencies)

Email: [redacted]

Backup Contact

[redacted], MD

[redacted]

Mobile: [redacted]

Phone: [redacted]

Phone: [redacted]
(medical emergencies)

Email: [redacted]

In addition, the investigator may also contact Shire:

[redacted], MD, PhD

[redacted]

Phone: [redacted]

Mobile: [redacted]

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (e.g., inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (e.g., wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	E-mail Address
North and South America	[redacted]
European Union and Rest of World	[redacted]

Telephone numbers (provided for reference, if needed):

Shire (USA)
[redacted]

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1.1**	**Amendment Date** **07 Aug 2018**	**France-specific**
Description of Change and Rationale		**Section(s) Affected by Change**
The Shire contact was updated to [redacted].		Emergency Contact Information
Added an exclusion criterion for Gilbert's disease and liver failure based on the values of the transaminases and of total bilirubin as requested by Agence Nationale de Sécurité du Medicament et des Produits de Santé (ANSM).		Synopsis, Section 4.2
Added an exclusion criterion for hypersensitivity to trace residues of tetracycline to be consistent with the European Summary of Product Characteristics of teduglutide as requested by ANSM.		Synopsis, Section 4.2
Added text to specify that efforts to minimize pain and discomfort during procedures such as peripheral venipuncture will be implemented.		Section 7.2.3

See Appendix 1 for protocol history, including all amendments.

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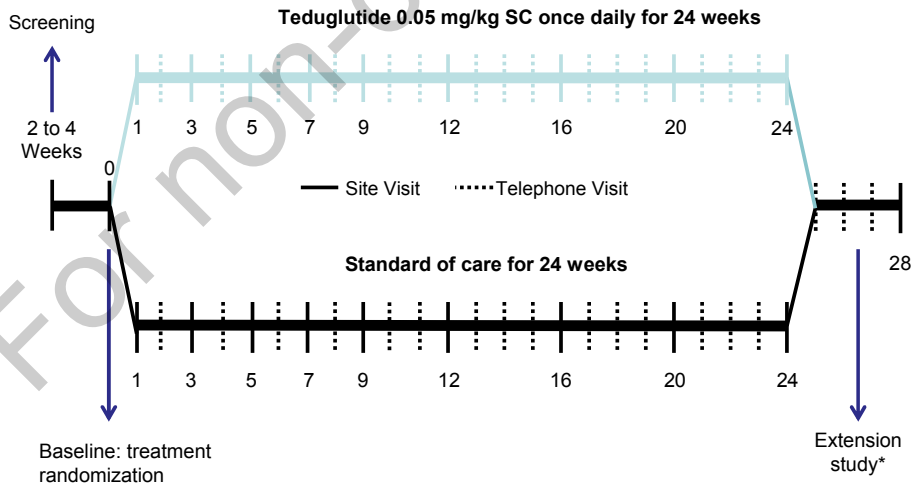
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
AUC_{ss}	area under the concentration-time curve at steady-state
$C_{max,ss}$	maximum plasma concentration at steady state
CRO	contract research organization
eCRF	electronic case report form
DMC	data monitoring committee
EDC	electronic data capture
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	glucagon-like peptide
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medicinal Journal Editors
I/O	oral fluid intake and urine output
IP	Investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PN	parenteral nutrition
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
SD	standard deviation
SOC	standard of care
ULN	upper limit of normal
US	United States

STUDY SYNOPSIS

Protocol number: SHP633-301	**Drug:** Teduglutide
Title of the study: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support	
Number of subjects (total and for each treatment arm): At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in a standard of care (SOC) comparator arm	
Investigator(s): Multicenter study	
Site(s) and Region(s): This study is planned to be conducted in approximately 5 to 10 sites globally.	
Study period (planned): 2017-2020	**Clinical phase:** 3
Objectives: The objectives of this clinical study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with short bowel syndrome (SBS) dependent on parenteral support.	
Investigational product, dose, and mode of administration: Teduglutide 0.05 mg/kg by subcutaneous (SC) injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm.	
Methodology: This is a randomized, multicenter, open-label study, consisting of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period.	



* At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least

one "escape" criteria is met.

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum 4 weeks). At the baseline visit (Week 0), subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for parenteral nutrition (PN) reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 or 12 (2 hours±10 minutes postdose).

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

Inclusion and Exclusion Criteria:

Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. Lack of terminal ileum and ileocecal valve
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.
8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.
9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µl due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2-week period
13. More than 3 serious complications of intestinal failure (e.g., catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.
19. Hypersensitivity to trace residues of tetracycline.

20. Signs of active severe or unstable, clinically significant hepatic impairment shown by any of the below laboratory test results at screening:

    a. Total bilirubin ≥2 x upper limit of normal (ULN)

    b. Aspartate aminotransferase (AST) ≥5 x ULN

    c. Alanine aminotransferase (ALT) ≥5 x ULN

    For subjects with Gilbert's disease:

    d. Indirect (unconjugated) bilirubin ≥2 x ULN

Maximum Duration of Subject Involvement in the Study:

The study consists of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

Endpoints:

Efficacy

Efficacy endpoints consist of the following:

Primary

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

Secondary

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by Week 24
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to Week 24/EOT

Pharmacokinetics

The pharmacokinetic endpoint is plasma teduglutide concentration at nominal time point.

Safety

Safety endpoints consist of the following:

- Adverse events (AEs)
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

Health Economics and Outcomes Research

Health economics and outcomes research (HEOR) endpoints include the following:

- Cumulative number of hospitalization days during the study

Statistical Methods:

Efficacy

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

Pharmacokinetics

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.

Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (e.g., number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, serious adverse events will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores; and descriptive statistics (e.g., n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

Health Economics and Outcomes Research

The HEOR endpoints will be summarized descriptively.

STUDY SCHEDULES

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X													
Eligibility	X	X												
Randomization		X												
Demographics	X													
SBS history	X													
Medical and surgical history	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight	X	X	X		X		X		X		X			X
Length and head circumference	X	X					X							X
UGI/SBFT	X													
Safety labs and urinalysis[b, c]	X	X[b]	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	(X)	X
PK sampling[a]		X							[X][d]					[X][d]
Antibodies to teduglutide[a,e]		X												X[e]
Native GLP-2[f]	X													
Provide intake and output diaries[g]	X	X	X		X		X		X		X			X
Review diaries and nutritional support		X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support as needed[h]		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IP[a, i]		X	X		X		X		X		X			X

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Adjust IP dose[j]														X

EN=enteral nutrition; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PK=pharmacokinetics; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] Applicable to the teduglutide treatment arm only.

[b] At baseline, safety labs (Table 4) and PK can be separated by 1 day if blood volumes are limiting. Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline, and repeated if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity. Urine collection should be attempted, but inability to obtain urinalysis is not a protocol deviation.

[d] Subjects will have blood samples taken for teduglutide PK analysis predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the treatment period.

[e] Samples for antibody analysis will be drawn at the baseline and Week 12 visits. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.

[f] Blood samples for native GLP-2 should be collected postprandial. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

[i] The initial dose will be calculated based on body weight measured at baseline (Visit 0).

[j] The dose will be adjusted as needed, based on body weight measured at Week 12 visit.

Note: (X) denotes optional assessments; [X] denotes possible PK sampling time point (Refer to footnote “e”.)

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Visit type	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**
Study day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**175**	**182**	**189**	**196**
±window (days)	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight				X				X				X				X
Length and head circumference				X				X				X				X
Safety labs and urinalysis[b,c]	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X
Antibodies to teduglutide[d,e]																X
Native GLP-2[f]												X				
Provide intake and output diaries				X				X				X				
Review diaries and nutritional support[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support as needed[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess follow-up period escape criteria[d]													X[i]	X[i]	X[i]	X
Dispense IP[d]				X				X								

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Visit type	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site
Study day	91	98	105	112	119	126	133	140	147	154	161	168	175	182	189	196
±window (days)	±3	±3	±3	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4

EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] At EOS subjects may enroll in an extension study, if subjects require treatment before the end of the 4-week follow-up they may enter the extension study immediately.

[b] Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR are tested if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity.

[d] Applicable to the teduglutide treatment arm only.

[e] Samples for antibody analysis will be drawn at the EOS (Week 28) visit.

[f] Blood samples for native GLP-2 should be collected postprandial. Blood samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.
Note: (X) denotes optional assessments.

[i] If a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.

1. BACKGROUND INFORMATION

1.1 Short Bowel Syndrome

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal diseases that result in major surgical resections of the small intestine (O'Keefe et al., 2006). Unlike the adult population, the majority of cases of SBS in pediatric subjects are due to congenital anomalies or catastrophic events that occur during infancy such as necrotizing enterocolitis, gastroschisis, intestinal atresia, midgut volvulus, or long-segment Hirschsprung disease (Beattie et al., 2010; Goulet and Ruemmele, 2006). A Canadian population-based study in neonates estimates an overall incidence of SBS to be 24.5 cases per 100,000 live births (Wales et al., 2004).

The small intestine is capable of remarkable adaptation, but excessive loss of absorptive surface area or specialized functions can lead to dependence on parenteral nutrition (PN)[1] fluids (O'Keefe et al., 2006). Although PN is life-sustaining in intestinal failure, it is associated with serious complications, including liver disease, life-threatening catheter-related blood stream infections, and central venous thrombosis (Beattie et al., 2010; Goulet and Ruemmele, 2006). Dependence on PN is also associated with reduced quality of life in both patients and caregivers and has an extremely high cost of care (Huisman-de Waal et al., 2007). About 30% of infants with SBS become independent of PN requirements within 12 months of the initial insult, and an additional 10% wean off PN within 24 months. After this time, linear intestinal growth slows. It is estimated that 42% to 86% of pediatric patients with SBS are able to become independent of PN within 1 to 3 years (Gonzalez-Hernandez et al., 2017; Khan et al., 2015; Squires et al., 2012). Nevertheless, despite optimal medical management, some children remain dependent on PN for many years (Squires et al., 2012). Infants who have less than 10% of expected small intestinal length for their gestational age have a low likelihood of ever achieving enteral autonomy (i.e., independence from parenteral support). Providing the maximum tolerated amount of enteral nutrition (EN) has been the primary strategy to promote enteral adaptation (Spencer et al., 2005).

Accelerating the adaptive process and achieving enteral autonomy is an urgent goal for all patients with SBS who are dependent on PN (Khan et al., 2015; Squires et al., 2012). The adaptive process is in part controlled by glucagon-like peptide 2 (GLP-2), a 33 amino acid peptide hormone secreted from L-type enteroendocrine cells in the terminal ileum and colon in response to luminal nutrients and bile acids (Martin et al., 2006). The post-prandial plasma concentration of GLP-2 in infants with SBS correlates with length of the remaining small intestine (Sigalet et al., 2004). Infants who lack terminal ileum may have impaired adaptation due to inadequate production of GLP-2.

[1] For the purpose of the study the terms parenteral support (PS) and parenteral nutrition (PN) are used interchangeably.

1.2 Teduglutide

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$), approximately 2 hours in healthy adult subjects, 1.3 hours in adult SBS subjects, and 0.22 hours in pediatric SBS subjects, compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines (Tappenden et al., 2013; Thymann et al., 2014).

A Phase 3 study, TED-C13-003, has been completed in pediatric SBS subjects. In this study, teduglutide was administered to 3 cohorts of pediatric subjects from ages 1-17 years. Thirty-seven pediatric subjects received teduglutide at doses of 0.0125, 0.025, or 0.05 mg/kg/day for 12 weeks. Five additional pediatric subjects were enrolled in an observational standard of care (SOC) cohort. There were clear dose-dependent effects of teduglutide seen at the 0.025 and 0.05 mg/kg/day doses compared to SOC and the 0.0125 mg/kg/day dose. In the 0.025 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 37%, including complete independence from PN support in 1 subject, and a reduction of 3.94 hours per day infusion time. In the 0.05 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 39%, including complete independence from PN support in 3 subjects, and a reduction of 4.18 hours per day infusion time. Teduglutide was generally safe and well tolerated by pediatric subjects in all dosing cohorts. There were no deaths during the study and no treatment-emergent serious adverse events (SAEs) related to teduglutide were reported. No discontinuations from study were due to adverse events (AEs). Additional studies in pediatric patients with SBS are ongoing.

Teduglutide (0.05 mg/kg/day) is currently approved for the treatment of adult patients with SBS in >30 countries. On 29 Jun 2016, the European Commission granted an extension of the Market Authorization for teduglutide for the treatment of patients aged 1 year and above with SBS.

Always refer to the latest version of the investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy and safety of teduglutide (SHP633).

2. OBJECTIVES

2.1 Rationale for the Study

There is no approved pharmacological therapy to improve intestinal adaptation in infants with SBS who are dependent on parenteral support. This study will evaluate whether teduglutide is safe and effective in this patient population.

2.2 Study Objectives

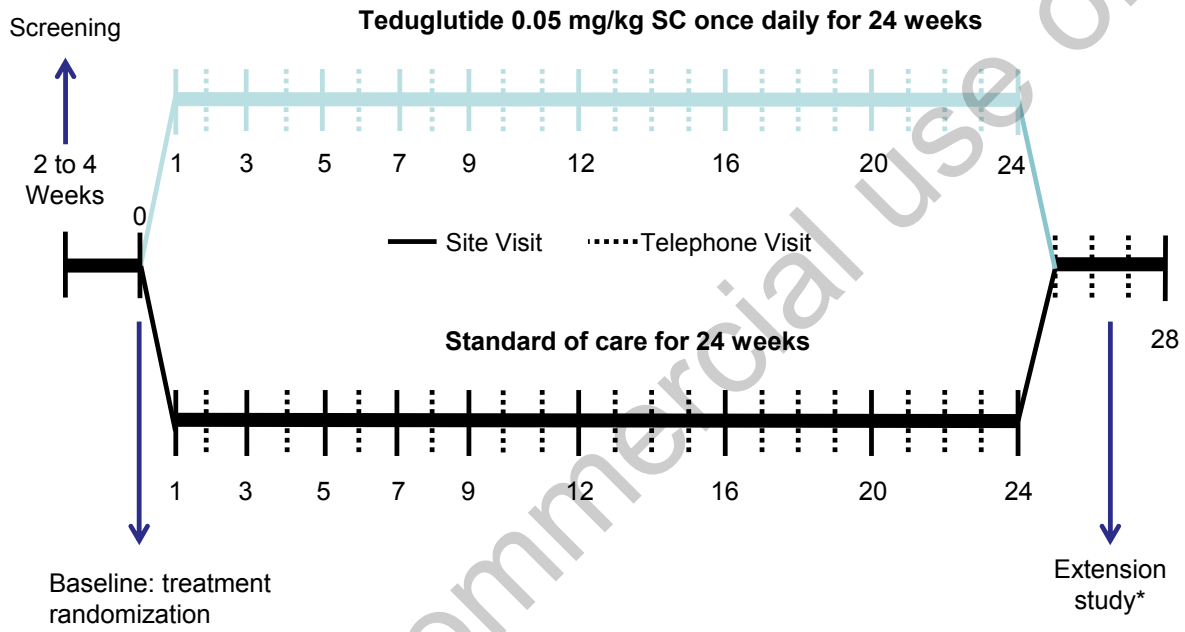
The objectives of this study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with SBS dependent on parenteral support.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a randomized, multicenter, open-label study, consisting of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. A schematic representation of the study design is presented in Figure 1.

Figure 1: Study Schematic



*At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one "escape" criteria is met.

3.1.1 Screening Period

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum: 4 weeks). The schedule of evaluations to be conducted during the Screening Period can be found in Table 1.

3.1.2 Treatment Period

At the baseline visit (Week 0), subjects will randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS, while those in the teduglutide arm will receive 0.05 mg/kg by subcutaneous (SC) injection once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for PN reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability (Appendix 2). Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 or 12 (2 hours±10 minutes postdose).

The schedule of evaluations for the Treatment Period can be found in Table 1 (Visits -1 to 12) and Table 2 (Visits 13 to 28).

3.1.3 Follow-up Period

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product (IP) will be administered. At EOS, all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS visit if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

The schedule of evaluations for the Follow-up Period can be found in Table 2 (Visits 13 to 28).

3.2 Study Duration

The study consists of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

3.3 Sites and Regions

This study is planned to be conducted at approximately 5 to 10 sites globally.

4. STUDY POPULATION

At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in an SOC comparator arm.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. Lack of terminal ileum and ileocecal valve.
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.
8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.

9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µL due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2 week period.
13. More than 3 serious complications of intestinal failure (e.g., catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.
19. Hypersensitivity to trace residues of tetracycline.
20. Signs of active severe or unstable, clinically significant hepatic impairment shown by any of the below laboratory test results at screening:
    a. Total bilirubin ≥2 x upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥5 x ULN
    c. Alanine aminotransferase (ALT) ≥5 x ULN

For subjects with Gilbert's disease:

    d. Indirect (unconjugated) bilirubin ≥2 x ULN

4.3 Reproductive Potential

Not applicable; this study will enroll infants.

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (e.g., in the interest of subject safety). The investigator should discuss withdrawal of a subject from investigational product with the medical monitor as soon as possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT/early termination are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period. Comments (spontaneous or elicited) or complaints pertaining to IP discontinuation made by the subject must be recorded in the source documents. The reason for discontinuation, the date and the total amount of investigational product administered must be recorded in the electronic case report form (eCRF) and source documents.

Subjects who discontinue will not be replaced.

4.4.1 Reasons for Discontinuation

The reason(s) for permanent discontinuation of treatment and/or withdrawal from the study must be determined by the investigator, and recorded in the subject's medical record and in the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document, and the most clinically relevant reason should be entered in the eCRF.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by parent/guardian
- Lack of efficacy
- Other

4.4.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact the parent(s)/guardian(s) of any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Medications and Procedures

Prior treatment includes all treatment and procedures (including but not limited to prescription treatments, herbal treatments, vitamins, non-pharmacological treatment, as appropriate) received within 14 days prior to the screening visit (Visit -1) (or pharmacokinetic equivalent of 5 half lives, whichever is longer, must be recorded on the appropriate eCRF page.

5.2 Concomitant Medications and Procedures

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins) and PN must be recorded from the first dose of investigational product and for the duration of the study in the appropriate sections of the eCRF. Any diagnostic, surgical or other therapeutic treatments received by a subject during the course of the study will also be recorded on the eCRF.

The mechanism of action of teduglutide may increase enteral absorption of oral drugs (e.g., drugs used for management of SBS such as motility medication, opioids, psychotropics, metronidazole), so consideration should be given to modifying concomitant enteral medication regimens. Titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic index (e.g., warfarin, digoxin, psychotropics) are given.

5.3 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.4 Prohibited Treatment

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the pretreatment visit (Table 3):

Table 3: Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pretreatment Visit
Teduglutide	Any
GLP-2, human growth hormone, or analogs of these hormones	6 months
Octreotide, GLP-1 analogs, and enteral glutamine	30 days

GLP=glucagon-like peptide

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

Teduglutide will be provided in sterile, single-use 3 mL vials containing 1.25 mg teduglutide as a white lyophilized powder to be reconstituted before use with 0.5 mL sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the current investigator's brochure.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

All investigative study sites will be initially provided with sufficient investigational product to randomly assign a subject into the study (for either of the proposed treatment groups). Randomization will occur through an interactive response system. Random assignment of a subject will trigger replacement supplies for that investigative study site.

6.2.2 Allocation of Subjects to Treatment

Subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy). The actual treatment given to individual subjects is determined by a randomization schedule.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined.

6.2.3 Dosing

The initial dose will be calculated based on body weight measured at baseline (Visit 0), and adjusted as needed, based on body weight measured at Week 12. No other adjustments to dose will be made during the teduglutide treatment period, unless discussed with the sponsor's medical monitor.

Following reconstitution, teduglutide will be administered by SC injection once daily (QD) into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used.

Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later.

The subject should be dosed at approximately the same time each day. Consecutive doses should be separated by at least 12 hours. Each day, the injection site should be alternated.

Any subject who achieves complete independence from PN support at any time during the treatment period will continue to receive teduglutide treatment.

The first SC injection in teduglutide-naïve subjects should be administered under the supervision of the investigator or designee and the subject observed for hypersensitivity reactions for at least 4 hours during their initial dosing visit. The site of administration (arm, thigh, and abdomen) of the first teduglutide dose must be specified and recorded in the eCRF.

Detailed instructions for reconstitution and injection of the investigational product can be found in the Instructions for Use.

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.2.5 Dose Selection Rationale

Teduglutide is approved for adult and pediatric use in the EU at a dose of 0.05 mg/kg SC once daily. A completed 12-week dose finding study (TED-C13-003) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit-risk profile most meaningful at the 0.05 mg/kg/day dose (Carter et al., 2017).

Population pharmacokinetic modeling and simulations were conducted to determine the optimal dose to be used in pediatric subjects using data from 8 adult clinical studies including adult Phase

1 studies and Phases 2/3 studies as well as TED-C13-003 and suggested the same adult dose (0.05mg/kg) in pediatric subjects (aged between 1.67-14.7 years) (Marier et al., 2017).

To support dosing in the current age group, further PK simulation was conducted based on the population PK model previously established and a virtual population of 1000 pediatric patients created based on Centers for Disease Control (CDC) growth charts in the target age group (4 to 12 months) and taking into consideration body weights of pediatric patients with SBS enrolled in study TED-C13-003 (approximately 15% lower than healthy subjects in the same age group). Monte Carlo simulations for all age groups were performed according to the SC dosing regimens of 0.0125, 0.025 and 0.05 mg/kg every 24 hours. Rich concentration-time profiles were simulated with the customized population PK model to derive the exposure metrics area under the concentration curve at steady state (AUC_{ss}) and maximum concentration at steady state ($C_{max,ss}$). Following 0.05 mg/kg daily SC administration, the median $C_{max,ss}$ of teduglutide in neonate patients (24.9 ng/mL) was within 20% of that observed in the 2 to 4 and 4 to 6 years age groups (26.9 and 29.4 ng/mL, respectively); and approximately ~28% lower than that in adult patients with SBS. The clinical package in conjunction with C_{max} was considered to support teduglutide dose selection since AUC_{ss} was previously shown not to correlate with efficacy. Thus, the 0.05 mg/kg dose is proposed for testing in this age group.

6.3 Labeling, Packaging, and Storage

6.3.1 Labeling

The investigational product will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of investigational product will be provided for this study. The vials will be labeled in accordance with applicable regulatory requirements.

Ancillary kits, containing supplies needed for the reconstitution and administration of the investigational product will also be provided and labeled in accordance with the applicable regulatory requirements.

All investigational product used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice.

6.3.2 Storage and Handling

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2-8°C (35.6-46.4°F) until dispensed to a subject. Once dispensed to a subject, the IP can be stored refrigerated or up to a controlled room temperature (acceptable range of 2-25°C, or 35.6-77°F). Parent/legal guardian will be instructed to keep the subject's IP and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot

be maintained, the IP may be refrigerated. The IP is for single use only, and should be used within 3 hours following reconstitution.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (i.e., certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), e.g., fumigation of a storage room.

Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels, as they are distributed.

6.4 Drug Accountability

Investigational product will not be dispatched to the study site until the sponsor or designee has received all required documents from the study site in accordance with applicable regulatory requirements and relevant standard operating procedures. Upon receipt, the study site's pharmacist or delegate is responsible for ensuring that all investigational product received at the site is inventoried and accounted for throughout the study. A copy of the shipping documents must be maintained for the investigator's records. Kits will be shipped to the site once the subject is screened.

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Investigational product kits will be dispensed at each of the applicable study visits at which the subject is required to be at the clinic. Each investigational product kit is sufficient for a treatment period of 1 week and enough kits will be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

Each subject will be given the investigational product according to the protocol. The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. All dispensed medication will be documented on the eCRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, subject returned investigational product, and empty/used investigational product packaging are to be sent to the sponsor or designee. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

Returned investigational product must be counted and verified by clinical site personnel and the sponsor (or study monitor). Shipment return forms, when used, must be signed prior to shipment from the site. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

The parent(s)/guardian(s) of subjects must be instructed to bring unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed and recorded at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (e.g., bottles, trays, vials) or at the individual count level for opened containers/packaging.

Subject compliance will be checked by site personnel at every visit by reviewing the subject diaries and asking the subject or the subject's parent or legally-authorized representative if they have administered the investigational product according to instructions. If any doses have been missed, the reason for missed dose should be documented in the subject's source documentation including, as applicable, the eCRF.

The investigator is responsible for contacting the sponsor or designee when the subject's daily investigational product dosing regimen is interrupted. Attempts should be made to contact the sponsor or designee prior to dose interruption. Reasons for dosage interruption may include but are not limited to hospitalization and AEs, a lapse in investigational product delivery, etc.

Subjects who have received 80% of the planned doses administered will be assessed as being compliant with the study protocol.

7. STUDY PROCEDURES

7.1 Study Schedule

Detailed study procedures and assessments to be performed for subjects throughout the study are outlined in the study schedules (Table 1 and Table 2) and must be referred to in conjunction with the instructions provided in this section.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period.

7.1.1 Screening

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the parent(s)/guardian(s) of the subject. The screening visit assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1.

7.1.2 Treatment Period

The randomized Treatment Period will comprise Weeks 1 to 24, during which all assessments will be performed as outlined in Table 1 and Table 2.

7.1.3 Follow-up Period

The Follow-up Period will comprise Weeks 25 to 28, during which all assessments will be performed as outlined in Table 2.

7.2 Study Evaluations and Procedures

7.2.1 Demographics and Other Baseline Characteristics

Demographics and Medical History

Demographic and/or other baseline variables obtained at the screening and/or baseline visits are listed below. Abnormal findings of clinical significance (if any) will be recorded as past medical history.

- Demography (including age, gestational age, sex, and race)
- Medical history (including surgical history)
- SBS history, including remnant anatomy

Upper Gastrointestinal Series with Small Bowel Follow-through

An upper GI contrast series with small bowel follow-through will be performed on all subjects during the screening period if one has not been done since the subject's last GI surgery.

It is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow-through performed since the subject's most recent surgery.

7.2.2 Efficacy Assessments

Subject Diaries

All available diary data will be reviewed by the investigator or their designee at each clinic and telephone visit to assess clinical status and opportunity for PN reduction and advance in feeds. Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

Intake Diary

Intake diaries will be used to collect and evaluate each subject's nutritional support. The parent/legally authorized representative/study site staff will complete the appropriate fields of the PN and EN sections of the intake diary daily throughout the study.

The following data will be captured in the intake diaries:

- Parenteral support volume and infusion duration
- Enteral nutrition (formula) including volume and calories

Site personnel will determine the actual PN and EN daily calories based on diary entries.

Output Diary

Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit; in addition, output should be recorded for subjects within 1 week of implementing a change in the PN prescription.

Urine data:

- Measure and record the weight of all urine-only diapers. Urine volume will be calculated using the following formula: 1 g (scale weight) = 1 mL or 1 cc
- At the discretion of the investigator, the parent or legal guardian/study site staff may be asked to collect the first void after the daily PN infusion to measure specific gravity

Stool data (includes diapers with mixed urine and stool):

- Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency (see Output diary). Stool volume will be calculated using the formula: 1 g (scale weight)=1 mL or 1 cc

All ostomy output volume should be recorded.

Native GLP-2

Blood samples for native GLP-2 should be collected postprandial. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

7.2.3 Safety Assessments

Laboratory Evaluations

Safety laboratory tests to be performed at site visits consist of clinical chemistry, hematology, and urinalysis and will be performed as outlined in the study plan (Table 1 and Table 2). Scheduled laboratory testing will be processed by a central lab. All laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the laboratory. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

During the Treatment Period, subjects will also have safety labs within approximately 5 to7 days after a PN adjustment. Safety labs performed after PN adjustment and between site visits will consist of clinical chemistry and urinalysis and may be processed by the central laboratory or a local laboratory. Local lab results are not required to be entered in the eCRFs; however, if the local lab results indicate any new clinically significant changes, they must be reported as an adverse event (see Section 8). Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

At baseline, blood samples for safety labs and PK can be separated by 1 day if blood volumes are limiting.

Safety labs at telephone visits will be collected at the discretion of the investigator.

For all subjects in the teduglutide treatment arm, prothrombin time (PT) and international normalized ratio (INR), tested at baseline, will be repeated if clinically indicated.

New clinically significant labs should be reported as AEs.

Close monitoring criteria related to liver test abnormalities:

The investigator should contact the medical monitor within 24 hours of their awareness if the subject develops any of the following changes in laboratory parameters:

- ALT or AST >5x ULN and >2x baseline value

- Total or direct bilirubin that is >2x baseline value or an absolute increase of ≥3 mg/dL (51.3 µmol/L)

If such changes are observed, the labs should be repeated along with an INR, and an inquiry should be made as to the presence of clinical symptoms consistent with new liver injury. The subject should be followed closely to determine the trajectory of the laboratory abnormalities and appropriate evaluations should be made, such as abdominal ultrasound with Doppler imaging to exclude vascular causes and biliary obstruction, consideration of sepsis, liver hypoperfusion, acute viral hepatitis (such as hepatitis A, EBV, or HSV), exposure to hepatotoxic medications, mitochondrial hepatopathy, or metabolic liver disease (such as hereditary fructose intolerance or arginosuccinate synthetase deficiency). Further evaluations can be performed at the discretion of the investigator in consultation with the Shire medical monitor.

The following clinical laboratory assessments will be performed according to the study schedules:

Table 4: List of Laboratory Tests

Biochemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bicarbonate
- Bilirubin (total and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- C-reactive protein
- Creatinine
- Estimated Glomerular Filtration Rate (Schwartz formula)
- Gamma-glutamyl transferase
- Glucose
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Triglycerides

Hematology[a]:
- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- Red blood cell morphology, if needed
- White blood cell count with differential

Coagulation[b]:
- Prothrombin time
- International normalized ratio

Urinalysis:
- Specific gravity
- Urine Sodium

[a] Hematology is not collected at Week 1 or at telephone visits.
[b] For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline and repeated only if clinically indicated.

Antibodies to Teduglutide

Blood samples will be drawn to test for antibodies to teduglutide. Samples will be taken before teduglutide administration at the screening visit (Visit -1) and at least 14 hours after the previous dose at Week 12 (Visit 12); samples may be drawn from a central line or peripheral access. One additional sample will be collected at the EOS 4 weeks after the EOT (i.e., Week 28 or EOS).

Volume of Blood

Efforts will be made to minimize the amount of blood drawn from all pediatric subjects participating in this study. The volumes of blood to be drawn from each subject will vary depending on clinical status. Approximate volumes of blood to be drawn from each subject are shown in Table 5.

Table 5: Approximate Volume of Blood to be Drawn from Each Subject

Assessment	Sample Volume (mL)	No. Samples	Total Volume (mL)	Notes
Subjects Receiving Teduglutide Treatment				
Biochemistry	0.6	12	7.2	
Hematology	0.6	11	6.6	
Coagulation Parameters	0.6	1	0.6	PT and INR tested at baseline only, repeat while on study only if clinically indicated.
Antibodies	1.5	5	7.5	
Pharmacokinetics	1.5	4	6.0	Baseline: 3 timepoints Week 7: 1 timepoint OR Week 12: 1 timepoint
Native GLP-2	1.5	3	4.5	
Total mL:	**6.3**	**36**	**32.4**	
Subjects Receiving Standard of Care				
Biochemistry	0.6	12	7.2	
Hematology	0.6	11	6.6	
Native GLP-2	1.5	3	4.5	
Total mL:	**2.7**	**26**	**18.3**	

GLP=glucagon-like peptide; INR=international normalized ratio; PT=prothrombin time

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments should be combined. Blood volume estimates do not include safety labs performed after PN adjustment, and anti-teduglutide antibody testing during no-teduglutide treatment.

Consistent with standard medical practice, efforts to minimize pain and discomfort during procedures such as peripheral venipuncture should be implemented as applicable. This may

include oral sucrose solutions, a pacifier, distraction techniques, and the use of topical anesthetic such as EMLA.

Physical Examinations, Vital Signs, Weight, Length, and Head Circumference

Physical examinations will be performed according to the study schedules (Table 1 and Table 2). Any new clinically significant findings noted during physical examinations should be recorded on the appropriate AE page of the eCRF.

Vital signs will be measured according to the study schedules. Measurements will include systolic and diastolic blood pressure (mmHg), pulse (beats per minute), and body temperature (°C/°F). Blood pressure should be determined by the appropriate size cuff (using the same method, the same leg, and in the supine position throughout the study, when possible). Blood pressure measurements should be attempted as part of the vital signs, but lack of blood pressure results will not constitute a protocol deviation. New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Length and head circumference will be measured at selected visits. A height z-score, weight Z-score, and weight/length ratio will be calculated by the sponsor using the site-provided height and weight data collected at each site visit.

7.2.4 Pharmacokinetic Assessments

Subjects will have blood samples taken for teduglutide PK analysis predose, and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the treatment period. Blood for PK sampling should be collected via peripheral IV or venipuncture, not from a central line. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified.

7.2.5 Health Economics and Outcomes Research

Hospitalizations

Each hospitalization that occurs during the study will be recorded, including date of admission, date of discharge, reasons for hospitalization, discharge diagnosis, and discharge status.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

AEs that are related to IP that are not resolved at EOS will be followed until the event resolves or stabilizes, as judged by the investigator.

Laboratory values, vital signs, and clinical findings at the scheduled physical examinations must be reported as AEs if the investigator considers the finding to be a clinically significant change from the baseline.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. It is assumed that some of the infants participating in this study may be hospitalized for planned surgery(ies) that will occur during their participation in the study. Such pre-planned, elective surgeries, do not need to be reported as SAEs for this protocol.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory or vital sign can represent an AE if the change is clinically relevant or if, during the study, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, during the study, there are abnormal clinical laboratory values or vital signs which were not present at the beginning of the study, further investigations should be performed until the values return to within the reference range or until a plausible explanation (e.g., concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory or vital sign is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

Not applicable.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.

- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Administration of a dose greater than the allocated dose of the study medication or at a frequency greater than the dosing interval specified by the protocol.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally-authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

All Adverse Events of Special Interest, as defined in Section 8.3, must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event even if the event does not fulfill seriousness criterion.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol, and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested). Fax or e-mail the completed form to the Shire Global Drug Safety Department. A copy of the completed Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the Shire medical monitor or designee using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3, and must be reported to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (i.e., the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (e.g., drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The Sponsor and/or Clinical Contract Research Organization (CRO) is responsible for notifying the relevant regulatory authorities, and US central Institutional Review Boards (IRBs)/EU central ethics committees (ECs), of related, unexpected SAEs.

In addition, the Clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP633 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

8.3 Adverse Events of Special Interest

An AE of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program and for which ongoing monitoring and immediate notification by the investigator to the sponsor is required.

The AEs of special interest that require expedited regulatory reporting include the following:

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the GI tract including the hepatobiliary system
- Tumor-promoting ability (e.g., benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

For AEs of special interest, the sponsor must be informed within 24 hours of first awareness as per the SAE notification instructions described in Section 8.2.2 even if the event does not fulfill the seriousness criteria.

8.4 Dose Interruption Criteria

The investigator is responsible for contacting the sponsor/designee when the subject's teduglutide dosing regimen is interrupted. The length of dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

Investigational product must be interrupted if any of the following events occur:

- An adverse event of special interest (see Section 8.3)
- Intestinal obstruction
- Biliary obstruction
- Pancreatic duct obstruction

Investigational product must be permanently discontinued if any of the following events occur:

- Severe hypersensitivity, such as anaphylaxis, determined by the investigator to be related to IP.
- Any malignancy

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject' s visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Process

The study will be analyzed by the sponsor or designee. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, US) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the definitions and statistical methods for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

9.4 Planned Interim Analysis, and Data Monitoring Committee

No interim analyses is planned for this the study.

A data monitoring committee (DMC) will be involved in the management of this study. The DMC members will review the data approximately every 3 months according to the DMC Charter. The DMC review will include all cumulative safety data (i.e., AEs, laboratory assessments, physical examinations, etc.) from study assessments through each cutoff period. Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of investigational product.

The DMC for this study will be conducted in accordance with the FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006).

The DMC will be an external, independent board comprised of physicians with relevant training. The DMC will be restricted to individuals free of significant conflicts of interest, including, but not limited to, financial, scientific, or regulatory in nature. The DMC will be governed by a Charter agreed to by members of the Board and the sponsor. Members of the Board may not be study investigators or be employed at the same institution as a study investigator, individuals employed by the sponsor, independent contractors hired by the sponsor, or members of regulatory agencies. The DMC may make recommendations to the sponsor regarding study aspects including stopping, modifying or continuing the study; however, the sponsor will have the final responsibility to determine whether the study should be modified or temporarily or permanently stopped.

9.5 Sample Size Calculation and Power Considerations

The sample size is determined based on enrollment feasibility for this rare condition and the age of the study population.

9.6 Study Population

Intent to treat (ITT) population: All subjects randomized in the study.

Safety analysis population: The safety analysis set will contain all subjects who meet the following criteria:

- Teduglutide treatment arm: subjects who receive at least 1 dose of teduglutide and have undergone at least 1 post-baseline safety assessment; analyses will be performed according to dose group as appropriate.
- Standard of care treatment arm: subjects who have undergone at least 1 post-baseline safety assessment.

Per-protocol population: All subjects in the ITT population without any major protocol deviation that affects interpretation of efficacy results.

Pharmacokinetic analysis population: All subjects who received at least 1 dose of teduglutide and have at least 1 evaluable postdose PK concentration value.

9.7 Efficacy Analyses

9.7.1 Efficacy Endpoints

Efficacy endpoints consist of the following:

9.7.1.1 Primary Efficacy Endpoint

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

9.7.1.2 Secondary Efficacy Endpoints

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by Week 24
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT

9.7.2 Method of Analysis-Efficacy Endpoints

Due to the limited size of the study population, descriptive statistics will be used with a goal of summarizing the sample. As such, no claims of significance will be made for any of the data. Continuous variables will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

9.8 Safety Analyses

9.8.1 Safety Endpoints

Safety endpoints consist of the following:

- Adverse events
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

9.8.2 Method of Analysis-Safety Endpoints

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (e.g., number and percentage of subjects). Adverse events will

be summarized by severity and relationship to treatment. In addition, SAEs will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores, and descriptive statistics (e.g., n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

9.9 Health Economics and Outcomes Research Analyses

Health economics and outcomes research endpoints consist of the following:

- Cumulative number of hospitalization days during the study

Health economics and outcomes research endpoints will be summarized using descriptive statistics (number, mean and standard deviation) at nominal time points.

9.10 Pharmacokinetics Analyses

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points.

Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (e.g., CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly. The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator will be appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.2.1 Documentation and Retention of Records

10.2.2.2 Electronic Case Report Forms

Electronic case report forms are supplied by the sponsor or designee and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data will be recorded directly onto the eCRF.

All data sent to the sponsor must be endorsed by the investigator.

The study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.2.3 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diaries, and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the parent/guardian agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (e.g., subject's medical file, appointment books, original laboratory reports, X-rays etc). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.2.4 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.2.5 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent, where applicable, from the parent(s)/guardian(s) of all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject's legally authorized representative is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject's parent or guardian has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject's legally authorized representative, as applicable. This document may require translation into the local

language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (i.e., sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor/designee has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor/designee.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market teduglutide; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (e.g., to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (e.g., Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2 to 4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on

medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

11. REFERENCES

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	03 Oct 2017	Global
Amendment 1	18 Jan 2018	Global
Amendment 1.1	07 Aug 2018	France-specific

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **18 Jan 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Updated emergency contact information to reflect the change of the Contract Research Organization's name.		Emergency Contact Information
Clarified the duration of the screening period and total time on study. Provided a clear definition of study completion. Updated the study schematic to reflect the study design changes.		Synopsis, Section 3.1, Section 3.2
Revised the telephone and clinic visit schedule to assure laboratory measurement could be collected without exceeding weekly/monthly total blood volume restrictions.		Synopsis, Table 1, Section 3.1.2
Moved the PK sampling from Week 6 to Week 7 so that the samples could be collected without exceeding weekly/monthly total blood volume restrictions. Clarified that blood for pharmacokinetic samples of postdose may be taken within ± 10 minutes of the time pre-specified.		Synopsis, Table 1, Section 3.1.2, Section 7.2.4, Table 5
Clarified that end jejunostomy or ileostomy are examples of small bowel ostomy rather than the stratification factors.		Synopsis, Section 3.1.2, Section 6.2.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **18 Jan 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Clarified that all subjects regardless of treatment arm are eligible for the extension study.		Synopsis, Section 3.1.3
Clarified that if a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.		Synopsis, Table 2, Section 3.1.3, Section 6.2.3
Clarified that subjects must be 4 to 12 months corrected gestational age at screening.		Synopsis, Section 4.1
Changed dose adjustments to Week 12 rather than at every clinic visit to reduce site burden.		Synopsis, Table 1, Section 6.2.3
Clarified the definition of enteral autonomy.		Synopsis, Section 9.7.2
Updated the pharmacokinetic endpoint and analysis to reflect that only descriptive statistics will be calculated on plasma teduglutide concentration values. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.		Synopsis, Section 9.10
Removed assessment of the 5-level EuroQol five dimensions questionnaire to reduce caregiver burden.		Synopsis, Table 1, Section 7.2.5, Section 9.9
Clarified that native GLP-2 samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.		Table 2, Section 7.2.2
Inserted a footnote to clarify that parenteral support and parenteral nutrition are used interchangeably.		Section 1.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **18 Jan 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Removed the 5 mg vial of teduglutide as this size vial will not be supplied for this study.		Section 6.1
Clarified the procedures for assessing subject compliance.		Section 6.5
Specified that it is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow through performed since the subject's most recent surgery.		Section 7.2.1
Corrected the volume of blood to be collected for native GLP-2.		Table 5
Removed references to subject assent as assent is not possible in a study of infants.		Section 7.1.1, Section 10.3.1
Clarified the definitions of the analysis sets.		Section 9.6
Clarified that an adjustment to enteral nutrition as appropriate is part of the PN/IV adjustment algorithm.		Figure A-1
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout protocol.

Appendix 2 Guidelines for Nutritional Support Management During the Study

The nutritional support adjustment guidelines are designed to standardize management of parenteral and enteral nutritional support in this study. Adjustments to nutritional support should be considered at every scheduled clinic visit. Adjustments at phone visits may also be performed, but nutritional assessments at phone visits serve primarily to confirm that nutritional adjustments at prior clinic visits were tolerated.

All attempts should be made to follow the guidelines, but departure from the guidelines will not constitute a protocol deviation.

Clinical judgment is required within the algorithm. Each decision point requires integrating multiple sources of information into a yes/no decision. When individual data points are conflicting, the investigator must use their best judgment in the assessment.

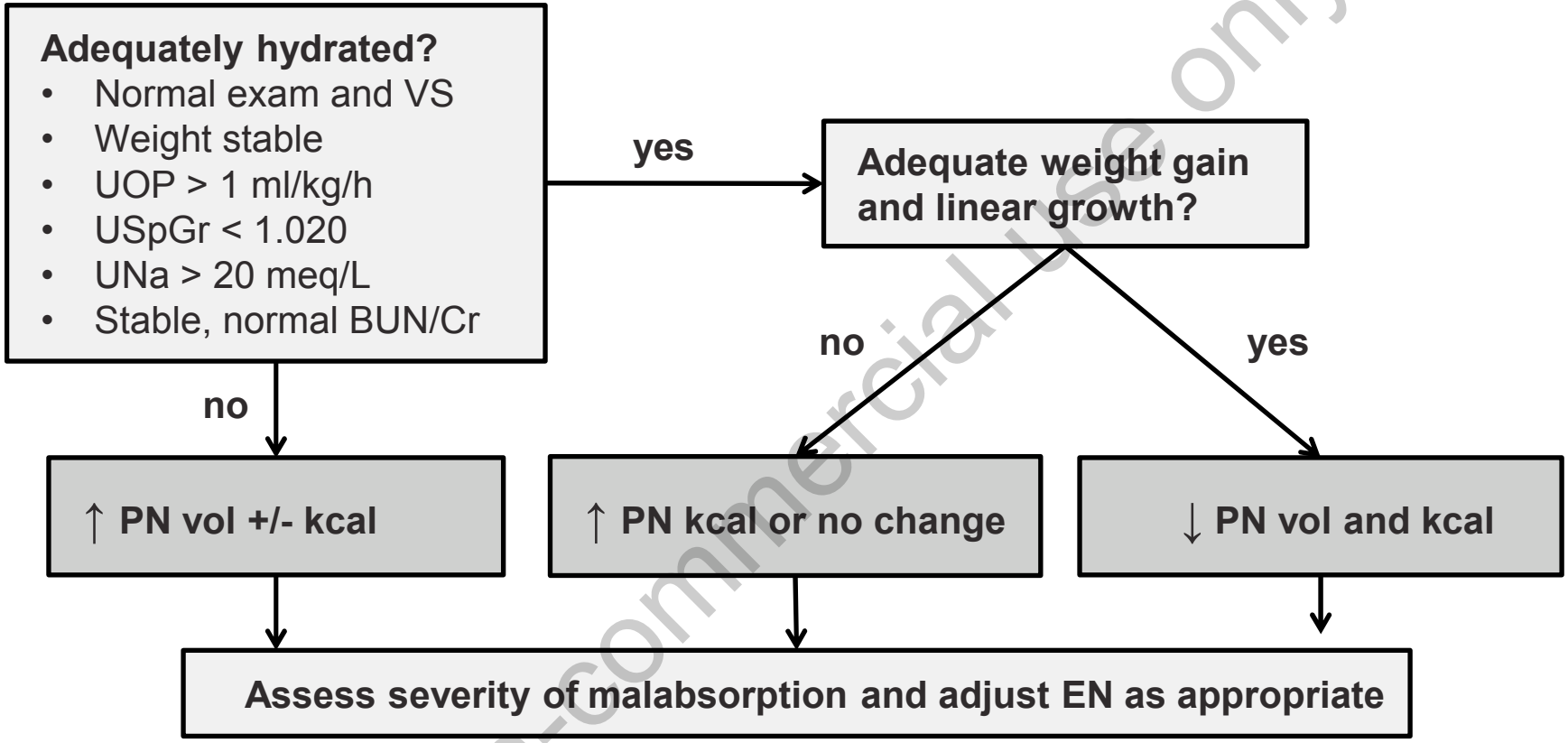
If intestinal adaptation is occurring, reductions in parenteral support volume and calories are expected to be in decrements of 5 to 10% relative to baseline values. Parenteral support components are at the discretion of the investigator, but care should be taken to balance carbohydrate, fat, and protein. Likewise, if intestinal adaptation is occurring, enteral nutrition volume and calories should be increased in increments of approximately 10% relative to baseline values.

Assessment of the severity of malabsorption may require estimation of stool output for children who have mixed stool and urine output.

Adjustments should be based on the actual nutritional support in volume and calories the subject infuses. Subjects should remain compliant with the nutritional support prescription in volume and calories during the study.

During the 48-hour output measurement period prior to the subject's scheduled visit, no further changes to the prescribed nutritional support should be made.

Figure A-1: Parenteral Nutrition/Intravenous Adjustment Algorithm for All Subjects



BUN=blood urea nitrogen; Cr=creatinine; PN=parenteral nutrition; UNa=urine sodium; UOP=urine output; USpGr=Urine specific gravity; VS=vital signs; vol=volume

Protocol Administrative Amendment
MEMORANDUM

To: SHP633-301 Trial Master File (TMF), SHP633-301 Study Sites
From: [redacted], MD
Date: 3 Oct 2018
Subject: Protocol Administrative Amendment: Change in Medical Monitor
EUDRACT NO: 2017-003606-40

Protocol Title: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support

Protocol Version: Original Protocol 03 Oct 2017

The following Administrative Amendment is for Protocol SHP633-301, Protocol Amendment 1 dated 18 Jan 2018. These changes are considered administrative in nature and the clarifications do not compromise the scope, design, or integrity of the study. These changes do not compromise subject safety in any way.

Administrative Change : A revision to the protocol that does not affect the overall study design. Examples include, but are not limited to: clarification , addition or removal of procedural details that do not affect the overall design, safety or scientific quality of the study (e.g., clarifying discrepancies between synopsis and methodology section of protocol); typographical, grammatical or minor logistical changes (e.g. change to name of medical monitor, change to contact information, change in personnel/vendors) . Administrative changes are documented (e.g., by memorandum , letter, note to file) and do not necessitate a protocol amendment.

The following revisions meet the definition of Administrative Change as noted above and will be incorporated into any subsequent amendment to the protocol.

Clarification in screening procedures:

Current Language:

Screening
Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the parent(s)/guardian(s) of the subject. The screening visit assessments and procedures, beginning with informed consent, will be performed as outlined in **Error! Reference source not found.**.

New Language:

Screening
Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the parent(s)/guardian(s) of the subject. The screening visit assessments and procedures, beginning with informed consent, will be performed as outlined in **Error! Reference source not found.**. Rescreening will not be allowed.

Impacted Section(s):

Section 7.1.1 Screening

Copies of this letter shall be distributed to the Principal Investigators of the study and should be forwarded to the site Ethics Committees as necessary.

If you have further questions, please do not hesitate to contact your CRA or Shire directly.

I have reviewed the above Memorandum and am in agreement with the specified administrative clarifications.

Thank you.

[redacted], MD

[redacted]

Date

[redacted]—Teduglutide
SHP633-301 Medical Monitor

cc: SHP633-301 TMF Main Study File

PROTOCOL: SHP633-301

TITLE:	A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support
NUMBER	SHP633-301
PHASE	3
DRUG:	Teduglutide
INDICATION:	Short bowel syndrome
EUDRACT NO.:	2017-003606-40
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA
PROTOCOL HISTORY:	Original Protocol: 03 Oct 2017 Amendment 1: 18 Jan 2018 Amendment 2 : 04 Dec 2018

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** [redacted]
[redacted], MD PhD [redacted] [redacted], Global Clinical Development	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-301.

Title: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: _____ (please hand print or type) _____ _____

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the Shire Medical Monitor by e-mail at [redacted].

For protocol- or safety-related issues, the investigator must contact IQVIA Medical Support:

Primary Contact	**Backup Contact**
[redacted], MD	[redacted], MD, PhD
[redacted]	[redacted]
Mobile: [redacted]	Mobile: [redacted]
Phone: [redacted] (medical emergencies)	Phone: [redacted] (medical emergencies)
Email: [redacted]	Email: [redacted]

In addition, the investigator may also contact Shire:

[redacted], MD

Mobile Phone: [redacted]

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (e.g., inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (e.g., wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the E-mail address below to report the Product Quality Complaint:

[redacted]

Telephone numbers (provided for reference, if needed):

Shire (USA)
[redacted]

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **04 Dec 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
The fax number currently used to send the Shire Medical Monitor a copy of the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol is now retired; a copy of the form must be sent by email only. Updated emergency contact information to reflect the change of Shire medical monitor to [redacted], IQVIA back up medical support to [redacted], and IQVIA phone number for medical emergencies.		Emergency Contact Information
A single email address ([redacted]) is now used to report a Product Quality Complaint, independently from where it has originated.		Product Quality Complaints
Added the new secondary efficacy endpoint "Time to achieve enteral autonomy" and statistical methodology to be used.		Synopsis, Section 9.7.1.2, Section 9.7.2
Updated the information on the clinical studies with teduglutide in pediatric subjects to include the results of TED-C14-006.		Section 1.2
Clarified that teduglutide is the investigational product for this study.		Section 6.1
Updated the dose selection rationale with results from a simulation work using the previous population pharmacokinetic model. Based on the totality of clinical data, 0.05 mg/kg once daily is expected to provide comparable C_{max} concentrations in infants as compared to pediatric patients with SBS and was recommended as an evaluation dosing regimen in Study SHP633-301.		Section 6.2.5
Clarified that rescreening of subjects in the study will not be allowed. (Administrative amendment dated 03 Oct 2018)		Section 7.1.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **04 Dec 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Clarifications were made to the definition of adverse events.		Section 8.1, Section 8.1.5, Section 8.2.4
Added heart failure with severe fluid overload, determined by the sponsor or investigator to be related to the investigational product, to the list of events leading to interruption of investigational product administration. This addition is in alignment with the warnings and special precautions listed in the investigator brochure.		Section 8.4
As recommended by the FDA, specified that if the DMC recommends termination of this pediatric study, the recommendations will be communicated to the relevant regulatory agencies within 7 calendar days.		Section 9.4
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout the protocol

See Appendix 1 for protocol history, including all amendments.

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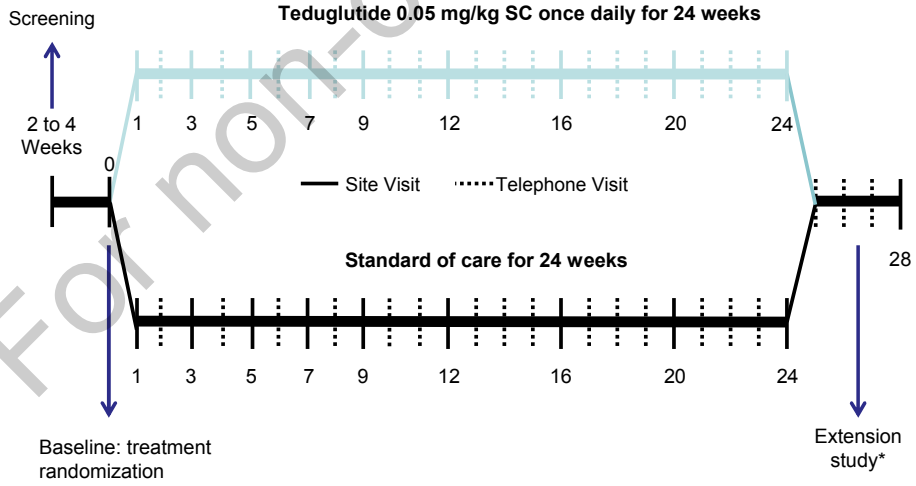
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
AUC_{ss}	area under the concentration-time curve at steady-state
$C_{max,ss}$	maximum plasma concentration at steady state
CRO	contract research organization
eCRF	electronic case report form
DMC	data monitoring committee
EDC	electronic data capture
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	glucagon-like peptide
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medicinal Journal Editors
I/O	oral fluid intake and urine output
IP	Investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PN	parenteral nutrition
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
SD	standard deviation
SOC	standard of care
ULN	upper limit of normal
US	United States

STUDY SYNOPSIS

Protocol number: SHP633-301	**Drug:** Teduglutide
Title of the study: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support	
Number of subjects (total and for each treatment arm): At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in a standard of care (SOC) comparator arm	
Investigator(s): Multicenter study	
Site(s) and Region(s): This study is planned to be conducted in approximately 5 to 10 sites globally.	
Study period (planned): 2017-2020	**Clinical phase:** 3
Objectives: The objectives of this clinical study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with short bowel syndrome (SBS) dependent on parenteral support.	
Investigational product, dose, and mode of administration: Teduglutide 0.05 mg/kg by subcutaneous (SC) injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm.	
Methodology: This is a randomized, multicenter, open-label study, consisting of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period.	



* At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment.

The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one "escape" criteria is met.

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum 4 weeks). At the baseline visit (Week 0), subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for parenteral nutrition (PN) reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 or 12 (2 hours±10 minutes postdose).

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

Inclusion and Exclusion Criteria:

Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. Lack of terminal ileum and ileocecal valve
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.
8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.
9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µl due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2-week period
13. More than 3 serious complications of intestinal failure (e.g., catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

Maximum Duration of Subject Involvement in the Study:

The study consists of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

Endpoints:

Efficacy

Efficacy endpoints consist of the following:

Primary

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

Secondary

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by week 24
- Time to achieve enteral autonomy
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to Week 24/EOT

Pharmacokinetics

The pharmacokinetic endpoint is plasma teduglutide concentration at nominal time point.

Safety

Safety endpoints consist of the following:

- Adverse events (AEs)
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

Health Economics and Outcomes Research

Health economics and outcomes research (HEOR) endpoints include the following:

- Cumulative number of hospitalization days during the study

Statistical Methods:

Efficacy

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm. Descriptive statistics will be used to summarize time to achievement of enteral autonomy by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

Pharmacokinetics

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.

Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (e.g., number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, serious adverse events will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores; and descriptive statistics (e.g., n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

Health Economics and Outcomes Research

The HEOR endpoints will be summarized descriptively.

STUDY SCHEDULES

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X													
Eligibility	X	X												
Randomization		X												
Demographics	X													
SBS history	X													
Medical and surgical history	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight	X	X	X		X		X		X		X			X
Length and head circumference	X	X					X							X
UGI/SBFT	X													
Safety labs and urinalysis[b, c]	X	X[b]	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	(X)	X
PK sampling[a]		X							[X][d]					[X][d]
Antibodies to teduglutide[a,e]		X												X[e]
Native GLP-2[f]	X													
Provide intake and output diaries[g]	X	X	X		X		X		X		X			X
Review diaries and nutritional support		X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support as needed[h]		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IP[a, i]		X	X		X		X		X		X			X

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Adjust IP dose[j]														X

EN=enteral nutrition; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PK=pharmacokinetics; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] Applicable to the teduglutide treatment arm only.

[b] At baseline, safety labs (Table 4) and PK can be separated by 1 day if blood volumes are limiting. Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline, and repeated if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity. Urine collection should be attempted, but inability to obtain urinalysis is not a protocol deviation.

[d] Subjects will have blood samples taken for teduglutide PK analysis predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the treatment period.

[e] Samples for antibody analysis will be drawn at the baseline and Week 12 visits. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.

[f] Blood samples for native GLP-2 should be collected postprandial. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

[i] The initial dose will be calculated based on body weight measured at baseline (Visit 0).

[j] The dose will be adjusted as needed, based on body weight measured at Week 12 visit.

Note: (X) denotes optional assessments; [X] denotes possible PK sampling time point (Refer to footnote "e".)

Table 2: Study Schedule: Visits 13-28

Procedures	**Week 13**	**Week 14**	**Week 15**	**Week 16**	**Week 17**	**Week 18**	**Week 19**	**Week 20**	**Week 21**	**Week 22**	**Week 23**	**Week 24 (EOT/ET)**	**Week 25**	**Week 26**	**Week 27**	**Week 28 (EOS)[a]**
Visit number	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Visit type	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**
Study day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**175**	**182**	**189**	**196**
±window (days)	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight				X				X				X				X
Length and head circumference				X				X				X				X
Safety labs and urinalysis[b,c]	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X
Antibodies to teduglutide[d,e]																X
Native GLP-2[f]												X				
Provide intake and output diaries				X				X				X				
Review diaries and nutritional support[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support as needed[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess follow-up period escape criteria[d]													X[i]	X[i]	X[i]	X
Dispense IP[d]				X				X								

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Visit type	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site
Study day	91	98	105	112	119	126	133	140	147	154	161	168	175	182	189	196
±window (days)	±3	±3	±3	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4

EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] At EOS subjects may enroll in an extension study, if subjects require treatment before the end of the 4-week follow-up they may enter the extension study immediately.

[b] Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR are tested if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity.

[d] Applicable to the teduglutide treatment arm only.

[e] Samples for antibody analysis will be drawn at the EOS (Week 28) visit.

[f] Blood samples for native GLP-2 should be collected postprandial. Blood samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.
Note: (X) denotes optional assessments.

[i] If a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.

1. BACKGROUND INFORMATION

1.1 Short Bowel Syndrome

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal diseases that result in major surgical resections of the small intestine (O'Keefe et al., 2006). Unlike the adult population, the majority of cases of SBS in pediatric subjects are due to congenital anomalies or catastrophic events that occur during infancy such as necrotizing enterocolitis, gastroschisis, intestinal atresia, midgut volvulus, or long-segment Hirschsprung disease (Beattie et al., 2010; Goulet and Ruemmele, 2006). A Canadian population-based study in neonates estimates an overall incidence of SBS to be 24.5 cases per 100,000 live births (Wales et al., 2004).

The small intestine is capable of remarkable adaptation, but excessive loss of absorptive surface area or specialized functions can lead to dependence on parenteral nutrition (PN)[1] fluids (O'Keefe et al., 2006). Although PN is life-sustaining in intestinal failure, it is associated with serious complications, including liver disease, life-threatening catheter-related blood stream infections, and central venous thrombosis (Beattie et al., 2010; Goulet and Ruemmele, 2006). Dependence on PN is also associated with reduced quality of life in both patients and caregivers and has an extremely high cost of care (Huisman-de Waal et al., 2007). About 30% of infants with SBS become independent of PN requirements within 12 months of the initial insult, and an additional 10% wean off PN within 24 months. After this time, linear intestinal growth slows. It is estimated that 42% to 86% of pediatric patients with SBS are able to become independent of PN within 1 to 3 years (Gonzalez-Hernandez et al., 2017; Khan et al., 2015; Squires et al., 2012). Nevertheless, despite optimal medical management, some children remain dependent on PN for many years (Squires et al., 2012). Infants who have less than 10% of expected small intestinal length for their gestational age have a low likelihood of ever achieving enteral autonomy (i.e., independence from parenteral support). Providing the maximum tolerated amount of enteral nutrition (EN) has been the primary strategy to promote enteral adaptation (Spencer et al., 2005).

Accelerating the adaptive process and achieving enteral autonomy is an urgent goal for all patients with SBS who are dependent on PN (Khan et al., 2015; Squires et al., 2012). The adaptive process is in part controlled by glucagon-like peptide 2 (GLP-2), a 33 amino acid peptide hormone secreted from L-type enteroendocrine cells in the terminal ileum and colon in response to luminal nutrients and bile acids (Martin et al., 2006). The post-prandial plasma concentration of GLP-2 in infants with SBS correlates with length of the remaining small intestine (Sigalet et al., 2004). Infants who lack terminal ileum may have impaired adaptation due to inadequate production of GLP-2.

[1] For the purpose of the study the terms parenteral support (PS) and parenteral nutrition (PN) are used interchangeably.

1.2 Teduglutide

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$), approximately 2 hours in healthy adult subjects, 1.3 hours in adult SBS subjects, and 0.22 hours in pediatric SBS subjects, compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines (Tappenden et al., 2013; Thymann et al., 2014).

A Phase 3 study, TED-C13-003, has been completed in pediatric SBS subjects. In this study, teduglutide was administered to 3 cohorts of pediatric subjects from ages 1-17 years. Thirty-seven pediatric subjects received teduglutide at doses of 0.0125, 0.025, or 0.05 mg/kg/day for 12 weeks. Five additional pediatric subjects were enrolled in an observational standard of care (SOC) cohort. There were clear dose-dependent effects of teduglutide seen at the 0.025 and 0.05 mg/kg/day doses compared to SOC and the 0.0125 mg/kg/day dose. In the 0.025 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 37%, including complete independence from PN support in 1 subject, and a reduction of 3.94 hours per day infusion time. In the 0.05 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 39%, including complete independence from PN support in 3 subjects, and a reduction of 4.18 hours per day infusion time. Teduglutide was generally safe and well tolerated by pediatric subjects in all dosing cohorts. There were no deaths during the study and no treatment-emergent serious adverse events (SAEs) related to teduglutide were reported. No discontinuations from study were due to adverse events (AEs). Additional studies in pediatric patients with SBS are ongoing.

TED-C14-006 is a recently completed study of pediatric subjects through 17 years which included 2 treatment arms: a teduglutide treatment arm and a SOC treatment arm. Subjects in both arms participated in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the screening period, subjects chose into which arm to enroll. During the 24-week treatment period, subjects in the SOC treatment arm received standard medical therapy for SBS; while those in the teduglutide treatment arm received daily subcutaneous (SC) injections of teduglutide (study drug) in addition to standard medical therapy. The subjects enrolling in the teduglutide treatment arm were randomized 1:1 in a double-blinded manner into 2 parallel dose groups: 0.025 mg/kg/day or 0.05 mg/kg/day of teduglutide administered subcutaneously for 24 weeks. Compared to the SOC, treatment of pediatric subjects with SBS with teduglutide resulted in clinically meaningful reductions in PN/IV volume, calories, days per week, and hours per day. A total 10% of subjects who received teduglutide achieved enteral autonomy within 24 weeks despite prior dependence on PN/IV for several years. Teduglutide treatment also resulted in increases in EN volume and caloric intake as well as plasma citrulline. Although the differences in efficacy between the 0.025 and 0.05 mg/kg dose groups were small, a consistently greater effect was seen in the 0.05 mg/kg dose in all efficacy

parameters. The pharmacokinetic (PK) properties were well characterized in this population and were consistent with the prior 12 week pediatric study. Teduglutide was generally well tolerated by pediatric subjects with SBS. The safety profile was favorable and consistent with the prior pediatric study, the underlying disease, and previous experience with teduglutide in adult subjects with SBS.

Teduglutide (0.05 mg/kg/day) is currently approved for the treatment of adult patients with SBS in >30 countries. On 29 Jun 2016, the European Commission granted an extension of the Market Authorization for teduglutide for the treatment of patients aged 1 year and above with SBS.

Always refer to the latest version of the investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy and safety of teduglutide (SHP633).

2. OBJECTIVES

2.1 Rationale for the Study

There is no approved pharmacological therapy to improve intestinal adaptation in infants with SBS who are dependent on parenteral support. This study will evaluate whether teduglutide is safe and effective in this patient population.

2.2 Study Objectives

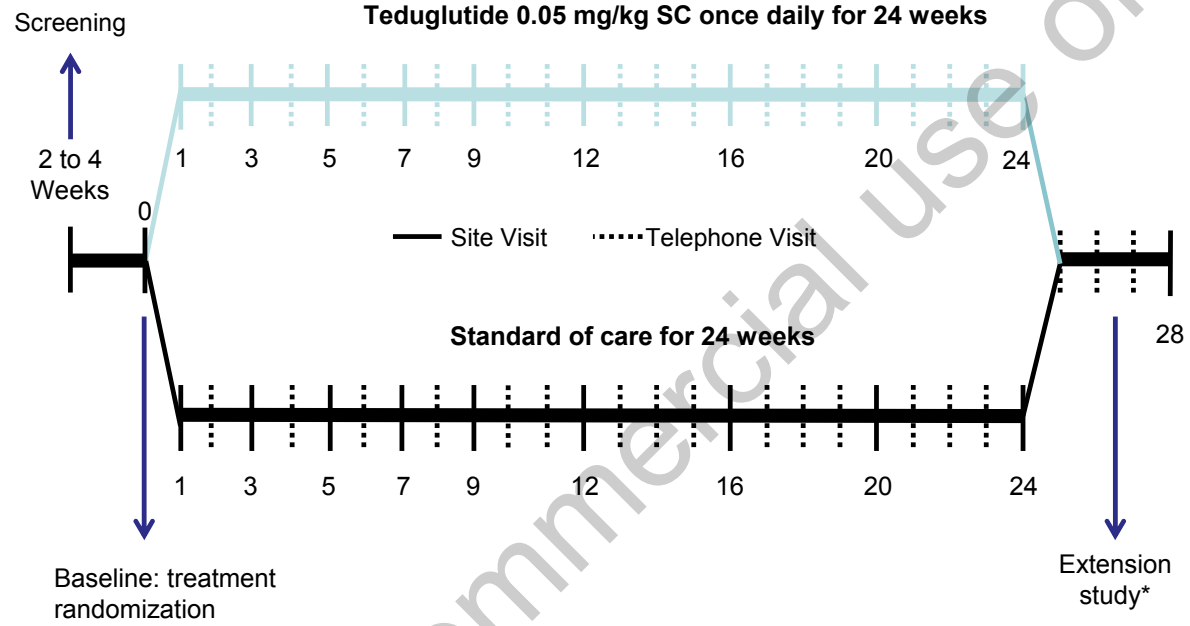
The objectives of this study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with SBS dependent on parenteral support.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a randomized, multicenter, open-label study, consisting of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. A schematic representation of the study design is presented in Figure 1.

Figure 1: Study Schematic



*At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one "escape" criteria is met.

3.1.1 Screening Period

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum: 4 weeks). The schedule of evaluations to be conducted during the Screening Period can be found in Table 1.

3.1.2 Treatment Period

At the baseline visit (Week 0), subjects will randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS, while those in the teduglutide arm will receive 0.05 mg/kg by SC injection once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12,

16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for PN reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability (Appendix 2). Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 or 12 (2 hours±10 minutes postdose).

The schedule of evaluations for the Treatment Period can be found in Table 1 (Visits -1 to 12) and Table 2 (Visits 13 to 28).

3.1.3 Follow-up Period

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product (IP) will be administered. At EOS, all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS visit if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

The schedule of evaluations for the Follow-up Period can be found in Table 2 (Visits 13 to 28).

3.2 Study Duration

The study consists of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

3.3 Sites and Regions

This study is planned to be conducted at approximately 5 to 10 sites globally.

4. STUDY POPULATION

At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in an SOC comparator arm.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. Lack of terminal ileum and ileocecal valve.
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.

8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.
9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µL due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2 week period.
13. More than 3 serious complications of intestinal failure (e.g., catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

4.3 Reproductive Potential

Not applicable; this study will enroll infants.

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (e.g., in the interest of subject safety). The investigator should discuss withdrawal of a subject from investigational product with the medical monitor as soon as possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT/early termination are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period. Comments (spontaneous or elicited) or complaints pertaining to IP discontinuation made by the subject must be recorded in the source documents. The reason for discontinuation, the date and the total amount of investigational product administered must be recorded in the electronic case report form (eCRF) and source documents.

Subjects who discontinue will not be replaced.

4.4.1 Reasons for Discontinuation

The reason(s) for permanent discontinuation of treatment and/or withdrawal from the study must be determined by the investigator, and recorded in the subject's medical record and in the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document, and the most clinically relevant reason should be entered in the eCRF.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by parent/guardian
- Lack of efficacy
- Other

4.4.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact the parent(s)/guardian(s) of any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Medications and Procedures

Prior treatment includes all treatment and procedures (including but not limited to prescription treatments, herbal treatments, vitamins, non-pharmacological treatment, as appropriate) received within 14 days prior to the screening visit (Visit -1) (or pharmacokinetic equivalent of 5 half lives, whichever is longer, must be recorded on the appropriate eCRF page.

5.2 Concomitant Medications and Procedures

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins) and PN must be recorded from the first dose of investigational product and for the duration of the study in the appropriate sections of the eCRF. Any diagnostic, surgical or other therapeutic treatments received by a subject during the course of the study will also be recorded on the eCRF.

The mechanism of action of teduglutide may increase enteral absorption of oral drugs (e.g., drugs used for management of SBS such as motility medication, opioids, psychotropics, metronidazole), so consideration should be given to modifying concomitant enteral medication regimens. Titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic index (e.g., warfarin, digoxin, psychotropics) are given.

5.3 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.4 Prohibited Treatment

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the pretreatment visit (Table 3):

Table 3: Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pretreatment Visit
Teduglutide	Any
GLP-2, human growth hormone, or analogs of these hormones	6 months
Octreotide, GLP-1 analogs, and enteral glutamine	30 days

GLP=glucagon-like peptide

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

The investigational product is teduglutide, which will be provided in sterile, single-use 3 mL vials containing 1.25 mg teduglutide as a white lyophilized powder to be reconstituted before use with 0.5 mL sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the current investigator's brochure.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

All investigative study sites will be initially provided with sufficient investigational product to randomly assign a subject into the study (for either of the proposed treatment groups). Randomization will occur through an interactive response system. Random assignment of a subject will trigger replacement supplies for that investigative study site.

6.2.2 Allocation of Subjects to Treatment

Subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy). The actual treatment given to individual subjects is determined by a randomization schedule.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined.

6.2.3 Dosing

The initial dose will be calculated based on body weight measured at baseline (Visit 0), and adjusted as needed, based on body weight measured at Week 12. No other adjustments to dose will be made during the teduglutide treatment period, unless discussed with the sponsor's medical monitor.

Following reconstitution, teduglutide will be administered by SC injection once daily (QD) into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used.

Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later.

The subject should be dosed at approximately the same time each day. Consecutive doses should be separated by at least 12 hours. Each day, the injection site should be alternated.

Any subject who achieves complete independence from PN support at any time during the treatment period will continue to receive teduglutide treatment.

The first SC injection in teduglutide-naïve subjects should be administered under the supervision of the investigator or designee and the subject observed for hypersensitivity reactions for at least 4 hours during their initial dosing visit. The site of administration (arm, thigh, and abdomen) of the first teduglutide dose must be specified and recorded in the eCRF.

Detailed instructions for reconstitution and injection of the investigational product can be found in the Instructions for Use.

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.2.5 Dose Selection Rationale

Teduglutide is approved for adult and pediatric use in the EU at a dose of 0.05 mg/kg SC once daily. A completed 12-week dose finding study (TED-C13-003) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit-risk profile most meaningful at the 0.05 mg/kg/day dose (Carter et al., 2017).

Population pharmacokinetic modeling and simulations were conducted to determine the optimal dose to be used in pediatric subjects using data from 8 adult clinical studies including adult Phase 1 studies and Phases 2/3 studies as well as TED-C13-003 and suggested the same adult dose (0.05mg/kg) in pediatric subjects (aged between 1.67-14.7 years) (Marier et al., 2017).

To support dosing in the current age group, further PK simulation was conducted based on the population PK model previously established and a virtual population of 1000 pediatric patients created based on Centers for Disease Control (CDC) growth charts in the target age group (4 to 12 months) and taking into consideration body weights of pediatric patients with SBS enrolled in study TED-C13-003 and TED-C14-006 (approximately 15% lower than healthy subjects in the same age group). The model was customized by including a maturation function on clearance (CL/F) as a function of estimated glomerular filtration rate. Monte Carlo simulations for all age groups were performed according to the SC dosing regimens of 0.0125, 0.025 and 0.05 mg/kg every 24 hours. Rich concentration-time profiles were simulated with the customized population PK model to derive the exposure metrics area under the concentration curve at steady state (AUC_{ss}) and maximum concentration at steady state ($C_{max,ss}$). Exposure parameters in infant patients were compared to those derived in pediatric (1-17 years) and adult (≥18 years) patients with SBS using a Bayesian approach. Based on the clinical observations, C_{max} is considered to be associated with clinical responses. Following 0.05 mg/kg daily SC administration, the median $C_{max,ss}$ of teduglutide in neonate patients (24.9 ng/mL) was within 20% of that observed in the 2 to 4 and 4 to 6 years age groups (26.9 and 29.4 ng/mL, respectively); and approximately ~28% lower than that in adult patients with SBS. The median $C_{max,ss}$ of teduglutide in infant patients 4 to 12 months (41.9 ng/mL) following 0.05 mg/kg once daily was within 8% of that previously observed in adult patients with SBS (39.0 ng/mL, refer to the attached Simulation Report). In addition, individual simulated $C_{max,ss}$ values of teduglutide in infant patients 4 to 12 months (25.6 to 65.1 ng/mL) were contained within the range of $C_{max,ss}$ previously observed in pediatric patients 1 to 17 years (20.7 to 77.4 ng/mL). The clinical package in conjunction with C_{max} was considered to support teduglutide dose selection since AUC_{ss} was previously shown not to correlate with efficacy. Individual simulated AUC_{ss} values of teduglutide in infant patients 4 to 12 months (66.9 to 160 ng.h/mL) following 0.05 mg/kg once daily were contained within the range of AUC_{ss} values previously observed in pediatric patients 1 to 17 years (63.5 to 421 ng.h/mL). Based on the totality of clinical data, 0.05 mg/kg once daily is expected to provide comparable C_{max} concentrations in infants as compared to pediatric patients with SBS and was recommended as an evaluation dosing regimen in Study SHP633-301.

6.3 Labeling, Packaging, and Storage

6.3.1 Labeling

The investigational product will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of investigational product will be provided for this study. The vials will be labeled in accordance with applicable regulatory requirements.

Ancillary kits, containing supplies needed for the reconstitution and administration of the investigational product will also be provided and labeled in accordance with the applicable regulatory requirements.

All investigational product used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice.

6.3.2 Storage and Handling

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2-8°C (35.6-46.4°F) until dispensed to a subject. Once dispensed to a subject, the IP can be stored refrigerated or up to a controlled room temperature (acceptable range of 2-25°C, or 35.6-77°F). Parent/legal guardian will be instructed to keep the subject's IP and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the IP may be refrigerated. The IP is for single use only, and should be used within 3 hours following reconstitution.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (i.e., certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), e.g., fumigation of a storage room.

Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels, as they are distributed.

6.4 Drug Accountability

Investigational product will not be dispatched to the study site until the sponsor or designee has received all required documents from the study site in accordance with applicable regulatory requirements and relevant standard operating procedures. Upon receipt, the study site's pharmacist or delegate is responsible for ensuring that all investigational product received at the site is inventoried and accounted for throughout the study. A copy of the shipping documents must be maintained for the investigator's records. Kits will be shipped to the site once the subject is screened.

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Investigational product kits will be dispensed at each of the applicable study visits at which the subject is required to be at the clinic. Each investigational product kit is sufficient for a treatment period of 1 week and enough kits will be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

Each subject will be given the investigational product according to the protocol. The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. All dispensed medication will be documented on the eCRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, subject returned investigational product, and empty/used investigational product packaging are to be sent to the sponsor or designee. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

Returned investigational product must be counted and verified by clinical site personnel and the sponsor (or study monitor). Shipment return forms, when used, must be signed prior to shipment from the site. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

The parent(s)/guardian(s) of subjects must be instructed to bring unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed and recorded at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (e.g., bottles, trays, vials) or at the individual count level for opened containers/packaging.

Subject compliance will be checked by site personnel at every visit by reviewing the subject diaries and asking the subject or the subject's parent or legally-authorized representative if they have administered the investigational product according to instructions. If any doses have been missed, the reason for missed dose should be documented in the subject's source documentation including, as applicable, the eCRF.

The investigator is responsible for contacting the sponsor or designee when the subject's daily investigational product dosing regimen is interrupted. Attempts should be made to contact the sponsor or designee prior to dose interruption. Reasons for dosage interruption may include but are not limited to hospitalization and AEs, a lapse in investigational product delivery, etc.

Subjects who have received 80% of the planned doses administered will be assessed as being compliant with the study protocol.

7. STUDY PROCEDURES

7.1 Study Schedule

Detailed study procedures and assessments to be performed for subjects throughout the study are outlined in the study schedules (Table 1 and Table 2) and must be referred to in conjunction with the instructions provided in this section.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period.

7.1.1 Screening

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the parent(s)/guardian(s) of the subject. The screening visit assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1. Rescreening will not be allowed.

7.1.2 Treatment Period

The randomized Treatment Period will comprise Weeks 1 to 24, during which all assessments will be performed as outlined in Table 1 and Table 2.

7.1.3 Follow-up Period

The Follow-up Period will comprise Weeks 25 to 28, during which all assessments will be performed as outlined in Table 2.

7.2 Study Evaluations and Procedures

7.2.1 Demographics and Other Baseline Characteristics

Demographics and Medical History

Demographic and/or other baseline variables obtained at the screening and/or baseline visits are listed below. Abnormal findings of clinical significance (if any) will be recorded as past medical history.

- Demography (including age, gestational age, sex, and race)
- Medical history (including surgical history)
- SBS history, including remnant anatomy

Upper Gastrointestinal Series with Small Bowel Follow-through

An upper GI contrast series with small bowel follow-through will be performed on all subjects during the screening period if one has not been done since the subject's last GI surgery.

It is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow-through performed since the subject's most recent surgery.

7.2.2 Efficacy Assessments

Subject Diaries

All available diary data will be reviewed by the investigator or their designee at each clinic and telephone visit to assess clinical status and opportunity for PN reduction and advance in feeds. Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

Intake Diary

Intake diaries will be used to collect and evaluate each subject's nutritional support. The parent/legally authorized representative/study site staff will complete the appropriate fields of the PN and EN sections of the intake diary daily throughout the study.

The following data will be captured in the intake diaries:

- Parenteral support volume and infusion duration
- Enteral nutrition (formula) including volume and calories

Site personnel will determine the actual PN and EN daily calories based on diary entries.

Output Diary

Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit; in addition, output should be recorded for subjects within 1 week of implementing a change in the PN prescription.

Urine data:

- Measure and record the weight of all urine-only diapers. Urine volume will be calculated using the following formula: 1 g (scale weight) = 1 mL or 1 cc
- At the discretion of the investigator, the parent or legal guardian/study site staff may be asked to collect the first void after the daily PN infusion to measure specific gravity

Stool data (includes diapers with mixed urine and stool):

- Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency (see Output diary). Stool volume will be calculated using the formula: 1 g (scale weight)=1 mL or 1 cc

All ostomy output volume should be recorded.

Native GLP-2

Blood samples for native GLP-2 should be collected postprandial. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

7.2.3 Safety Assessments

Laboratory Evaluations

Safety laboratory tests to be performed at site visits consist of clinical chemistry, hematology, and urinalysis and will be performed as outlined in the study plan (Table 1 and Table 2). Scheduled laboratory testing will be processed by a central lab. All laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the laboratory. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

During the Treatment Period, subjects will also have safety labs within approximately 5 to7 days after a PN adjustment. Safety labs performed after PN adjustment and between site visits will consist of clinical chemistry and urinalysis and may be processed by the central laboratory or a local laboratory. Local lab results are not required to be entered in the eCRFs; however, if the local lab results indicate any new clinically significant changes, they must be reported as an adverse event (see Section 8). Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

At baseline, blood samples for safety labs and PK can be separated by 1 day if blood volumes are limiting.

Safety labs at telephone visits will be collected at the discretion of the investigator.

For all subjects in the teduglutide treatment arm, prothrombin time (PT) and international normalized ratio (INR), tested at baseline, will be repeated if clinically indicated.

New clinically significant labs should be reported as AEs.

Close Monitoring Criteria Related To Liver Test Abnormalities:

The investigator should contact the medical monitor within 24 hours of their awareness if the subject develops any of the following changes in laboratory parameters:

- ALT or AST >5x ULN and >2x baseline value
- Total or direct bilirubin that is >2x baseline value or an absolute increase of ≥3 mg/dL (51.3 µmol/L)

If such changes are observed, the labs should be repeated along with an INR, and an inquiry should be made as to the presence of clinical symptoms consistent with new liver injury. The subject should be followed closely to determine the trajectory of the laboratory abnormalities and appropriate evaluations should be made, such as abdominal ultrasound with Doppler imaging to exclude vascular causes and biliary obstruction, consideration of sepsis, liver hypoperfusion, acute viral hepatitis (such as hepatitis A, EBV, or HSV), exposure to hepatotoxic medications, mitochondrial hepatopathy, or metabolic liver disease (such as hereditary fructose intolerance or arginosuccinate synthetase deficiency). Further evaluations can be performed at the discretion of the investigator in consultation with the Shire medical monitor.

The following clinical laboratory assessments will be performed according to the study schedules:

Table 4: List of Laboratory Tests

Biochemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bicarbonate
- Bilirubin (total and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- C-reactive protein
- Creatinine
- Estimated Glomerular Filtration Rate (Schwartz formula)
- Gamma-glutamyl transferase
- Glucose
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Triglycerides

Hematology[a]:
- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- Red blood cell morphology, if needed
- White blood cell count with differential

Coagulation[b]:
- Prothrombin time
- International normalized ratio

Urinalysis:
- Specific gravity
- Urine Sodium

[a] Hematology is not collected at Week 1 or at telephone visits.
[b] For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline and repeated only if clinically indicated.

Antibodies to Teduglutide

Blood samples will be drawn to test for antibodies to teduglutide. Samples will be taken before teduglutide administration at the screening visit (Visit -1) and at least 14 hours after the previous

dose at Week 12 (Visit 12); samples may be drawn from a central line or peripheral access. One additional sample will be collected at the EOS 4 weeks after the EOT (i.e., Week 28 or EOS).

Volume of Blood

Efforts will be made to minimize the amount of blood drawn from all pediatric subjects participating in this study. The volumes of blood to be drawn from each subject will vary depending on clinical status. Approximate volumes of blood to be drawn from each subject are shown in Table 5.

Table 5: Approximate Volume of Blood to be Drawn from Each Subject

Assessment	Sample Volume (mL)	No. Samples	Total Volume (mL)	Notes
Subjects Receiving Teduglutide Treatment				
Biochemistry	0.6	12	7.2	
Hematology	0.6	11	6.6	
Coagulation Parameters	0.6	1	0.6	PT and INR tested at baseline only, repeat while on study only if clinically indicated.
Antibodies	1.5	5	7.5	
Pharmacokinetics	1.5	4	6.0	Baseline: 3 timepoints Week 7: 1 timepoint OR Week 12: 1 timepoint
Native GLP-2	1.5	3	4.5	
Total mL:	**6.3**	**36**	**32.4**	
Subjects Receiving Standard of Care				
Biochemistry	0.6	12	7.2	
Hematology	0.6	11	6.6	
Native GLP-2	1.5	3	4.5	
Total mL:	**2.7**	**26**	**18.3**	

GLP=glucagon-like peptide; INR=international normalized ratio; PT=prothrombin time

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments should be combined. Blood volume estimates do not include safety labs performed after PN adjustments.

Physical Examinations, Vital Signs, Weight, Length, and Head Circumference

Physical examinations will be performed according to the study schedules (Table 1 and Table 2). Any new clinically significant findings noted during physical examinations should be recorded on the appropriate AE page of the eCRF.

Vital signs will be measured according to the study schedules. Measurements will include systolic and diastolic blood pressure (mmHg), pulse (beats per minute), and body temperature

(°C/°F). Blood pressure should be determined by the appropriate size cuff (using the same method, the same leg, and in the supine position throughout the study, when possible). Blood pressure measurements should be attempted as part of the vital signs, but lack of blood pressure results will not constitute a protocol deviation. New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Length and head circumference will be measured at selected visits. A height z-score, weight Z-score, and weight/length ratio will be calculated by the sponsor using the site-provided height and weight data collected at each site visit.

7.2.4 Pharmacokinetic Assessments

Subjects will have blood samples taken for teduglutide PK analysis predose, and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the treatment period. Blood for PK sampling should be collected via peripheral IV or venipuncture, not from a central line. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified.

7.2.5 Health Economics and Outcomes Research

Hospitalizations

Each hospitalization that occurs during the study will be recorded, including date of admission, date of discharge, reasons for hospitalization, discharge diagnosis, and discharge status.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, or a symptom is more severe or prolonged than expected given the diagnosis, then symptom(s) should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects

clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	**Relationship Definition**
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

AEs that are related to IP that are not resolved at EOS will be followed until the event resolves or stabilizes, as judged by the investigator.

Laboratory values, vital signs, and clinical findings at the scheduled physical examinations must be reported as AEs if the investigator considers the finding to be a clinically significant change from the baseline.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. It is assumed that some of the infants participating in this study may be hospitalized for planned surgery(ies) that will occur during their participation in the study. Such pre-planned, elective surgeries, do not need to be reported as SAEs for this protocol.

8.1.5 Clinical Laboratory and Other Safety Evaluations

An untoward change in the value of a clinical laboratory parameter, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. Clinical significance is defined as any abnormal finding that results in further clinical investigation(s), treatment(s), or the diagnosis of new or progression of established condition. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, or ECG values which were not present at the beginning of the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory value, vital sign, or ECG parameter is clinically significant and represents an AE.

8.1.6 Pregnancy

Not applicable.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.

- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Administration of a dose greater than the allocated dose of the study medication or at a frequency greater than the dosing interval specified by the protocol.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally-authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

All Adverse Events of Special Interest, as defined in Section 8.3, must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event even if the event does not fulfill seriousness criterion.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol, and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested). Fax or e-mail the completed form to the Shire Global Drug Safety Department. A copy of the completed Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the Shire medical monitor or designee using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3, and must be reported to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (i.e., the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (e.g., drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The Sponsor and/or Clinical Contract Research Organization (CRO) is responsible for notifying the relevant regulatory authorities, and US central Institutional Review Boards (IRBs)/EU central ethics committees (ECs), of related, unexpected SAEs.

In addition, the Clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP633 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

8.3 Adverse Events of Special Interest

An AE of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program and for which ongoing monitoring and immediate notification by the investigator to the sponsor is required.

The AEs of special interest that require expedited regulatory reporting include the following:

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the GI tract including the hepatobiliary system
- Tumor-promoting ability (e.g., benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

For AEs of special interest, the sponsor must be informed within 24 hours of first awareness as per the SAE notification instructions described in Section 8.2.2 even if the event does not fulfill the seriousness criteria.

8.4 Dose Interruption Criteria

The investigator is responsible for contacting the sponsor/designee when the subject's teduglutide dosing regimen is interrupted. The length of dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

Investigational product must be interrupted if any of the following events occur:

- An adverse event of special interest (see Section 8.3)
- Intestinal obstruction
- Biliary obstruction
- Pancreatic duct obstruction
- Heart failure with severe fluid overload determined by the sponsor or investigator to be related to IP.

Investigational product must be permanently discontinued if any of the following events occur:

- Severe hypersensitivity, such as anaphylaxis, determined by the investigator to be related to IP.
- Any malignancy

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Process

The study will be analyzed by the sponsor or designee. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, US) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the definitions and statistical methods for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

9.4 Planned Interim Analysis, and Data Monitoring Committee

No interim analyses is planned for this the study.

A data monitoring committee (DMC) will be involved in the management of this study. The DMC members will review the data approximately every 3 months according to the DMC Charter. The DMC review will include all cumulative safety data (i.e., AEs, laboratory assessments, physical examinations, etc.) from study assessments through each cutoff period. Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of investigational product.

The DMC for this study will be conducted in accordance with the FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006).

The DMC will be an external, independent board comprised of physicians with relevant training. The DMC will be restricted to individuals free of significant conflicts of interest, including, but not limited to, financial, scientific, or regulatory in nature. The DMC will be governed by a Charter agreed to by members of the Board and the sponsor. Members of the Board may not be study investigators or be employed at the same institution as a study investigator, individuals employed by the sponsor, independent contractors hired by the sponsor, or members of regulatory agencies. The DMC may make recommendations to the sponsor regarding study aspects including stopping, modifying or continuing the study; however, the sponsor will have the final responsibility to determine whether the study should be modified or temporarily or permanently stopped. If the DMC recommends termination of this pediatric study, the recommendations will be communicated to the relevant regulatory agencies within 7 calendar days.

9.5 Sample Size Calculation and Power Considerations

The sample size is determined based on enrollment feasibility for this rare condition and the age of the study population.

9.6 Study Population

Intent to treat (ITT) population: All subjects randomized in the study.

Safety analysis population: The safety analysis set will contain all subjects who meet the following criteria:

- Teduglutide treatment arm: subjects who receive at least 1 dose of teduglutide and have undergone at least 1 post-baseline safety assessment; analyses will be performed according to dose group as appropriate.
- Standard of care treatment arm: subjects who have undergone at least 1 post-baseline safety assessment.

Per-protocol population: All subjects in the ITT population without any major protocol deviation that affects interpretation of efficacy results.

Pharmacokinetic analysis population: All subjects who received at least 1 dose of teduglutide and have at least 1 evaluable postdose PK concentration value.

9.7 Efficacy Analyses

9.7.1 Efficacy Endpoints

Efficacy endpoints consist of the following:

9.7.1.1 Primary Efficacy Endpoint

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

9.7.1.2 Secondary Efficacy Endpoints

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by Week 24
- Time to achieve enteral autonomy
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT

9.7.2 Method of Analysis-Efficacy Endpoints

Due to the limited size of the study population, descriptive statistics will be used with a goal of summarizing the sample. As such, no claims of significance will be made for any of the data. Continuous variables will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of

subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm. Descriptive statistics will be used to summarize time to achievement of enteral autonomy by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

9.8 Safety Analyses

9.8.1 Safety Endpoints

Safety endpoints consist of the following:

- Adverse events
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

9.8.2 Method of Analysis-Safety Endpoints

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (e.g., number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, SAEs will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores, and descriptive statistics (e.g., n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

9.9 Health Economics and Outcomes Research Analyses

Health economics and outcomes research endpoints consist of the following:

- Cumulative number of hospitalization days during the study

Health economics and outcomes research endpoints will be summarized using descriptive statistics (number, mean and standard deviation) at nominal time points.

9.10 Pharmacokinetics Analyses

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points.

Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (e.g., CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of

the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly. The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator will be appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The

investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Electronic Case Report Forms

Electronic case report forms are supplied by the sponsor or designee and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data will be recorded directly onto the eCRF.

All data sent to the sponsor must be endorsed by the investigator.

The study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diaries, and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the parent/guardian agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (e.g., subject's medical file, appointment books, original laboratory reports, X-rays etc). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent, where applicable, from the parent(s)/guardian(s) of all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject's legally authorized representative is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject's parent or guardian has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (i.e., sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor/designee has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor/designee.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market teduglutide; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (e.g., to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (e.g., Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2 to 4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	03 Oct 2017	Global
Amendment 1	18 Jan 2018	Global
Amendment 2	04 Dec 2018	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 18 Jan 2018	Global
Description of Change		Section(s) Affected by Change
Updated emergency contact information to reflect the change of the Contract Research Organization's name.		Emergency Contact Information
Clarified the duration of the screening period and total time on study. Provided a clear definition of study completion. Updated the study schematic to reflect the study design changes.		Synopsis, Section 3.1, Section 3.2
Revised the telephone and clinic visit schedule to assure laboratory measurement could be collected without exceeding weekly/monthly total blood volume restrictions.		Synopsis, Table 1, Section 3.1.2
Moved the PK sampling from Week 6 to Week 7 so that the samples could be collected without exceeding weekly/monthly total blood volume restrictions. Clarified that blood for pharmacokinetic samples of postdose may be taken within ± 10 minutes of the time pre-specified.		Synopsis, Table 1, Section 3.1.2, Section 7.2.4, Table 5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 18 Jan 2018	Global
Description of Change		Section(s) Affected by Change
Clarified that end jejunostomy or ileostomy are examples of small bowel ostomy rather than the stratification factors.		Synopsis, Section 3.1.2, Section 6.2.2
Clarified that all subjects regardless of treatment arm are eligible for the extension study.		Synopsis, Section 3.1.3
Clarified that if a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.		Synopsis, Table 2, Section 3.1.3, Section 6.2.3
Clarified that subjects must be 4 to 12 months corrected gestational age at screening.		Synopsis, Section 4.1
Changed dose adjustments to Week 12 rather than at every clinic visit to reduce site burden.		Synopsis, Table 1, Section 6.2.3
Clarified the definition of enteral autonomy.		Synopsis, Section 9.7.2
Updated the pharmacokinetic endpoint and analysis to reflect that only descriptive statistics will be calculated on plasma teduglutide concentration values. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.		Synopsis, Section 9.10
Removed assessment of the 5-level EuroQol five dimensions questionnaire to reduce caregiver burden.		Synopsis, Table 1, Section 7.2.5, Section 9.9
Clarified that native GLP-2 samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after		Table 2, Section 7.2.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 18 Jan 2018	Global
Description of Change		Section(s) Affected by Change
the previous dose.		
Inserted a footnote to clarify that parenteral support and parenteral nutrition are used interchangeably.		Section 1.1
Removed the 5 mg vial of teduglutide as this size vial will not be supplied for this study.		Section 6.1
Clarified the procedures for assessing subject compliance.		Section 6.5
Specified that it is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow through performed since the subject's most recent surgery.		Section 7.2.1
Corrected the volume of blood to be collected for native GLP-2.		Table 5
Removed references to subject assent as assent is not possible in a study of infants.		Section 7.1.1, Section 10.3.1
Clarified the definitions of the analysis sets.		Section 9.6
Clarified that an adjustment to enteral nutrition as appropriate is part of the PN/IV adjustment algorithm.		Figure A-1
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout protocol.

Appendix 2 Guidelines for Nutritional Support Management During the Study

The nutritional support adjustment guidelines are designed to standardize management of parenteral and enteral nutritional support in this study. Adjustments to nutritional support should be considered at every scheduled clinic visit. Adjustments at phone visits may also be performed, but nutritional assessments at phone visits serve primarily to confirm that nutritional adjustments at prior clinic visits were tolerated.

All attempts should be made to follow the guidelines, but departure from the guidelines will not constitute a protocol deviation.

Clinical judgment is required within the algorithm. Each decision point requires integrating multiple sources of information into a yes/no decision. When individual data points are conflicting, the investigator must use their best judgment in the assessment.

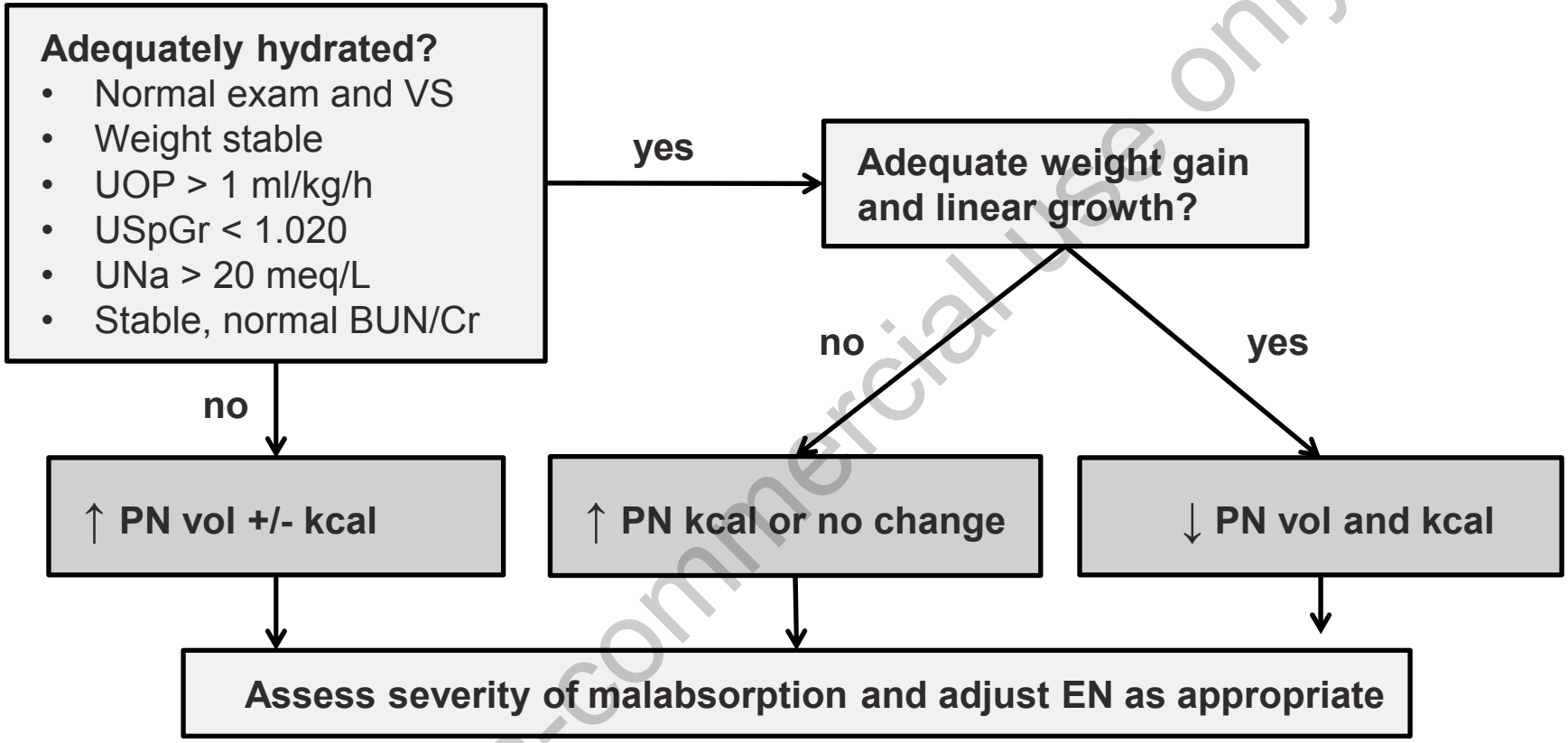
If intestinal adaptation is occurring, reductions in parenteral support volume and calories are expected to be in decrements of 5 to 10% relative to baseline values. Parenteral support components are at the discretion of the investigator, but care should be taken to balance carbohydrate, fat, and protein. Likewise, if intestinal adaptation is occurring, enteral nutrition volume and calories should be increased in increments of approximately 10% relative to baseline values.

Assessment of the severity of malabsorption may require estimation of stool output for children who have mixed stool and urine output.

Adjustments should be based on the actual nutritional support in volume and calories the subject infuses. Subjects should remain compliant with the nutritional support prescription in volume and calories during the study.

During the 48-hour output measurement period prior to the subject's scheduled visit, no further changes to the prescribed nutritional support should be made.

Figure A-1: Parenteral Nutrition/Intravenous Adjustment Algorithm for All Subjects



BUN=blood urea nitrogen; Cr=creatinine; PN=parenteral nutrition; UNa=urine sodium; UOP=urine output; USpGr=Urine specific gravity; VS=vital signs; vol=volume

PROTOCOL: SHP633-301

TITLE:	A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support
NUMBER	SHP633-301
PHASE	3
DRUG:	Teduglutide
INDICATION:	Short bowel syndrome
EUDRACT NO.:	2017-003606-40
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA
PROTOCOL HISTORY:	Original Protocol: 03 Oct 2017 Amendment 1: 18 Jan 2018 Amendment 1.1: 07 Aug 2018 (France-specific) Amendment 2.1: 04 Dec 2018 (France-specific)

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** [redacted]
[redacted], MD PhD [redacted], Global Clinical Development	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-301.

Title: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: _____
(please hand print or type) _____
_____
_____

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the Shire Medical Monitor by e-mail at [redacted].

For protocol- or safety-related issues, the investigator must contact IQVIA Medical Support:

Primary Contact	**Backup Contact**
[redacted], MD	[redacted], MD, PhD
[redacted]	[redacted]
Mobile: [redacted]	Mobile: [redacted]
Phone: [redacted] (medical emergencies)	Phone: [redacted] (medical emergencies)
Email: [redacted]	Email: [redacted]

In addition, the investigator may also contact Shire:

[redacted], MD

Mobile Phone: [redacted]

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (e.g., inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (e.g., wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the E-mail address below to report the Product Quality Complaint:

[redacted]

Telephone numbers (provided for reference, if needed):

Shire (USA)
[redacted]

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2.1**	**Amendment Date** **04 Dec 2018**	**France-specific**
Description of Change and Rationale		**Section(s) Affected by Change**
The fax number currently used to send the Shire Medical Monitor a copy of the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol is now retired; a copy of the form must be sent by email only. Updated emergency contact information to reflect the change of Shire medical monitor to [redacted], IQVIA back up medical support to [redacted], and IQVIA phone number for medical emergencies.		Emergency Contact Information
A single email address ([redacted]) is now used to report a Product Quality Complaint, independently from where it has originated.		Product Quality Complaints
Added the new secondary efficacy endpoint "Time to achieve enteral autonomy" and statistical methodology to be used.		Synopsis, Section 9.7.1.2, Section 9.7.2
Updated the information on the clinical studies with teduglutide in pediatric subjects to include the results of TED-C14-006.		Section 1.2
Clarified that teduglutide is the investigational product for this study.		Section 6.1
Updated the dose selection rationale with results from a simulation work using the previous population pharmacokinetic model. Based on the totality of clinical data, 0.05 mg/kg once daily is expected to provide comparable C_{max} concentrations in infants as compared to pediatric patients with SBS and was recommended as an evaluation dosing regimen in Study SHP633-301.		Section 6.2.5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2.1**	**Amendment Date** **04 Dec 2018**	**France-specific**
Description of Change and Rationale		**Section(s) Affected by Change**
Clarified that rescreening of subjects in the study will not be allowed. (Administrative amendment dated 03 Oct 2018)		Section 7.1.1
Clarifications were made to the definition of adverse events.		Section 8.1, Section 8.1.5, Section 8.2.4
Added heart failure with severe fluid overload, determined by the sponsor or investigator to be related to the investigational product, to the list of events leading to interruption of investigational product administration. This addition is in alignment with the warnings and special precautions listed in the investigator brochure.		Section 8.4
As recommended by the FDA, specified that if the DMC recommends termination of this pediatric study, the recommendations will be communicated to the relevant regulatory agencies within 7 calendar days.		Section 9.4
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout the protocol

See Appendix 1 for protocol history, including all amendments.

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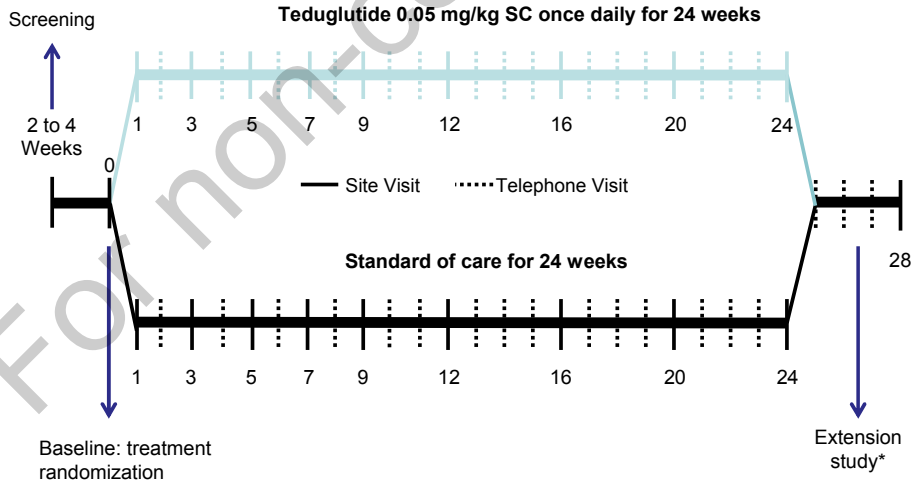
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
AUC_{ss}	area under the concentration-time curve at steady-state
$C_{max,ss}$	maximum plasma concentration at steady state
CRO	contract research organization
eCRF	electronic case report form
DMC	data monitoring committee
EDC	electronic data capture
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	glucagon-like peptide
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medicinal Journal Editors
I/O	oral fluid intake and urine output
IP	Investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PN	parenteral nutrition
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
SD	standard deviation
SOC	standard of care
ULN	upper limit of normal
US	United States

STUDY SYNOPSIS

Protocol number: SHP633-301	**Drug:** Teduglutide
Title of the study: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support	
Number of subjects (total and for each treatment arm): At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in a standard of care (SOC) comparator arm	
Investigator(s): Multicenter study	
Site(s) and Region(s): This study is planned to be conducted in approximately 5 to 10 sites globally.	
Study period (planned): 2017-2020	**Clinical phase:** 3
Objectives: The objectives of this clinical study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with short bowel syndrome (SBS) dependent on parenteral support.	
Investigational product, dose, and mode of administration: Teduglutide 0.05 mg/kg by subcutaneous (SC) injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm.	
Methodology: This is a randomized, multicenter, open-label study, consisting of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period.  * At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one "escape" criteria is met.	

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum 4 weeks). At the baseline visit (Week 0), subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for parenteral nutrition (PN) reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 or 12 (2 hours±10 minutes postdose).

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

Inclusion and Exclusion Criteria:

Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. Lack of terminal ileum and ileocecal valve
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.
8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.
9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µl due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2-week period
13. More than 3 serious complications of intestinal failure (e.g., catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.
19. Hypersensitivity to trace residues of tetracycline.

20. Signs of active severe or unstable, clinically significant hepatic impairment shown by any of the below laboratory test results at screening:

    a. Total bilirubin ≥2 x upper limit of normal (ULN)

    b. Aspartate aminotransferase (AST) ≥5 x ULN

    c. Alanine aminotransferase (ALT) ≥5 x ULN

    For subjects with Gilbert's disease:

    d. Indirect (unconjugated) bilirubin ≥2 x ULN

Maximum Duration of Subject Involvement in the Study:

The study consists of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

Endpoints:

Efficacy

Efficacy endpoints consist of the following:

Primary

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

Secondary

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by Week 24
- Time to achieve enteral autonomy
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to Week 24/EOT

Pharmacokinetics

The pharmacokinetic endpoint is plasma teduglutide concentration at nominal time point.

Safety

Safety endpoints consist of the following:

- Adverse events (AEs)
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

Health Economics and Outcomes Research

Health economics and outcomes research (HEOR) endpoints include the following:

- Cumulative number of hospitalization days during the study

Statistical Methods:

Efficacy

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm. Descriptive statistics will be used to summarize time to achievement of enteral autonomy by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

Pharmacokinetics

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.

Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (e.g., number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, serious adverse events will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores; and descriptive statistics (e.g., n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

Health Economics and Outcomes Research

The HEOR endpoints will be summarized descriptively.

STUDY SCHEDULES

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X													
Eligibility	X	X												
Randomization		X												
Demographics	X													
SBS history	X													
Medical and surgical history	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight	X	X	X		X		X		X		X			X
Length and head circumference	X	X					X							X
UGI/SBFT	X													
Safety labs and urinalysis[b, c]	X	X[b]	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	(X)	X
PK sampling[a]		X							[X][d]					[X][d]
Antibodies to teduglutide[a,e]		X												X[e]
Native GLP-2[f]	X													
Provide intake and output diaries[g]	X	X	X		X		X		X		X			X
Review diaries and nutritional support		X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support as needed[h]		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IP[a, i]		X	X		X		X		X		X			X

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Adjust IP dose[j]														X

EN=enteral nutrition; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PK=pharmacokinetics; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] Applicable to the teduglutide treatment arm only.

[b] At baseline, safety labs (Table 4) and PK can be separated by 1 day if blood volumes are limiting. Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline, and repeated if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity. Urine collection should be attempted, but inability to obtain urinalysis is not a protocol deviation.

[d] Subjects will have blood samples taken for teduglutide PK analysis predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the treatment period.

[e] Samples for antibody analysis will be drawn at the baseline and Week 12 visits. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.

[f] Blood samples for native GLP-2 should be collected postprandial. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

[i] The initial dose will be calculated based on body weight measured at baseline (Visit 0).

[j] The dose will be adjusted as needed, based on body weight measured at Week 12 visit.

Note: (X) denotes optional assessments; [X] denotes possible PK sampling time point (Refer to footnote "e".)

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Visit type	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**
Study day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**175**	**182**	**189**	**196**
±window (days)	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight				X				X				X				X
Length and head circumference				X				X				X				X
Safety labs and urinalysis[b,c]	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X
Antibodies to teduglutide[d,e]																X
Native GLP-2[f]												X				
Provide intake and output diaries				X				X				X				
Review diaries and nutritional support[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support as needed[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess follow-up period escape criteria[d]													X[i]	X[i]	X[i]	X
Dispense IP[d]				X				X								

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Visit type	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site
Study day	91	98	105	112	119	126	133	140	147	154	161	168	175	182	189	196
±window (days)	±3	±3	±3	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4

EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] At EOS subjects may enroll in an extension study, if subjects require treatment before the end of the 4-week follow-up they may enter the extension study immediately.

[b] Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR are tested if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity.

[d] Applicable to the teduglutide treatment arm only.

[e] Samples for antibody analysis will be drawn at the EOS (Week 28) visit.

[f] Blood samples for native GLP-2 should be collected postprandial. Blood samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.
Note: (X) denotes optional assessments.

[i] If a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.

1. BACKGROUND INFORMATION

1.1 Short Bowel Syndrome

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal diseases that result in major surgical resections of the small intestine (O'Keefe et al., 2006). Unlike the adult population, the majority of cases of SBS in pediatric subjects are due to congenital anomalies or catastrophic events that occur during infancy such as necrotizing enterocolitis, gastroschisis, intestinal atresia, midgut volvulus, or long-segment Hirschsprung disease (Beattie et al., 2010; Goulet and Ruemmele, 2006). A Canadian population-based study in neonates estimates an overall incidence of SBS to be 24.5 cases per 100,000 live births (Wales et al., 2004).

The small intestine is capable of remarkable adaptation, but excessive loss of absorptive surface area or specialized functions can lead to dependence on parenteral nutrition (PN)[1] fluids (O'Keefe et al., 2006). Although PN is life-sustaining in intestinal failure, it is associated with serious complications, including liver disease, life-threatening catheter-related blood stream infections, and central venous thrombosis (Beattie et al., 2010; Goulet and Ruemmele, 2006). Dependence on PN is also associated with reduced quality of life in both patients and caregivers and has an extremely high cost of care (Huisman-de Waal et al., 2007). About 30% of infants with SBS become independent of PN requirements within 12 months of the initial insult, and an additional 10% wean off PN within 24 months. After this time, linear intestinal growth slows. It is estimated that 42% to 86% of pediatric patients with SBS are able to become independent of PN within 1 to 3 years (Gonzalez-Hernandez et al., 2017; Khan et al., 2015; Squires et al., 2012). Nevertheless, despite optimal medical management, some children remain dependent on PN for many years (Squires et al., 2012). Infants who have less than 10% of expected small intestinal length for their gestational age have a low likelihood of ever achieving enteral autonomy (i.e., independence from parenteral support). Providing the maximum tolerated amount of enteral nutrition (EN) has been the primary strategy to promote enteral adaptation (Spencer et al., 2005).

Accelerating the adaptive process and achieving enteral autonomy is an urgent goal for all patients with SBS who are dependent on PN (Khan et al., 2015; Squires et al., 2012). The adaptive process is in part controlled by glucagon-like peptide 2 (GLP-2), a 33 amino acid peptide hormone secreted from L-type enteroendocrine cells in the terminal ileum and colon in response to luminal nutrients and bile acids (Martin et al., 2006). The post-prandial plasma concentration of GLP-2 in infants with SBS correlates with length of the remaining small intestine (Sigalet et al., 2004). Infants who lack terminal ileum may have impaired adaptation due to inadequate production of GLP-2.

[1] For the purpose of the study the terms parenteral support (PS) and parenteral nutrition (PN) are used interchangeably.

1.2 Teduglutide

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$), approximately 2 hours in healthy adult subjects, 1.3 hours in adult SBS subjects, and 0.22 hours in pediatric SBS subjects, compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines (Tappenden et al., 2013; Thymann et al., 2014).

A Phase 3 study, TED-C13-003, has been completed in pediatric SBS subjects. In this study, teduglutide was administered to 3 cohorts of pediatric subjects from ages 1-17 years. Thirty-seven pediatric subjects received teduglutide at doses of 0.0125, 0.025, or 0.05 mg/kg/day for 12 weeks. Five additional pediatric subjects were enrolled in an observational standard of care (SOC) cohort. There were clear dose-dependent effects of teduglutide seen at the 0.025 and 0.05 mg/kg/day doses compared to SOC and the 0.0125 mg/kg/day dose. In the 0.025 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 37%, including complete independence from PN support in 1 subject, and a reduction of 3.94 hours per day infusion time. In the 0.05 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 39%, including complete independence from PN support in 3 subjects, and a reduction of 4.18 hours per day infusion time. Teduglutide was generally safe and well tolerated by pediatric subjects in all dosing cohorts. There were no deaths during the study and no treatment-emergent serious adverse events (SAEs) related to teduglutide were reported. No discontinuations from study were due to adverse events (AEs). Additional studies in pediatric patients with SBS are ongoing.

TED-C14-006 is a recently completed study of pediatric subjects through 17 years which included 2 treatment arms: a teduglutide treatment arm and a SOC treatment arm. Subjects in both arms participated in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the screening period, subjects chose into which arm to enroll. During the 24-week treatment period, subjects in the SOC treatment arm received standard medical therapy for SBS; while those in the teduglutide treatment arm received daily subcutaneous (SC) injections of teduglutide (study drug) in addition to standard medical therapy. The subjects enrolling in the teduglutide treatment arm were randomized 1:1 in a double-blinded manner into 2 parallel dose groups: 0.025 mg/kg/day or 0.05 mg/kg/day of teduglutide administered subcutaneously for 24 weeks. Compared to the SOC, treatment of pediatric subjects with SBS with teduglutide resulted in clinically meaningful reductions in PN/IV volume, calories, days per week, and hours per day. A total 10% of subjects who received teduglutide achieved enteral autonomy within 24 weeks despite prior dependence on PN/IV for several years. Teduglutide treatment also resulted in increases in EN volume and caloric intake as well as plasma citrulline.

Although the differences in efficacy between the 0.025 and 0.05 mg/kg dose groups were small, a consistently greater effect was seen in the 0.05 mg/kg dose in all efficacy parameters. The pharmacokinetic (PK) properties were well characterized in this population and were consistent with the prior 12 week pediatric study. Teduglutide was generally well tolerated by pediatric subjects with SBS. The safety profile was favorable and consistent with the prior pediatric study, the underlying disease, and previous experience with teduglutide in adult subjects with SBS.

Teduglutide (0.05 mg/kg/day) is currently approved for the treatment of adult patients with SBS in >30 countries. On 29 Jun 2016, the European Commission granted an extension of the Market Authorization for teduglutide for the treatment of patients aged 1 year and above with SBS.

Always refer to the latest version of the investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy and safety of teduglutide (SHP633).

2. OBJECTIVES

2.1 Rationale for the Study

There is no approved pharmacological therapy to improve intestinal adaptation in infants with SBS who are dependent on parenteral support. This study will evaluate whether teduglutide is safe and effective in this patient population.

2.2 Study Objectives

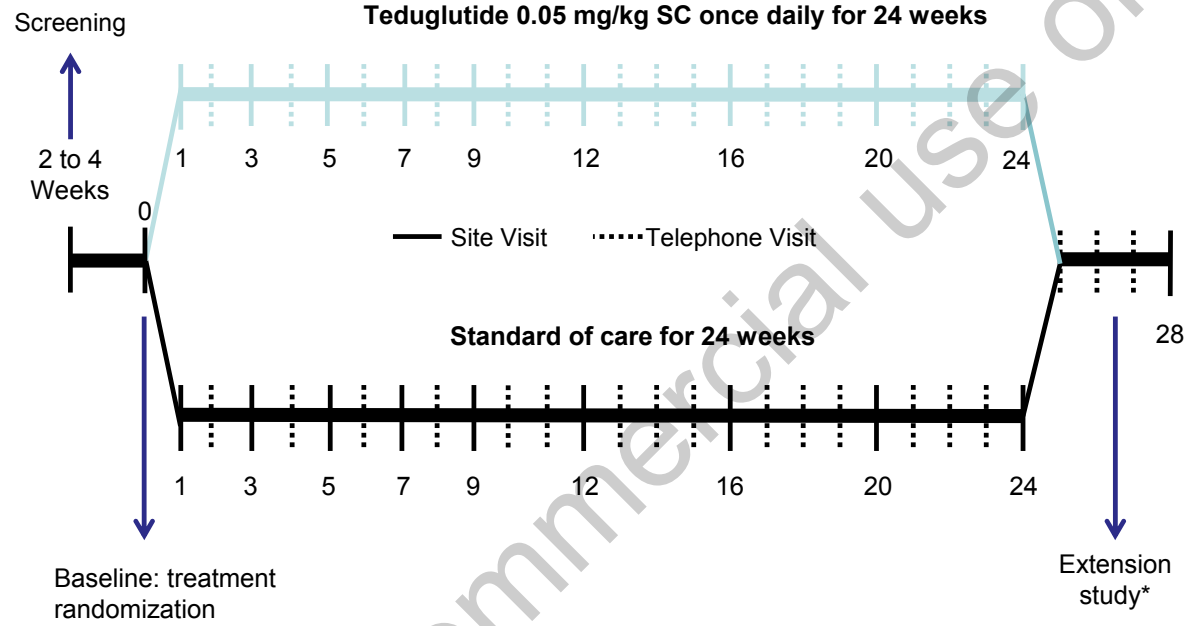
The objectives of this study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with SBS dependent on parenteral support.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a randomized, multicenter, open-label study, consisting of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. A schematic representation of the study design is presented in Figure 1.

Figure 1: Study Schematic



*At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one "escape" criteria is met.

3.1.1 Screening Period

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum: 4 weeks). The schedule of evaluations to be conducted during the Screening Period can be found in Table 1.

3.1.2 Treatment Period

At the baseline visit (Week 0), subjects will randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS, while those in the teduglutide arm will receive 0.05 mg/kg by SC injection once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for PN reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability (Appendix 2). Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 or 12 (2 hours±10 minutes postdose).

The schedule of evaluations for the Treatment Period can be found in Table 1 (Visits -1 to 12) and Table 2 (Visits 13 to 28).

3.1.3 Follow-up Period

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product (IP) will be administered. At EOS, all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS visit if at least one of the following “escape” criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

The schedule of evaluations for the Follow-up Period can be found in Table 2 (Visits 13 to 28).

3.2 Study Duration

The study consists of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

3.3 Sites and Regions

This study is planned to be conducted at approximately 5 to 10 sites globally.

4. STUDY POPULATION

At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in an SOC comparator arm.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. Lack of terminal ileum and ileocecal valve.
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.
8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.

9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µL due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2 week period.
13. More than 3 serious complications of intestinal failure (e.g., catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.
19. Hypersensitivity to trace residues of tetracycline.
20. Signs of active severe or unstable, clinically significant hepatic impairment shown by any of the below laboratory test results at screening:
    a. Total bilirubin ≥2 x upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥5 x ULN
    c. Alanine aminotransferase (ALT) ≥5 x ULN

For subjects with Gilbert's disease:

    d. Indirect (unconjugated) bilirubin ≥2 x ULN

4.3 Reproductive Potential

Not applicable; this study will enroll infants.

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (e.g., in the interest of subject safety). The investigator should discuss withdrawal of a subject from investigational product with the medical monitor as soon as possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT/early termination are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period. Comments (spontaneous or elicited) or complaints pertaining to IP discontinuation made by the subject must be recorded in the source documents. The reason for discontinuation, the date and the total amount of investigational product administered must be recorded in the electronic case report form (eCRF) and source documents.

Subjects who discontinue will not be replaced.

4.4.1 Reasons for Discontinuation

The reason(s) for permanent discontinuation of treatment and/or withdrawal from the study must be determined by the investigator, and recorded in the subject's medical record and in the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document, and the most clinically relevant reason should be entered in the eCRF.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by parent/guardian
- Lack of efficacy
- Other

4.4.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact the parent(s)/guardian(s) of any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Medications and Procedures

Prior treatment includes all treatment and procedures (including but not limited to prescription treatments, herbal treatments, vitamins, non-pharmacological treatment, as appropriate) received within 14 days prior to the screening visit (Visit -1) (or pharmacokinetic equivalent of 5 half lives, whichever is longer, must be recorded on the appropriate eCRF page.

5.2 Concomitant Medications and Procedures

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins) and PN must be recorded from the first dose of investigational product and for the duration of the study in the appropriate sections of the eCRF. Any diagnostic, surgical or other therapeutic treatments received by a subject during the course of the study will also be recorded on the eCRF.

The mechanism of action of teduglutide may increase enteral absorption of oral drugs (e.g., drugs used for management of SBS such as motility medication, opioids, psychotropics, metronidazole), so consideration should be given to modifying concomitant enteral medication regimens. Titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic index (e.g., warfarin, digoxin, psychotropics) are given.

5.3 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.4 Prohibited Treatment

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the pretreatment visit (Table 3):

Table 3: Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pretreatment Visit
Teduglutide	Any
GLP-2, human growth hormone, or analogs of these hormones	6 months
Octreotide, GLP-1 analogs, and enteral glutamine	30 days

GLP=glucagon-like peptide

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

The investigational product is teduglutide, which will be provided in sterile, single-use 3 mL vials containing 1.25 mg teduglutide as a white lyophilized powder to be reconstituted before use with 0.5 mL sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the current investigator's brochure.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

All investigative study sites will be initially provided with sufficient investigational product to randomly assign a subject into the study (for either of the proposed treatment groups). Randomization will occur through an interactive response system. Random assignment of a subject will trigger replacement supplies for that investigative study site.

6.2.2 Allocation of Subjects to Treatment

Subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy). The actual treatment given to individual subjects is determined by a randomization schedule.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined.

6.2.3 Dosing

The initial dose will be calculated based on body weight measured at baseline (Visit 0), and adjusted as needed, based on body weight measured at Week 12. No other adjustments to dose will be made during the teduglutide treatment period, unless discussed with the sponsor's medical monitor.

Following reconstitution, teduglutide will be administered by SC injection once daily (QD) into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used.

Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later.

The subject should be dosed at approximately the same time each day. Consecutive doses should be separated by at least 12 hours. Each day, the injection site should be alternated.

Any subject who achieves complete independence from PN support at any time during the treatment period will continue to receive teduglutide treatment.

The first SC injection in teduglutide-naïve subjects should be administered under the supervision of the investigator or designee and the subject observed for hypersensitivity reactions for at least 4 hours during their initial dosing visit. The site of administration (arm, thigh, and abdomen) of the first teduglutide dose must be specified and recorded in the eCRF.

Detailed instructions for reconstitution and injection of the investigational product can be found in the Instructions for Use.

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (e.g., weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.2.5 Dose Selection Rationale

Teduglutide is approved for adult and pediatric use in the EU at a dose of 0.05 mg/kg SC once daily. A completed 12-week dose finding study (TED-C13-003) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit-risk profile most meaningful at the 0.05 mg/kg/day dose (Carter et al., 2017).

Population pharmacokinetic modeling and simulations were conducted to determine the optimal dose to be used in pediatric subjects using data from 8 adult clinical studies including adult Phase 1 studies and Phases 2/3 studies as well as TED-C13-003 and suggested the same adult dose (0.05mg/kg) in pediatric subjects (aged between 1.67-14.7 years) (Marier et al., 2017).

To support dosing in the current age group, further PK simulation was conducted based on the population PK model previously established and a virtual population of 1000 pediatric patients created based on Centers for Disease Control (CDC) growth charts in the target age group (4 to 12 months) and taking into consideration body weights of pediatric patients with SBS enrolled in study TED-C13-003 and TED-C14-006 (approximately 15% lower than healthy subjects in the same age group). The model was customized by including a maturation function on clearance (CL/F) as a function of estimated glomerular filtration rate. Monte Carlo simulations for all age groups were performed according to the SC dosing regimens of 0.0125, 0.025 and 0.05 mg/kg every 24 hours. Rich concentration-time profiles were simulated with the customized population PK model to derive the exposure metrics area under the concentration curve at steady state (AUC_{ss}) and maximum concentration at steady state ($C_{max,ss}$). Exposure parameters in infant patients were compared to those derived in pediatric (1-17 years) and adult (≥18 years) patients with SBS using a Bayesian approach. Based on the clinical observations, C_{max} is considered to be associated with clinical responses. Following 0.05 mg/kg daily SC administration, the median $C_{max,ss}$ of teduglutide in neonate patients (24.9 ng/mL) was within 20% of that observed in the 2 to 4 and 4 to 6 years age groups (26.9 and 29.4 ng/mL, respectively); and approximately ~28% lower than that in adult patients with SBS. The median $C_{max,ss}$ of teduglutide in infant patients 4 to 12 months (41.9 ng/mL) following 0.05 mg/kg once daily was within 8% of that previously observed in adult patients with SBS (39.0 ng/mL, refer to the attached Simulation Report). In addition, individual simulated $C_{max,ss}$ values of teduglutide in infant patients 4 to 12 months (25.6 to 65.1 ng/mL) were contained within the range of $C_{max,ss}$ previously observed in pediatric patients 1 to 17 years (20.7 to 77.4 ng/mL). The clinical package in conjunction with C_{max} was considered to support teduglutide dose selection since AUC_{ss} was previously shown not to correlate with efficacy. Individual simulated AUC_{ss} values of teduglutide in infant patients 4 to 12 months (66.9 to 160 ng.h/mL) following 0.05 mg/kg once daily were contained within the range of AUC_{ss} values previously observed in pediatric patients 1 to 17 years (63.5 to 421 ng.h/mL). Based on the totality of clinical data, 0.05 mg/kg once daily is expected to provide comparable C_{max} concentrations in infants as compared to pediatric patients with SBS and was recommended as an evaluation dosing regimen in Study SHP633-301.

6.3 Labeling, Packaging, and Storage

6.3.1 Labeling

The investigational product will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of investigational product will be provided for this study. The vials will be labeled in accordance with applicable regulatory requirements.

Ancillary kits, containing supplies needed for the reconstitution and administration of the investigational product will also be provided and labeled in accordance with the applicable regulatory requirements.

All investigational product used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice.

6.3.2 Storage and Handling

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2-8°C (35.6-46.4°F) until dispensed to a subject. Once dispensed to a subject, the IP can be stored refrigerated or up to a controlled room temperature (acceptable range of 2-25°C, or 35.6-77°F). Parent/legal guardian will be instructed to keep the subject's IP and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the IP may be refrigerated. The IP is for single use only, and should be used within 3 hours following reconstitution.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (i.e., certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), e.g., fumigation of a storage room.

Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels, as they are distributed.

6.4 Drug Accountability

Investigational product will not be dispatched to the study site until the sponsor or designee has received all required documents from the study site in accordance with applicable regulatory requirements and relevant standard operating procedures. Upon receipt, the study site's pharmacist or delegate is responsible for ensuring that all investigational product received at the site is inventoried and accounted for throughout the study. A copy of the shipping documents must be maintained for the investigator's records. Kits will be shipped to the site once the subject is screened.

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (e.g., a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Investigational product kits will be dispensed at each of the applicable study visits at which the subject is required to be at the clinic. Each investigational product kit is sufficient for a treatment period of 1 week and enough kits will be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

Each subject will be given the investigational product according to the protocol. The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. All dispensed medication will be documented on the eCRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, subject returned investigational product, and empty/used investigational product packaging are to be sent to the sponsor or designee. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

Returned investigational product must be counted and verified by clinical site personnel and the sponsor (or study monitor). Shipment return forms, when used, must be signed prior to shipment from the site. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

The parent(s)/guardian(s) of subjects must be instructed to bring unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed and recorded at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (e.g., bottles, trays, vials) or at the individual count level for opened containers/packaging.

Subject compliance will be checked by site personnel at every visit by reviewing the subject diaries and asking the subject or the subject's parent or legally-authorized representative if they have administered the investigational product according to instructions. If any doses have been missed, the reason for missed dose should be documented in the subject's source documentation including, as applicable, the eCRF.

The investigator is responsible for contacting the sponsor or designee when the subject's daily investigational product dosing regimen is interrupted. Attempts should be made to contact the sponsor or designee prior to dose interruption. Reasons for dosage interruption may include but are not limited to hospitalization and AEs, a lapse in investigational product delivery, etc.

Subjects who have received 80% of the planned doses administered will be assessed as being compliant with the study protocol.

7. STUDY PROCEDURES

7.1 Study Schedule

Detailed study procedures and assessments to be performed for subjects throughout the study are outlined in the study schedules (Table 1 and Table 2) and must be referred to in conjunction with the instructions provided in this section.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period.

7.1.1 Screening

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the parent(s)/guardian(s) of the subject. The screening visit assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1. Rescreening will not be allowed.

7.1.2 Treatment Period

The randomized Treatment Period will comprise Weeks 1 to 24, during which all assessments will be performed as outlined in Table 1 and Table 2.

7.1.3 Follow-up Period

The Follow-up Period will comprise Weeks 25 to 28, during which all assessments will be performed as outlined in Table 2.

7.2 Study Evaluations and Procedures

7.2.1 Demographics and Other Baseline Characteristics

Demographics and Medical History

Demographic and/or other baseline variables obtained at the screening and/or baseline visits are listed below. Abnormal findings of clinical significance (if any) will be recorded as past medical history.

- Demography (including age, gestational age, sex, and race)
- Medical history (including surgical history)
- SBS history, including remnant anatomy

Upper Gastrointestinal Series with Small Bowel Follow-through

An upper GI contrast series with small bowel follow-through will be performed on all subjects during the screening period if one has not been done since the subject's last GI surgery.

It is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow-through performed since the subject's most recent surgery.

7.2.2 Efficacy Assessments

Subject Diaries

All available diary data will be reviewed by the investigator or their designee at each clinic and telephone visit to assess clinical status and opportunity for PN reduction and advance in feeds. Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

Intake Diary

Intake diaries will be used to collect and evaluate each subject's nutritional support. The parent/legally authorized representative/study site staff will complete the appropriate fields of the PN and EN sections of the intake diary daily throughout the study.

The following data will be captured in the intake diaries:

- Parenteral support volume and infusion duration
- Enteral nutrition (formula) including volume and calories

Site personnel will determine the actual PN and EN daily calories based on diary entries.

Output Diary

Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit; in addition, output should be recorded for subjects within 1 week of implementing a change in the PN prescription.

Urine data:

- Measure and record the weight of all urine-only diapers. Urine volume will be calculated using the following formula: 1 g (scale weight) = 1 mL or 1 cc
- At the discretion of the investigator, the parent or legal guardian/study site staff may be asked to collect the first void after the daily PN infusion to measure specific gravity

Stool data (includes diapers with mixed urine and stool):

- Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency (see Output diary). Stool volume will be calculated using the formula: 1 g (scale weight)=1 mL or 1 cc

All ostomy output volume should be recorded.

Native GLP-2

Blood samples for native GLP-2 should be collected postprandial. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

7.2.3 Safety Assessments

Laboratory Evaluations

Safety laboratory tests to be performed at site visits consist of clinical chemistry, hematology, and urinalysis and will be performed as outlined in the study plan (Table 1 and Table 2). Scheduled laboratory testing will be processed by a central lab. All laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the laboratory. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

During the Treatment Period, subjects will also have safety labs within approximately 5 to7 days after a PN adjustment. Safety labs performed after PN adjustment and between site visits will consist of clinical chemistry and urinalysis and may be processed by the central laboratory or a local laboratory. Local lab results are not required to be entered in the eCRFs; however, if the local lab results indicate any new clinically significant changes, they must be reported as an adverse event (see Section 8). Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

At baseline, blood samples for safety labs and PK can be separated by 1 day if blood volumes are limiting.

Safety labs at telephone visits will be collected at the discretion of the investigator.

For all subjects in the teduglutide treatment arm, prothrombin time (PT) and international normalized ratio (INR), tested at baseline, will be repeated if clinically indicated.

New clinically significant labs should be reported as AEs.

Close Monitoring Criteria Related To Liver Test Abnormalities:

The investigator should contact the medical monitor within 24 hours of their awareness if the subject develops any of the following changes in laboratory parameters:

- ALT or AST >5x ULN and >2x baseline value
- Total or direct bilirubin that is >2x baseline value or an absolute increase of ≥3 mg/dL (51.3 µmol/L)

If such changes are observed, the labs should be repeated along with an INR, and an inquiry should be made as to the presence of clinical symptoms consistent with new liver injury. The subject should be followed closely to determine the trajectory of the laboratory abnormalities and appropriate evaluations should be made, such as abdominal ultrasound with Doppler imaging to exclude vascular causes and biliary obstruction, consideration of sepsis, liver hypoperfusion, acute viral hepatitis (such as hepatitis A, EBV, or HSV), exposure to hepatotoxic medications, mitochondrial hepatopathy, or metabolic liver disease (such as hereditary fructose intolerance or arginosuccinate synthetase deficiency). Further evaluations can be performed at the discretion of the investigator in consultation with the Shire medical monitor.

The following clinical laboratory assessments will be performed according to the study schedules:

Table 4: List of Laboratory Tests

Biochemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bicarbonate
- Bilirubin (total and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- C-reactive protein
- Creatinine
- Estimated Glomerular Filtration Rate (Schwartz formula)
- Gamma-glutamyl transferase
- Glucose
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Triglycerides

Hematology[a]:
- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- Red blood cell morphology, if needed
- White blood cell count with differential

Coagulation[b]:
- Prothrombin time
- International normalized ratio

Urinalysis:
- Specific gravity
- Urine Sodium

[a] Hematology is not collected at Week 1 or at telephone visits.
[b] For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline and repeated only if clinically indicated.

Antibodies to Teduglutide

Blood samples will be drawn to test for antibodies to teduglutide. Samples will be taken before teduglutide administration at the screening visit (Visit -1) and at least 14 hours after the previous dose at Week 12 (Visit 12); samples may be drawn from a central line or peripheral access. One additional sample will be collected at the EOS 4 weeks after the EOT (i.e., Week 28 or EOS).

Volume of Blood

Efforts will be made to minimize the amount of blood drawn from all pediatric subjects participating in this study. The volumes of blood to be drawn from each subject will vary depending on clinical status. Approximate volumes of blood to be drawn from each subject are shown in Table 5.

Table 5: Approximate Volume of Blood to be Drawn from Each Subject

Assessment	Sample Volume (mL)	No. Samples	Total Volume (mL)	Notes
Subjects Receiving Teduglutide Treatment				
Biochemistry	0.6	12	7.2	
Hematology	0.6	11	6.6	
Coagulation Parameters	0.6	1	0.6	PT and INR tested at baseline only, repeat while on study only if clinically indicated.
Antibodies	1.5	5	7.5	
Pharmacokinetics	1.5	4	6.0	Baseline: 3 timepoints Week 7: 1 timepoint OR Week 12: 1 timepoint
Native GLP-2	1.5	3	4.5	
Total mL:	**6.3**	**36**	**32.4**	
Subjects Receiving Standard of Care				
Biochemistry	0.6	12	7.2	
Hematology	0.6	11	6.6	
Native GLP-2	1.5	3	4.5	
Total mL:	**2.7**	**26**	**18.3**	

GLP=glucagon-like peptide; INR=international normalized ratio; PT=prothrombin time

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments should be combined. Blood volume estimates do not include safety labs performed after PN adjustments.

Consistent with standard medical practice, efforts to minimize pain and discomfort during procedures such as peripheral venipuncture should be implemented as applicable. This may include oral sucrose solutions, a pacifier, distraction techniques, and the use of topical anesthetic such as EMLA.

Physical Examinations, Vital Signs, Weight, Length, and Head Circumference

Physical examinations will be performed according to the study schedules (Table 1 and Table 2). Any new clinically significant findings noted during physical examinations should be recorded on the appropriate AE page of the eCRF.

Vital signs will be measured according to the study schedules. Measurements will include systolic and diastolic blood pressure (mmHg), pulse (beats per minute), and body temperature (°C/°F). Blood pressure should be determined by the appropriate size cuff (using the same method, the same leg, and in the supine position throughout the study, when possible). Blood pressure measurements should be attempted as part of the vital signs, but lack of blood pressure results will not constitute a protocol deviation. New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Length and head circumference will be measured at selected visits. A height z-score, weight Z-score, and weight/length ratio will be calculated by the sponsor using the site-provided height and weight data collected at each site visit.

7.2.4 Pharmacokinetic Assessments

Subjects will have blood samples taken for teduglutide PK analysis predose, and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the treatment period. Blood for PK sampling should be collected via peripheral IV or venipuncture, not from a central line. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified.

7.2.5 Health Economics and Outcomes Research

Hospitalizations

Each hospitalization that occurs during the study will be recorded, including date of admission, date of discharge, reasons for hospitalization, discharge diagnosis, and discharge status.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, or a symptom is more severe or prolonged than expected given the diagnosis, then symptom(s) should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

AEs that are related to IP that are not resolved at EOS will be followed until the event resolves or stabilizes, as judged by the investigator.

Laboratory values, vital signs, and clinical findings at the scheduled physical examinations must be reported as AEs if the investigator considers the finding to be a clinically significant change from the baseline.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. It is assumed that some of the infants participating in this study may be hospitalized for planned surgery(ies) that will occur during their participation in the study. Such pre-planned, elective surgeries, do not need to be reported as SAEs for this protocol.

8.1.5 Clinical Laboratory and Other Safety Evaluations

An untoward change in the value of a clinical laboratory parameter, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. Clinical significance is defined as any abnormal finding that results in further clinical investigation(s), treatment(s), or the diagnosis of new or progression of established condition. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, or ECG values which were not present at the beginning of the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory value, vital sign, or ECG parameter is clinically significant and represents an AE.

8.1.6 Pregnancy

Not applicable.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (e.g., to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.

- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Administration of a dose greater than the allocated dose of the study medication or at a frequency greater than the dosing interval specified by the protocol.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally-authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

All Adverse Events of Special Interest, as defined in Section 8.3, must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event even if the event does not fulfill seriousness criterion.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol, and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested). Fax or e-mail the completed form to the Shire Global Drug Safety Department. A copy of the completed Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the Shire medical monitor or designee using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3, and must be reported to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (i.e., the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (e.g., drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The Sponsor and/or Clinical Contract Research Organization (CRO) is responsible for notifying the relevant regulatory authorities, and US central Institutional Review Boards (IRBs)/EU central ethics committees (ECs), of related, unexpected SAEs.

In addition, the Clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP633 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

8.3 Adverse Events of Special Interest

An AE of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program and for which ongoing monitoring and immediate notification by the investigator to the sponsor is required.

The AEs of special interest that require expedited regulatory reporting include the following:

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the GI tract including the hepatobiliary system
- Tumor-promoting ability (e.g., benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

For AEs of special interest, the sponsor must be informed within 24 hours of first awareness as per the SAE notification instructions described in Section 8.2.2 even if the event does not fulfill the seriousness criteria.

8.4 Dose Interruption Criteria

The investigator is responsible for contacting the sponsor/designee when the subject's teduglutide dosing regimen is interrupted. The length of dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

Investigational product must be interrupted if any of the following events occur:

- An adverse event of special interest (see Section 8.3)
- Intestinal obstruction
- Biliary obstruction
- Pancreatic duct obstruction
- Heart failure with severe fluid overload determined by the sponsor or investigator to be related to IP.

Investigational product must be permanently discontinued if any of the following events occur:

- Severe hypersensitivity, such as anaphylaxis, determined by the investigator to be related to IP.
- Any malignancy

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Process

The study will be analyzed by the sponsor or designee. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, US) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the definitions and statistical methods for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

9.4 Planned Interim Analysis, and Data Monitoring Committee

No interim analyses is planned for this the study.

A data monitoring committee (DMC) will be involved in the management of this study. The DMC members will review the data approximately every 3 months according to the DMC Charter. The DMC review will include all cumulative safety data (i.e., AEs, laboratory assessments, physical examinations, etc.) from study assessments through each cutoff period. Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of investigational product.

The DMC for this study will be conducted in accordance with the FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006).

The DMC will be an external, independent board comprised of physicians with relevant training. The DMC will be restricted to individuals free of significant conflicts of interest, including, but not limited to, financial, scientific, or regulatory in nature. The DMC will be governed by a Charter agreed to by members of the Board and the sponsor. Members of the Board may not be study investigators or be employed at the same institution as a study investigator, individuals employed by the sponsor, independent contractors hired by the sponsor, or members of regulatory agencies. The DMC may make recommendations to the sponsor regarding study aspects including stopping, modifying or continuing the study; however, the sponsor will have the final responsibility to determine whether the study should be modified or temporarily or permanently stopped. If the DMC recommends termination of this pediatric study, the recommendations will be communicated to the relevant regulatory agencies within 7 calendar days.

9.5 Sample Size Calculation and Power Considerations

The sample size is determined based on enrollment feasibility for this rare condition and the age of the study population.

9.6 Study Population

Intent to treat (ITT) population: All subjects randomized in the study.

Safety analysis population: The safety analysis set will contain all subjects who meet the following criteria:

- Teduglutide treatment arm: subjects who receive at least 1 dose of teduglutide and have undergone at least 1 post-baseline safety assessment; analyses will be performed according to dose group as appropriate.
- Standard of care treatment arm: subjects who have undergone at least 1 post-baseline safety assessment.

Per-protocol population: All subjects in the ITT population without any major protocol deviation that affects interpretation of efficacy results.

Pharmacokinetic analysis population: All subjects who received at least 1 dose of teduglutide and have at least 1 evaluable postdose PK concentration value.

9.7 Efficacy Analyses

9.7.1 Efficacy Endpoints

Efficacy endpoints consist of the following:

9.7.1.1 Primary Efficacy Endpoint

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

9.7.1.2 Secondary Efficacy Endpoints

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by Week 24
- Time to achieve enteral autonomy
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT

9.7.2 Method of Analysis-Efficacy Endpoints

Due to the limited size of the study population, descriptive statistics will be used with a goal of summarizing the sample. As such, no claims of significance will be made for any of the data. Continuous variables will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm. Descriptive statistics will be used to summarize time to achievement of enteral autonomy by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

9.8 Safety Analyses

9.8.1 Safety Endpoints

Safety endpoints consist of the following:

- Adverse events
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

9.8.2 Method of Analysis-Safety Endpoints

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (e.g., number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, SAEs will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores, and descriptive statistics (e.g., n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

9.9 Health Economics and Outcomes Research Analyses

Health economics and outcomes research endpoints consist of the following:

- Cumulative number of hospitalization days during the study

Health economics and outcomes research endpoints will be summarized using descriptive statistics (number, mean and standard deviation) at nominal time points.

9.10 Pharmacokinetics Analyses

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points.

Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (e.g., CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP.

This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly. The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator will be appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Electronic Case Report Forms

Electronic case report forms are supplied by the sponsor or designee and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data will be recorded directly onto the eCRF.

All data sent to the sponsor must be endorsed by the investigator.

The study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diaries, and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the parent/guardian agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (e.g., subject's medical file, appointment books, original laboratory reports, X-rays etc). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (e.g., the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent, where applicable, from the parent(s)/guardian(s) of all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject's legally authorized representative is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject's parent or guardian has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (i.e., a complete set of subject information sheets and fully executed signature pages) must be given to the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (i.e., sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor/designee has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor/designee.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market teduglutide; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (e.g., to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (e.g., Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2 to 4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

11. REFERENCES

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	03 Oct 2017	Global
Amendment 1	18 Jan 2018	Global
Amendment 1.1	07 Aug 2018	France-specific
Amendment 2.1	04 Dec 2018	France-specific

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1.1**	**Amendment Date** **07 Aug 2018**	**France-specific**
Description of Change and Rationale		**Section(s) Affected by Change**
The Shire contact was updated to [redacted].		Emergency Contact Information
Added an exclusion criterion for Gilbert's disease and liver failure based on the values of the transaminases and of total bilirubin as requested by Agence Nationale de Sécurité du Medicament et des Produits de Santé (ANSM).		Synopsis, Section 4.2
Added an exclusion criterion for hypersensitivity to trace residues of tetracycline to be consistent with the European Summary of Product Characteristics of teduglutide as requested by ANSM.		Synopsis, Section 4.2
Added text to specify that efforts to minimize pain and discomfort during procedures such as peripheral venipuncture will be implemented.		Section 7.2.3

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **18 Jan 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Updated emergency contact information to reflect the change of the Contract Research Organization's name.		Emergency Contact Information
Clarified the duration of the screening period and total time on study. Provided a clear definition of study completion. Updated the study schematic to reflect the study design changes.		Synopsis, Section 3.1, Section 3.2
Revised the telephone and clinic visit schedule to assure laboratory measurement could be collected without exceeding weekly/monthly total blood volume restrictions.		Synopsis, Table 1, Section 3.1.2
Moved the PK sampling from Week 6 to Week 7 so that the samples could be collected without exceeding weekly/monthly total blood volume restrictions. Clarified that blood for pharmacokinetic samples of postdose may be taken within ± 10 minutes of the time pre-specified.		Synopsis, Table 1, Section 3.1.2, Section 7.2.4, Table 5
Clarified that end jejunostomy or ileostomy are examples of small bowel ostomy rather than the stratification factors.		Synopsis, Section 3.1.2, Section 6.2.2
Clarified that all subjects regardless of treatment arm are eligible for the extension study.		Synopsis, Section 3.1.3
Clarified that if a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.		Synopsis, Table 2, Section 3.1.3, Section 6.2.3

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **18 Jan 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Clarified that subjects must be 4 to 12 months corrected gestational age at screening.		Synopsis, Section 4.1
Changed dose adjustments to Week 12 rather than at every clinic visit to reduce site burden.		Synopsis, Table 1, Section 6.2.3
Clarified the definition of enteral autonomy.		Synopsis, Section 9.7.2
Updated the pharmacokinetic endpoint and analysis to reflect that only descriptive statistics will be calculated on plasma teduglutide concentration values. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.		Synopsis, Section 9.10
Removed assessment of the 5-level EuroQol five dimensions questionnaire to reduce caregiver burden.		Synopsis, Table 1, Section 7.2.5, Section 9.9
Clarified that native GLP-2 samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.		Table 2, Section 7.2.2
Inserted a footnote to clarify that parenteral support and parenteral nutrition are used interchangeably.		Section 1.1
Removed the 5 mg vial of teduglutide as this size vial will not be supplied for this study.		Section 6.1
Clarified the procedures for assessing subject compliance.		Section 6.5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **18 Jan 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Specified that it is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow through performed since the subject's most recent surgery.		Section 7.2.1
Corrected the volume of blood to be collected for native GLP-2.		Table 5
Removed references to subject assent as assent is not possible in a study of infants.		Section 7.1.1, Section 10.3.1
Clarified the definitions of the analysis sets.		Section 9.6
Clarified that an adjustment to enteral nutrition as appropriate is part of the PN/IV adjustment algorithm.		Figure A-1
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout protocol.

Appendix 2 Guidelines for Nutritional Support Management During the Study

The nutritional support adjustment guidelines are designed to standardize management of parenteral and enteral nutritional support in this study. Adjustments to nutritional support should be considered at every scheduled clinic visit. Adjustments at phone visits may also be performed, but nutritional assessments at phone visits serve primarily to confirm that nutritional adjustments at prior clinic visits were tolerated.

All attempts should be made to follow the guidelines, but departure from the guidelines will not constitute a protocol deviation.

Clinical judgment is required within the algorithm. Each decision point requires integrating multiple sources of information into a yes/no decision. When individual data points are conflicting, the investigator must use their best judgment in the assessment.

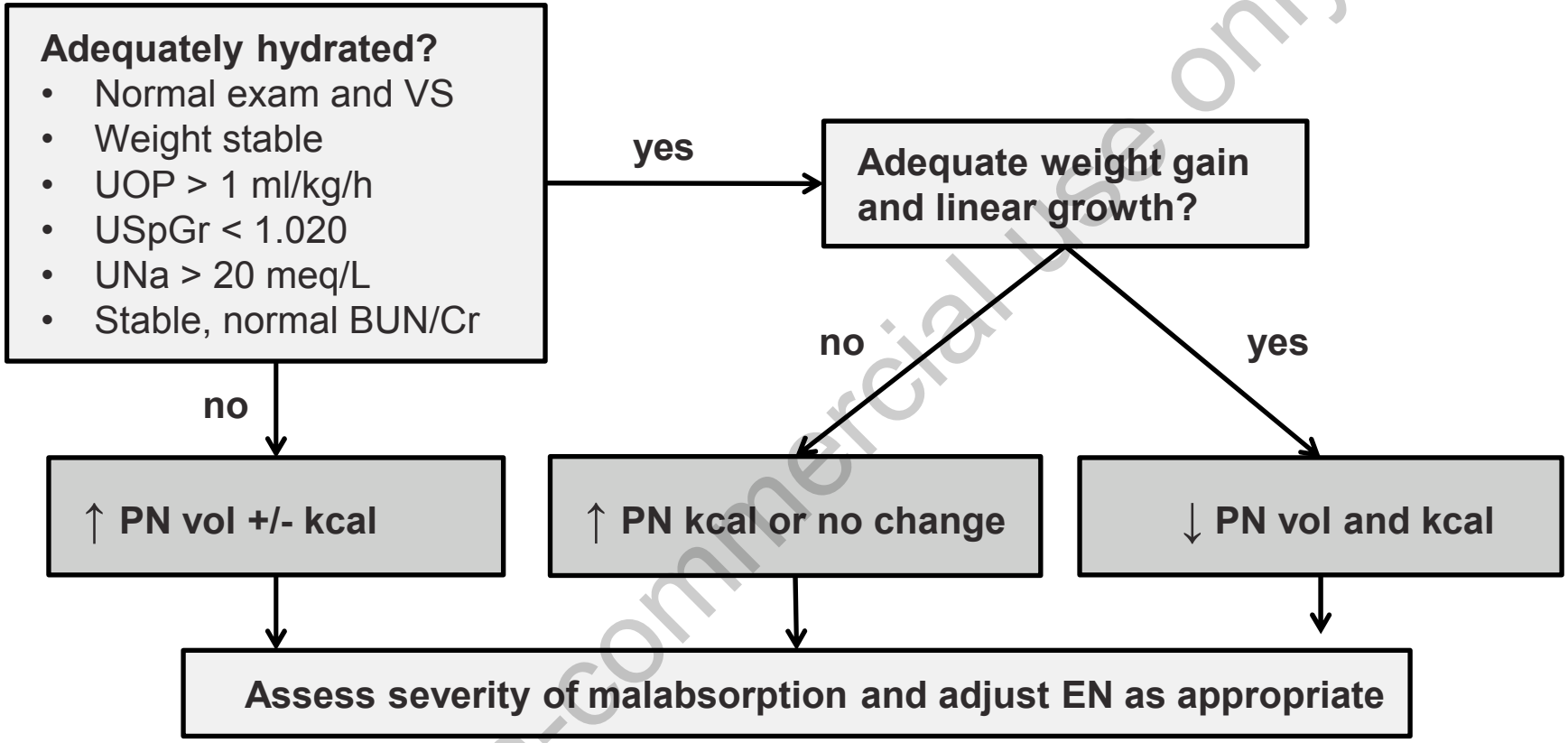
If intestinal adaptation is occurring, reductions in parenteral support volume and calories are expected to be in decrements of 5 to 10% relative to baseline values. Parenteral support components are at the discretion of the investigator, but care should be taken to balance carbohydrate, fat, and protein. Likewise, if intestinal adaptation is occurring, enteral nutrition volume and calories should be increased in increments of approximately 10% relative to baseline values.

Assessment of the severity of malabsorption may require estimation of stool output for children who have mixed stool and urine output.

Adjustments should be based on the actual nutritional support in volume and calories the subject infuses. Subjects should remain compliant with the nutritional support prescription in volume and calories during the study.

During the 48-hour output measurement period prior to the subject's scheduled visit, no further changes to the prescribed nutritional support should be made.

Figure A-1: Parenteral Nutrition/Intravenous Adjustment Algorithm for All Subjects



BUN=blood urea nitrogen; Cr=creatinine; PN=parenteral nutrition; UNa=urine sodium; UOP=urine output; USpGr=Urine specific gravity; VS=vital signs; vol=volume

PROTOCOL: SHP633-301

TITLE:	A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support
NUMBER	SHP633-301
PHASE	3
DRUG:	Teduglutide
INDICATION:	Short bowel syndrome
EUDRACT NO.:	2017-003606-40
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA
PROTOCOL HISTORY:	Original Protocol: 03 Oct 2017 Amendment 1: 18 Jan 2018 Amendment 2: 04 Dec 2018 Amendment 3: 24 May 2019

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** [redacted]
[redacted], MD PhD [redacted], Global Clinical Development	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-301.

Title: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	_____ _____ _____

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the Shire Medical Monitor by e-mail at [redacted].

For protocol- or safety-related issues, the investigator must contact IQVIA Medical Support:

Primary Contact	**Backup Contact**
[redacted], MD	[redacted], MD, PhD
[redacted]	[redacted]
Mobile: [redacted]	Mobile: [redacted]
Phone: [redacted] (medical emergencies)	Phone: [redacted] (medical emergencies)
Email: [redacted]	Email: [redacted]

In addition, the investigator may also contact Shire:

[redacted], MD

Mobile Phone: [redacted]

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the E-mail address below to report the Product Quality Complaint:

[redacted]

Telephone numbers (provided for reference, if needed):

Shire (USA)
[redacted]

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **24 May 2019**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Deleted Inclusion Criteria #6, Lack of terminal ileum and ileocecal valve, due to difficulties in enrollment.		Synopsis, Section 4.1
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout the protocol

See Appendix 1 for protocol history, including all amendments.

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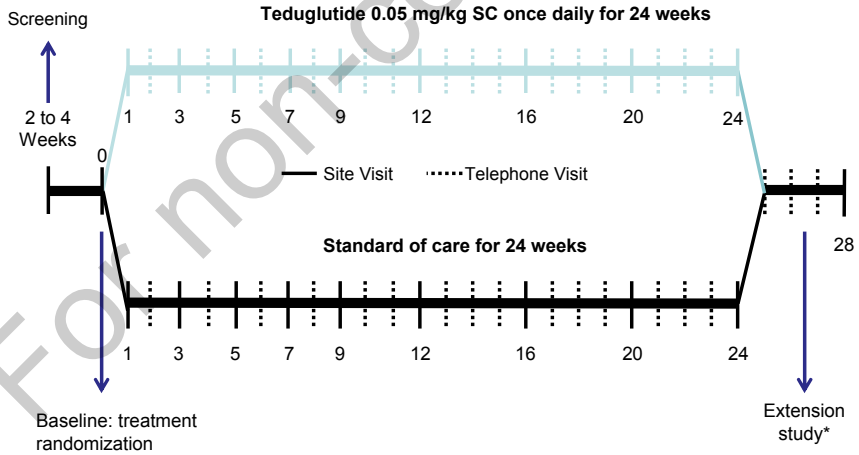
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
AUC_{ss}	area under the concentration-time curve at steady-state
$C_{max,ss}$	maximum plasma concentration at steady state
CRO	contract research organization
eCRF	electronic case report form
DMC	data monitoring committee
EDC	electronic data capture
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	glucagon-like peptide
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medicinal Journal Editors
I/O	oral fluid intake and urine output
IP	Investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PN	parenteral nutrition
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
SD	standard deviation
SOC	standard of care
ULN	upper limit of normal
US	United States

STUDY SYNOPSIS

Protocol number: SHP633-301	**Drug:** Teduglutide
Title of the study: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support	
Number of subjects (total and for each treatment arm): At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in a standard of care (SOC) comparator arm	
Investigator(s): Multicenter study	
Site(s) and Region(s): This study is planned to be conducted in approximately 5 to 10 sites globally.	
Study period (planned): 2017-2020	**Clinical phase:** 3
Objectives: The objectives of this clinical study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with short bowel syndrome (SBS) dependent on parenteral support.	
Investigational product, dose, and mode of administration: Teduglutide 0.05 mg/kg by subcutaneous (SC) injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm.	
Methodology: This is a randomized, multicenter, open-label study, consisting of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period.  * At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one "escape" criteria is met.	

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum 4 weeks). At the baseline visit (Week 0), subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for parenteral nutrition (PN) reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 or 12 (2 hours±10 minutes postdose).

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

Inclusion and Exclusion Criteria:

Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. This criteria was deleted.
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.
8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.
9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µl due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2-week period
13. More than 3 serious complications of intestinal failure (eg, catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

Maximum Duration of Subject Involvement in the Study:

The study consists of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

Endpoints:

Efficacy

Efficacy endpoints consist of the following:

Primary

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

Secondary

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by week 24
- Time to achieve enteral autonomy
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to Week 24/EOT

Pharmacokinetics

The pharmacokinetic endpoint is plasma teduglutide concentration at nominal time point.

Safety

Safety endpoints consist of the following:

- Adverse events (AEs)
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

Health Economics and Outcomes Research

Health economics and outcomes research (HEOR) endpoints include the following:

- Cumulative number of hospitalization days during the study

Statistical Methods:

Efficacy

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm. Descriptive statistics will be used to summarize time to achievement of enteral autonomy by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

Pharmacokinetics

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.

Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg, number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, serious adverse events will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores; and descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

Health Economics and Outcomes Research

The HEOR endpoints will be summarized descriptively.

STUDY SCHEDULES

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X													
Eligibility	X	X												
Randomization		X												
Demographics	X													
SBS history	X													
Medical and surgical history	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight	X	X	X		X		X		X		X			X
Length and head circumference	X	X					X							X
UGI/SBFT	X													
Safety labs and urinalysis[b, c]	X	X[b]	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	(X)	X
PK sampling[a]		X							[X][d]					[X][d]
Antibodies to teduglutide[a,e]		X												X[e]
Native GLP-2[f]	X													
Provide intake and output diaries[g]	X	X	X		X		X		X		X			X
Review diaries and nutritional support		X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support as needed[h]		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IP[a, i]		X	X		X		X		X		X			X

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Adjust IP dose[j]														X

EN=enteral nutrition; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PK=pharmacokinetics; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] Applicable to the teduglutide treatment arm only.

[b] At baseline, safety labs (Table 4) and PK can be separated by 1 day if blood volumes are limiting. Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline, and repeated if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity. Urine collection should be attempted, but inability to obtain urinalysis is not a protocol deviation.

[d] Subjects will have blood samples taken for teduglutide PK analysis predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the treatment period.

[e] Samples for antibody analysis will be drawn at the baseline and Week 12 visits. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.

[f] Blood samples for native GLP-2 should be collected postprandial. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

[i] The initial dose will be calculated based on body weight measured at baseline (Visit 0).

[j] The dose will be adjusted as needed, based on body weight measured at Week 12 visit.

Note: (X) denotes optional assessments; [X] denotes possible PK sampling time point (Refer to footnote "e".)

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Visit type	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**
Study day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**175**	**182**	**189**	**196**
±window (days)	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight				X				X				X				X
Length and head circumference				X				X				X				X
Safety labs and urinalysis[b,c]	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X
Antibodies to teduglutide[d,e]																X
Native GLP-2[f]												X				
Provide intake and output diaries				X				X				X				
Review diaries and nutritional support[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support as needed[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess follow-up period escape criteria[d]													X[i]	X[i]	X[i]	X
Dispense IP[d]				X				X								

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Visit type	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site
Study day	91	98	105	112	119	126	133	140	147	154	161	168	175	182	189	196
±window (days)	±3	±3	±3	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4

EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] At EOS subjects may enroll in an extension study, if subjects require treatment before the end of the 4-week follow-up they may enter the extension study immediately.

[b] Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR are tested if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity.

[d] Applicable to the teduglutide treatment arm only.

[e] Samples for antibody analysis will be drawn at the EOS (Week 28) visit.

[f] Blood samples for native GLP-2 should be collected postprandial. Blood samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.
Note: (X) denotes optional assessments.

[i] If a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.

1. BACKGROUND INFORMATION

1.1 Short Bowel Syndrome

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal diseases that result in major surgical resections of the small intestine (O'Keefe et al., 2006). Unlike the adult population, the majority of cases of SBS in pediatric subjects are due to congenital anomalies or catastrophic events that occur during infancy such as necrotizing enterocolitis, gastroschisis, intestinal atresia, midgut volvulus, or long-segment Hirschsprung disease (Beattie et al., 2010; Goulet and Ruemmele, 2006). A Canadian population-based study in neonates estimates an overall incidence of SBS to be 24.5 cases per 100,000 live births (Wales et al., 2004).

The small intestine is capable of remarkable adaptation, but excessive loss of absorptive surface area or specialized functions can lead to dependence on parenteral nutrition (PN)[1] fluids (O'Keefe et al., 2006). Although PN is life-sustaining in intestinal failure, it is associated with serious complications, including liver disease, life-threatening catheter-related blood stream infections, and central venous thrombosis (Beattie et al., 2010; Goulet and Ruemmele, 2006). Dependence on PN is also associated with reduced quality of life in both patients and caregivers and has an extremely high cost of care (Huisman-de Waal et al., 2007). About 30% of infants with SBS become independent of PN requirements within 12 months of the initial insult, and an additional 10% wean off PN within 24 months. After this time, linear intestinal growth slows. It is estimated that 42% to 86% of pediatric patients with SBS are able to become independent of PN within 1 to 3 years (Gonzalez-Hernandez et al., 2017; Khan et al., 2015; Squires et al., 2012). Nevertheless, despite optimal medical management, some children remain dependent on PN for many years (Squires et al., 2012). Infants who have less than 10% of expected small intestinal length for their gestational age have a low likelihood of ever achieving enteral autonomy (ie, independence from parenteral support). Providing the maximum tolerated amount of enteral nutrition (EN) has been the primary strategy to promote enteral adaptation (Spencer et al., 2005).

Accelerating the adaptive process and achieving enteral autonomy is an urgent goal for all patients with SBS who are dependent on PN (Khan et al., 2015; Squires et al., 2012). The adaptive process is in part controlled by glucagon-like peptide 2 (GLP-2), a 33 amino acid peptide hormone secreted from L-type enteroendocrine cells in the terminal ileum and colon in response to luminal nutrients and bile acids (Martin et al., 2006). The post-prandial plasma concentration of GLP-2 in infants with SBS correlates with length of the remaining small intestine (Sigalet et al., 2004). Infants who lack terminal ileum may have impaired adaptation due to inadequate production of GLP-2.

[1] For the purpose of the study the terms parenteral support (PS) and parenteral nutrition (PN) are used interchangeably.

1.2 Teduglutide

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$), approximately 2 hours in healthy adult subjects, 1.3 hours in adult SBS subjects, and 0.22 hours in pediatric SBS subjects, compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines (Tappenden et al., 2013; Thymann et al., 2014).

A Phase 3 study, TED-C13-003, has been completed in pediatric SBS subjects. In this study, teduglutide was administered to 3 cohorts of pediatric subjects from ages 1-17 years. Thirty-seven pediatric subjects received teduglutide at doses of 0.0125, 0.025, or 0.05 mg/kg/day for 12 weeks. Five additional pediatric subjects were enrolled in an observational standard of care (SOC) cohort. There were clear dose-dependent effects of teduglutide seen at the 0.025 and 0.05 mg/kg/day doses compared to SOC and the 0.0125 mg/kg/day dose. In the 0.025 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 37%, including complete independence from PN support in 1 subject, and a reduction of 3.94 hours per day infusion time. In the 0.05 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 39%, including complete independence from PN support in 3 subjects, and a reduction of 4.18 hours per day infusion time. Teduglutide was generally safe and well tolerated by pediatric subjects in all dosing cohorts. There were no deaths during the study and no treatment-emergent serious adverse events (SAEs) related to teduglutide were reported. No discontinuations from study were due to adverse events (AEs). Additional studies in pediatric patients with SBS are ongoing.

TED-C14-006 is a recently completed study of pediatric subjects through 17 years which included 2 treatment arms: a teduglutide treatment arm and a SOC treatment arm. Subjects in both arms participated in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the screening period, subjects chose into which arm to enroll. During the 24-week treatment period, subjects in the SOC treatment arm received standard medical therapy for SBS; while those in the teduglutide treatment arm received daily subcutaneous (SC) injections of teduglutide (study drug) in addition to standard medical therapy. The subjects enrolling in the teduglutide treatment arm were randomized 1:1 in a double-blinded manner into 2 parallel dose groups: 0.025 mg/kg/day or 0.05 mg/kg/day of teduglutide administered subcutaneously for 24 weeks. Compared to the SOC, treatment of pediatric subjects with SBS with teduglutide resulted in clinically meaningful reductions in PN/IV volume, calories, days per week, and hours per day. A total 10% of subjects who received teduglutide achieved enteral autonomy within 24 weeks despite prior dependence on PN/IV for several years. Teduglutide treatment also resulted in increases in EN volume and caloric intake as well as plasma citrulline. Although the differences in efficacy between the 0.025 and 0.05 mg/kg dose groups were small, a consistently greater effect was seen in the 0.05 mg/kg dose in all efficacy parameters.

The pharmacokinetic (PK) properties were well characterized in this population and were consistent with the prior 12 week pediatric study. Teduglutide was generally well tolerated by pediatric subjects with SBS. The safety profile was favorable and consistent with the prior pediatric study, the underlying disease, and previous experience with teduglutide in adult subjects with SBS.

Teduglutide (0.05 mg/kg/day) is currently approved for the treatment of adult patients with SBS in >30 countries. On 29 Jun 2016, the European Commission granted an extension of the Market Authorization for teduglutide for the treatment of patients aged 1 year and above with SBS.

Always refer to the latest version of the investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy and safety of teduglutide (SHP633).

2. OBJECTIVES

2.1 Rationale for the Study

There is no approved pharmacological therapy to improve intestinal adaptation in infants with SBS who are dependent on parenteral support. This study will evaluate whether teduglutide is safe and effective in this patient population.

2.2 Study Objectives

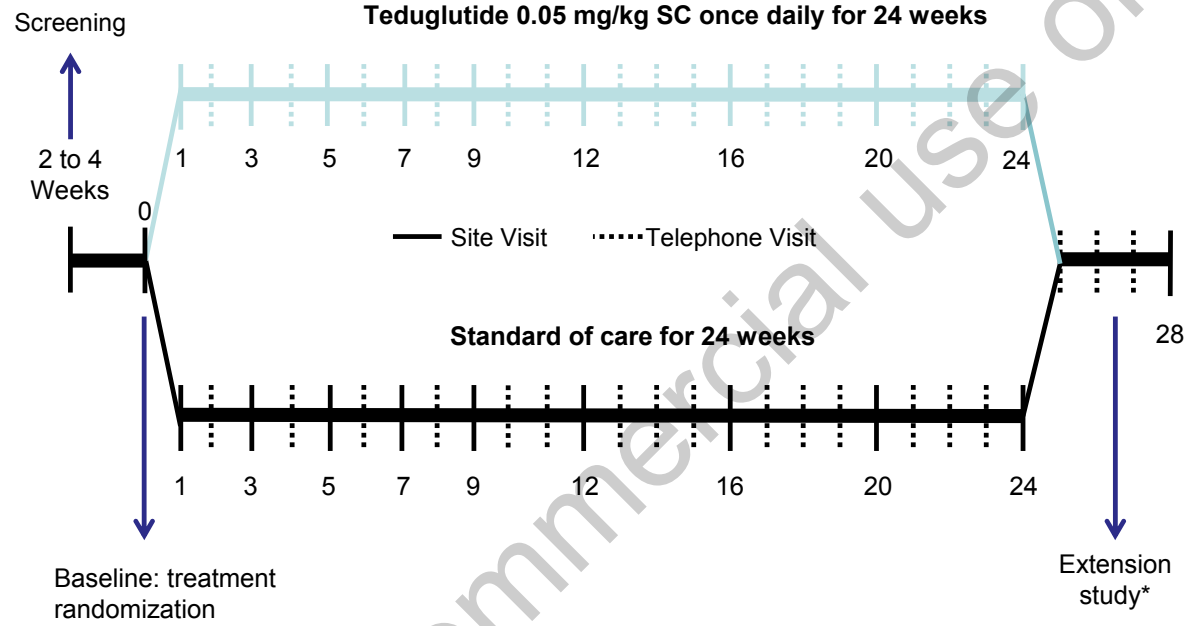
The objectives of this study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with SBS dependent on parenteral support.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a randomized, multicenter, open-label study, consisting of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. A schematic representation of the study design is presented in Figure 1.

Figure 1: Study Schematic



*At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one "escape" criteria is met.

3.1.1 Screening Period

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum: 4 weeks). The schedule of evaluations to be conducted during the Screening Period can be found in Table 1.

3.1.2 Treatment Period

At the baseline visit (Week 0), subjects will randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS, while those in the teduglutide arm will receive 0.05 mg/kg by SC injection once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits.

Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for PN reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability (Appendix 2). Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 or 12 (2 hours±10 minutes postdose).

The schedule of evaluations for the Treatment Period can be found in Table 1 (Visits -1 to 12) and Table 2 (Visits 13 to 28).

3.1.3 Follow-up Period

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product (IP) will be administered. At EOS, all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS visit if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

The schedule of evaluations for the Follow-up Period can be found in Table 2 (Visits 13 to 28).

3.2 Study Duration

The study consists of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

3.3 Sites and Regions

This study is planned to be conducted at approximately 5 to 10 sites globally.

4. STUDY POPULATION

At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in an SOC comparator arm.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. This criteria was deleted.
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.

8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.
9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µL due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2 week period.
13. More than 3 serious complications of intestinal failure (eg, catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

4.3 Reproductive Potential

Not applicable; this study will enroll infants.

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator should discuss withdrawal of a subject from investigational product with the medical monitor as soon as possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT/early termination are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period. Comments (spontaneous or elicited) or complaints pertaining to IP discontinuation made by the subject must be recorded in the source documents. The reason for discontinuation, the date and the total amount of investigational product administered must be recorded in the electronic case report form (eCRF) and source documents.

Subjects who discontinue will not be replaced.

4.4.1 Reasons for Discontinuation

The reason(s) for permanent discontinuation of treatment and/or withdrawal from the study must be determined by the investigator, and recorded in the subject's medical record and in the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document, and the most clinically relevant reason should be entered in the eCRF.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by parent/guardian
- Lack of efficacy
- Other

4.4.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact the parent(s)/guardian(s) of any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Medications and Procedures

Prior treatment includes all treatment and procedures (including but not limited to prescription treatments, herbal treatments, vitamins, non-pharmacological treatment, as appropriate) received within 14 days prior to the screening visit (Visit -1) (or pharmacokinetic equivalent of 5 half lives, whichever is longer, must be recorded on the appropriate eCRF page.

5.2 Concomitant Medications and Procedures

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins) and PN must be recorded from the first dose of investigational product and for the duration of the study in the appropriate sections of the eCRF. Any diagnostic, surgical or other therapeutic treatments received by a subject during the course of the study will also be recorded on the eCRF.

The mechanism of action of teduglutide may increase enteral absorption of oral drugs (eg, drugs used for management of SBS such as motility medication, opioids, psychotropics, metronidazole), so consideration should be given to modifying concomitant enteral medication regimens. Titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic index (eg, warfarin, digoxin, psychotropics) are given.

5.3 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.4 Prohibited Treatment

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the pretreatment visit (Table 3):

Table 3: Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pretreatment Visit
Teduglutide	Any
GLP-2, human growth hormone, or analogs of these hormones	6 months
Octreotide, GLP-1 analogs, and enteral glutamine	30 days

GLP=glucagon-like peptide

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

The investigational product is teduglutide, which will be provided in sterile, single-use 3 mL vials containing 1.25 mg teduglutide as a white lyophilized powder to be reconstituted before use with 0.5 mL sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the current investigator's brochure.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

All investigative study sites will be initially provided with sufficient investigational product to randomly assign a subject into the study (for either of the proposed treatment groups). Randomization will occur through an interactive response system. Random assignment of a subject will trigger replacement supplies for that investigative study site.

6.2.2 Allocation of Subjects to Treatment

Subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). The actual treatment given to individual subjects is determined by a randomization schedule.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined.

6.2.3 Dosing

The initial dose will be calculated based on body weight measured at baseline (Visit 0), and adjusted as needed, based on body weight measured at Week 12. No other adjustments to dose will be made during the teduglutide treatment period, unless discussed with the sponsor's medical monitor.

Following reconstitution, teduglutide will be administered by SC injection once daily (QD) into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used. Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later.

The subject should be dosed at approximately the same time each day. Consecutive doses should be separated by at least 12 hours. Each day, the injection site should be alternated.

Any subject who achieves complete independence from PN support at any time during the treatment period will continue to receive teduglutide treatment.

The first SC injection in teduglutide-naïve subjects should be administered under the supervision of the investigator or designee and the subject observed for hypersensitivity reactions for at least 4 hours during their initial dosing visit. The site of administration (arm, thigh, and abdomen) of the first teduglutide dose must be specified and recorded in the eCRF.

Detailed instructions for reconstitution and injection of the investigational product can be found in the Instructions for Use.

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.2.5 Dose Selection Rationale

Teduglutide is approved for adult and pediatric use in the EU at a dose of 0.05 mg/kg SC once daily. A completed 12-week dose finding study (TED-C13-003) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit-risk profile most meaningful at the 0.05 mg/kg/day dose (Carter et al., 2017).

Population pharmacokinetic modeling and simulations were conducted to determine the optimal dose to be used in pediatric subjects using data from 8 adult clinical studies including adult Phase 1 studies and Phases 2/3 studies as well as TED-C13-003 and suggested the same adult dose (0.05mg/kg) in pediatric subjects (aged between 1.67-14.7 years) (Marier et al., 2017).

To support dosing in the current age group, further PK simulation was conducted based on the population PK model previously established and a virtual population of 1000 pediatric patients created based on Centers for Disease Control (CDC) growth charts in the target age group (4 to 12 months) and taking into consideration body weights of pediatric patients with SBS enrolled in study TED-C13-003 and TED-C14-006 (approximately 15% lower than healthy subjects in the same age group). The model was customized by including a maturation function on clearance (CL/F) as a function of estimated glomerular filtration rate. Monte Carlo simulations for all age groups were performed according to the SC dosing regimens of 0.0125, 0.025 and 0.05 mg/kg every 24 hours. Rich concentration-time profiles were simulated with the customized population PK model to derive the exposure metrics area under the concentration curve at steady state (AUC_{ss}) and maximum concentration at steady state ($C_{max,ss}$). Exposure parameters in infant patients were compared to those derived in pediatric (1-17 years) and adult (≥18 years) patients with SBS using a Bayesian approach. Based on the clinical observations, C_{max} is considered to be associated with clinical responses. Following 0.05 mg/kg daily SC administration, the median $C_{max,ss}$ of teduglutide in neonate patients (24.9 ng/mL) was within 20% of that observed in the 2 to 4 and 4 to 6 years age groups (26.9 and 29.4 ng/mL, respectively); and approximately ~28% lower than that in adult patients with SBS. The median $C_{max,ss}$ of teduglutide in infant patients 4 to 12 months (41.9 ng/mL) following 0.05 mg/kg once daily was within 8% of that previously observed in adult patients with SBS (39.0 ng/mL, refer to the attached Simulation Report). In addition, individual simulated $C_{max,ss}$ values of teduglutide in infant patients 4 to 12 months (25.6 to 65.1 ng/mL) were contained within the range of $C_{max,ss}$ previously observed in pediatric patients 1 to 17 years (20.7 to 77.4 ng/mL). The clinical package in conjunction with C_{max} was considered to support teduglutide dose selection since AUC_{ss} was previously shown not to correlate with efficacy. Individual simulated AUC_{ss} values of teduglutide in infant patients 4 to 12 months (66.9 to 160 ng.h/mL) following 0.05 mg/kg once daily were contained within the range of AUC_{ss} values previously observed in pediatric patients 1 to 17 years (63.5 to 421 ng.h/mL). Based on the totality of clinical data, 0.05 mg/kg once daily is expected to provide comparable C_{max} concentrations in infants as compared to pediatric patients with SBS and was recommended as an evaluation dosing regimen in Study SHP633-301.

6.3 Labeling, Packaging, and Storage

6.3.1 Labeling

The investigational product will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of investigational product will be provided for this study. The vials will be labeled in accordance with applicable regulatory requirements.

Ancillary kits, containing supplies needed for the reconstitution and administration of the investigational product will also be provided and labeled in accordance with the applicable regulatory requirements.

All investigational product used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice.

6.3.2 Storage and Handling

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2-8°C (35.6-46.4°F) until dispensed to a subject. Once dispensed to a subject, the IP can be stored refrigerated or up to a controlled room temperature (acceptable range of 2-25°C, or 35.6-77°F). Parent/legal guardian will be instructed to keep the subject's IP and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the IP may be refrigerated. The IP is for single use only, and should be used within 3 hours following reconstitution.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels, as they are distributed.

6.4 Drug Accountability

Investigational product will not be dispatched to the study site until the sponsor or designee has received all required documents from the study site in accordance with applicable regulatory requirements and relevant standard operating procedures. Upon receipt, the study site's pharmacist or delegate is responsible for ensuring that all investigational product received at the site is inventoried and accounted for throughout the study. A copy of the shipping documents must be maintained for the investigator's records. Kits will be shipped to the site once the subject is screened.

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Investigational product kits will be dispensed at each of the applicable study visits at which the subject is required to be at the clinic. Each investigational product kit is sufficient for a treatment period of 1 week and enough kits will be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

Each subject will be given the investigational product according to the protocol. The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. All dispensed medication will be documented on the eCRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, subject returned investigational product, and empty/used investigational product packaging are to be sent to the sponsor or designee. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

Returned investigational product must be counted and verified by clinical site personnel and the sponsor (or study monitor). Shipment return forms, when used, must be signed prior to shipment from the site. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

The parent(s)/guardian(s) of subjects must be instructed to bring unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed and recorded at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging.

Subject compliance will be checked by site personnel at every visit by reviewing the subject diaries and asking the subject or the subject's parent or legally-authorized representative if they have administered the investigational product according to instructions. If any doses have been missed, the reason for missed dose should be documented in the subject's source documentation including, as applicable, the eCRF.

The investigator is responsible for contacting the sponsor or designee when the subject's daily investigational product dosing regimen is interrupted. Attempts should be made to contact the sponsor or designee prior to dose interruption. Reasons for dosage interruption may include but are not limited to hospitalization and AEs, a lapse in investigational product delivery, etc.

Subjects who have received 80% of the planned doses administered will be assessed as being compliant with the study protocol.

7. STUDY PROCEDURES

7.1 Study Schedule

Detailed study procedures and assessments to be performed for subjects throughout the study are outlined in the study schedules (Table 1 and Table 2) and must be referred to in conjunction with the instructions provided in this section.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period.

7.1.1 Screening

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the parent(s)/guardian(s) of the subject. The screening visit assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1. Rescreening will not be allowed.

7.1.2 Treatment Period

The randomized Treatment Period will comprise Weeks 1 to 24, during which all assessments will be performed as outlined in Table 1 and Table 2.

7.1.3 Follow-up Period

The Follow-up Period will comprise Weeks 25 to 28, during which all assessments will be performed as outlined in Table 2.

7.2 Study Evaluations and Procedures

7.2.1 Demographics and Other Baseline Characteristics

Demographics and Medical History

Demographic and/or other baseline variables obtained at the screening and/or baseline visits are listed below. Abnormal findings of clinical significance (if any) will be recorded as past medical history.

- Demography (including age, gestational age, sex, and race)
- Medical history (including surgical history)
- SBS history, including remnant anatomy

Upper Gastrointestinal Series with Small Bowel Follow-through

An upper GI contrast series with small bowel follow-through will be performed on all subjects during the screening period if one has not been done since the subject's last GI surgery.

It is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow-through performed since the subject's most recent surgery.

7.2.2 Efficacy Assessments

Subject Diaries

All available diary data will be reviewed by the investigator or their designee at each clinic and telephone visit to assess clinical status and opportunity for PN reduction and advance in feeds. Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

Intake Diary

Intake diaries will be used to collect and evaluate each subject's nutritional support. The parent/legally authorized representative/study site staff will complete the appropriate fields of the PN and EN sections of the intake diary daily throughout the study.

The following data will be captured in the intake diaries:

- Parenteral support volume and infusion duration
- Enteral nutrition (formula) including volume and calories

Site personnel will determine the actual PN and EN daily calories based on diary entries.

Output Diary

Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit; in addition, output should be recorded for subjects within 1 week of implementing a change in the PN prescription.

Urine data:

- Measure and record the weight of all urine-only diapers. Urine volume will be calculated using the following formula: 1 g (scale weight) = 1 mL or 1 cc
- At the discretion of the investigator, the parent or legal guardian/study site staff may be asked to collect the first void after the daily PN infusion to measure specific gravity

Stool data (includes diapers with mixed urine and stool):

- Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency (see Output diary). Stool volume will be calculated using the formula: 1 g (scale weight)=1 mL or 1 cc

All ostomy output volume should be recorded.

Native GLP-2

Blood samples for native GLP-2 should be collected postprandial. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

7.2.3 Safety Assessments

Laboratory Evaluations

Safety laboratory tests to be performed at site visits consist of clinical chemistry, hematology, and urinalysis and will be performed as outlined in the study plan (Table 1 and Table 2). Scheduled laboratory testing will be processed by a central lab. All laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the laboratory. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

During the Treatment Period, subjects will also have safety labs within approximately 5 to7 days after a PN adjustment. Safety labs performed after PN adjustment and between site visits will consist of clinical chemistry and urinalysis and may be processed by the central laboratory or a local laboratory. Local lab results are not required to be entered in the eCRFs; however, if the local lab results indicate any new clinically significant changes, they must be reported as an adverse event (see Section 8). Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

At baseline, blood samples for safety labs and PK can be separated by 1 day if blood volumes are limiting.

Safety labs at telephone visits will be collected at the discretion of the investigator.

For all subjects in the teduglutide treatment arm, prothrombin time (PT) and international normalized ratio (INR), tested at baseline, will be repeated if clinically indicated.

New clinically significant labs should be reported as AEs.

Close Monitoring Criteria Related To Liver Test Abnormalities:

The investigator should contact the medical monitor within 24 hours of their awareness if the subject develops any of the following changes in laboratory parameters:

- ALT or AST >5x ULN and >2x baseline value
- Total or direct bilirubin that is >2x baseline value or an absolute increase of ≥3 mg/dL (51.3 µmol/L)

If such changes are observed, the labs should be repeated along with an INR, and an inquiry should be made as to the presence of clinical symptoms consistent with new liver injury. The subject should be followed closely to determine the trajectory of the laboratory abnormalities and appropriate evaluations should be made, such as abdominal ultrasound with Doppler imaging to exclude vascular causes and biliary obstruction, consideration of sepsis, liver hypoperfusion, acute viral hepatitis (such as hepatitis A, EBV, or HSV), exposure to hepatotoxic medications, mitochondrial hepatopathy, or metabolic liver disease (such as hereditary fructose intolerance or arginosuccinate synthetase deficiency). Further evaluations can be performed at the discretion of the investigator in consultation with the Shire medical monitor.

The following clinical laboratory assessments will be performed according to the study schedules:

Table 4: List of Laboratory Tests

Biochemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bicarbonate
- Bilirubin (total and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- C-reactive protein
- Creatinine
- Estimated Glomerular Filtration Rate (Schwartz formula)
- Gamma-glutamyl transferase
- Glucose
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Triglycerides

Hematology[a]:
- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- Red blood cell morphology, if needed
- White blood cell count with differential

Coagulation[b]:
- Prothrombin time
- International normalized ratio

Urinalysis:
- Specific gravity
- Urine Sodium

[a] Hematology is not collected at Week 1 or at telephone visits.
[b] For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline and repeated only if clinically indicated.

Antibodies to Teduglutide

Blood samples will be drawn to test for antibodies to teduglutide. Samples will be taken before teduglutide administration at the screening visit (Visit -1) and at least 14 hours after the previous dose at Week 12 (Visit 12); samples may be drawn from a central line or peripheral access. One additional sample will be collected at the EOS 4 weeks after the EOT (ie, Week 28 or EOS).

Volume of Blood

Efforts will be made to minimize the amount of blood drawn from all pediatric subjects participating in this study. The volumes of blood to be drawn from each subject will vary depending on clinical status. Approximate volumes of blood to be drawn from each subject are shown in Table 5.

Table 5: Approximate Volume of Blood to be Drawn from Each Subject

Assessment	Sample Volume (mL)	No. Samples	Total Volume (mL)	Notes
Subjects Receiving Teduglutide Treatment				
Biochemistry	0.6	12	7.2	
Hematology	0.6	11	6.6	
Coagulation Parameters	0.6	1	0.6	PT and INR tested at baseline only, repeat while on study only if clinically indicated.
Antibodies	1.5	5	7.5	
Pharmacokinetics	1.5	4	6.0	Baseline: 3 timepoints Week 7: 1 timepoint OR Week 12: 1 timepoint
Native GLP-2	1.5	3	4.5	
Total mL:	**6.3**	**36**	**32.4**	
Subjects Receiving Standard of Care				
Biochemistry	0.6	12	7.2	
Hematology	0.6	11	6.6	
Native GLP-2	1.5	3	4.5	
Total mL:	**2.7**	**26**	**18.3**	

GLP=glucagon-like peptide; INR=international normalized ratio; PT=prothrombin time

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments should be combined. Blood volume estimates do not include safety labs performed after PN adjustments.

Physical Examinations, Vital Signs, Weight, Length, and Head Circumference

Physical examinations will be performed according to the study schedules (Table 1 and Table 2). Any new clinically significant findings noted during physical examinations should be recorded on the appropriate AE page of the eCRF.

Vital signs will be measured according to the study schedules. Measurements will include systolic and diastolic blood pressure (mmHg), pulse (beats per minute), and body temperature (°C/°F). Blood pressure should be determined by the appropriate size cuff (using the same method, the same leg, and in the supine position throughout the study, when possible). Blood pressure measurements should be attempted as part of the vital signs, but lack of blood pressure results will not constitute a protocol deviation. New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Length and head circumference will be measured at selected visits. A height z-score, weight Z-score, and weight/length ratio will be calculated by the sponsor using the site-provided height and weight data collected at each site visit.

7.2.4 Pharmacokinetic Assessments

Subjects will have blood samples taken for teduglutide PK analysis predose, and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the treatment period. Blood for PK sampling should be collected via peripheral IV or venipuncture, not from a central line. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified.

7.2.5 Health Economics and Outcomes Research

Hospitalizations

Each hospitalization that occurs during the study will be recorded, including date of admission, date of discharge, reasons for hospitalization, discharge diagnosis, and discharge status.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, or a symptom is more severe or prolonged than expected given the diagnosis, then symptom(s) should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

AEs that are related to IP that are not resolved at EOS will be followed until the event resolves or stabilizes, as judged by the investigator.

Laboratory values, vital signs, and clinical findings at the scheduled physical examinations must be reported as AEs if the investigator considers the finding to be a clinically significant change from the baseline.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. It is assumed that some of the infants participating in this study may be hospitalized for planned surgery(ies) that will occur during their participation in the study. Such pre-planned, elective surgeries, do not need to be reported as SAEs for this protocol.

8.1.5 Clinical Laboratory and Other Safety Evaluations

An untoward change in the value of a clinical laboratory parameter, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. Clinical significance is defined as any abnormal finding that results in further clinical investigation(s), treatment(s), or the diagnosis of new or progression of established condition. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, or ECG values which were not present at the beginning of the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory value, vital sign, or ECG parameter is clinically significant and represents an AE.

8.1.6 Pregnancy

Not applicable.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.

- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Administration of a dose greater than the allocated dose of the study medication or at a frequency greater than the dosing interval specified by the protocol.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally-authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

All Adverse Events of Special Interest, as defined in Section 8.3, must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event even if the event does not fulfill seriousness criterion.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol, and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested). Fax or e-mail the completed form to the Shire Global Drug Safety Department. A copy of the completed Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the Shire medical monitor or designee using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3, and must be reported to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The Sponsor and/or Clinical Contract Research Organization (CRO) is responsible for notifying the relevant regulatory authorities, and US central Institutional Review Boards (IRBs)/EU central ethics committees (ECs), of related, unexpected SAEs.

In addition, the Clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP633 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

8.3 Adverse Events of Special Interest

An AE of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program and for which ongoing monitoring and immediate notification by the investigator to the sponsor is required.

The AEs of special interest that require expedited regulatory reporting include the following:

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the GI tract including the hepatobiliary system
- Tumor-promoting ability (eg, benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

For AEs of special interest, the sponsor must be informed within 24 hours of first awareness as per the SAE notification instructions described in Section 8.2.2 even if the event does not fulfill the seriousness criteria.

8.4 Dose Interruption Criteria

The investigator is responsible for contacting the sponsor/designee when the subject's teduglutide dosing regimen is interrupted. The length of dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

Investigational product must be interrupted if any of the following events occur:

- An adverse event of special interest (see Section 8.3)
- Intestinal obstruction
- Biliary obstruction
- Pancreatic duct obstruction
- Heart failure with severe fluid overload determined by the sponsor or investigator to be related to IP.

Investigational product must be permanently discontinued if any of the following events occur:

- Severe hypersensitivity, such as anaphylaxis, determined by the investigator to be related to IP.
- Any malignancy

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Process

The study will be analyzed by the sponsor or designee. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, US) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the definitions and statistical methods for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

9.4 Planned Interim Analysis, and Data Monitoring Committee

No interim analyses is planned for this the study.

A data monitoring committee (DMC) will be involved in the management of this study. The DMC members will review the data approximately every 3 months according to the DMC Charter. The DMC review will include all cumulative safety data (ie, AEs, laboratory assessments, physical examinations, etc.) from study assessments through each cutoff period. Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of investigational product.

The DMC for this study will be conducted in accordance with the FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006).

The DMC will be an external, independent board comprised of physicians with relevant training. The DMC will be restricted to individuals free of significant conflicts of interest, including, but not limited to, financial, scientific, or regulatory in nature. The DMC will be governed by a Charter agreed to by members of the Board and the sponsor. Members of the Board may not be study investigators or be employed at the same institution as a study investigator, individuals employed by the sponsor, independent contractors hired by the sponsor, or members of regulatory agencies. The DMC may make recommendations to the sponsor regarding study aspects including stopping, modifying or continuing the study; however, the sponsor will have the final responsibility to determine whether the study should be modified or temporarily or permanently stopped. If the DMC recommends termination of this pediatric study, the recommendations will be communicated to the relevant regulatory agencies within 7 calendar days.

9.5 Sample Size Calculation and Power Considerations

The sample size is determined based on enrollment feasibility for this rare condition and the age of the study population.

9.6 Study Population

Intent to treat (ITT) population: All subjects randomized in the study.

Safety analysis population: The safety analysis set will contain all subjects who meet the following criteria:

- Teduglutide treatment arm: subjects who receive at least 1 dose of teduglutide and have undergone at least 1 post-baseline safety assessment; analyses will be performed according to dose group as appropriate.
- Standard of care treatment arm: subjects who have undergone at least 1 post-baseline safety assessment.

Per-protocol population: All subjects in the ITT population without any major protocol deviation that affects interpretation of efficacy results.

Pharmacokinetic analysis population: All subjects who received at least 1 dose of teduglutide and have at least 1 evaluable postdose PK concentration value.

9.7 Efficacy Analyses

9.7.1 Efficacy Endpoints

Efficacy endpoints consist of the following:

9.7.1.1 Primary Efficacy Endpoint

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

9.7.1.2 Secondary Efficacy Endpoints

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by Week 24
- Time to achieve enteral autonomy
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT

9.7.2 Method of Analysis-Efficacy Endpoints

Due to the limited size of the study population, descriptive statistics will be used with a goal of summarizing the sample. As such, no claims of significance will be made for any of the data. Continuous variables will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm. Descriptive statistics will be used to summarize time to achievement of enteral autonomy by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

9.8 Safety Analyses

9.8.1 Safety Endpoints

Safety endpoints consist of the following:

- Adverse events
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

9.8.2 Method of Analysis-Safety Endpoints

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg, number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, SAEs will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores, and descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

9.9 Health Economics and Outcomes Research Analyses

Health economics and outcomes research endpoints consist of the following:

- Cumulative number of hospitalization days during the study

Health economics and outcomes research endpoints will be summarized using descriptive statistics (number, mean and standard deviation) at nominal time points.

9.10 Pharmacokinetics Analyses

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points.

Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP.

This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly. The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator will be appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Electronic Case Report Forms

Electronic case report forms are supplied by the sponsor or designee and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data will be recorded directly onto the eCRF.

All data sent to the sponsor must be endorsed by the investigator.

The study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diaries, and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the parent/guardian agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent, where applicable, from the parent(s)/guardian(s) of all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject's legally authorized representative is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject's parent or guardian has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval.

A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor/designee has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor/designee.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study.

These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market teduglutide; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2 to 4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	03 Oct 2017	Global
Amendment 1	18 Jan 2018	Global
Amendment 2	04 Dec 2018	Global
Amendment 3	24 May 2019	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 18 Jan 2018	Global
Description of Change		Section(s) Affected by Change
Updated emergency contact information to reflect the change of the Contract Research Organization's name.		Emergency Contact Information
Clarified the duration of the screening period and total time on study. Provided a clear definition of study completion. Updated the study schematic to reflect the study design changes.		Synopsis, Section 3.1, Section 3.2
Revised the telephone and clinic visit schedule to assure laboratory measurement could be collected without exceeding weekly/monthly total blood volume restrictions.		Synopsis, Table 1, Section 3.1.2
Moved the PK sampling from Week 6 to Week 7 so that the samples could be collected without exceeding weekly/monthly total blood volume restrictions. Clarified that blood for pharmacokinetic samples of postdose may be taken within ± 10 minutes of the time pre-specified.		Synopsis, Table 1, Section 3.1.2, Section 7.2.4, Table 5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 18 Jan 2018	Global
Description of Change		Section(s) Affected by Change
Clarified that end jejunostomy or ileostomy are examples of small bowel ostomy rather than the stratification factors.		Synopsis, Section 3.1.2, Section 6.2.2
Clarified that all subjects regardless of treatment arm are eligible for the extension study.		Synopsis, Section 3.1.3
Clarified that if a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.		Synopsis, Table 2, Section 3.1.3, Section 6.2.3
Clarified that subjects must be 4 to 12 months corrected gestational age at screening.		Synopsis, Section 4.1
Changed dose adjustments to Week 12 rather than at every clinic visit to reduce site burden.		Synopsis, Table 1, Section 6.2.3
Clarified the definition of enteral autonomy.		Synopsis, Section 9.7.2
Updated the pharmacokinetic endpoint and analysis to reflect that only descriptive statistics will be calculated on plasma teduglutide concentration values. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.		Synopsis, Section 9.10
Removed assessment of the 5-level EuroQol five dimensions questionnaire to reduce caregiver burden.		Synopsis, Table 1, Section 7.2.5, Section 9.9
Clarified that native GLP-2 samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.		Table 2, Section 7.2.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	Amendment Date 18 Jan 2018	Global
Description of Change		Section(s) Affected by Change
Inserted a footnote to clarify that parenteral support and parenteral nutrition are used interchangeably.		Section 1.1
Removed the 5 mg vial of teduglutide as this size vial will not be supplied for this study.		Section 6.1
Clarified the procedures for assessing subject compliance.		Section 6.5
Specified that it is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow through performed since the subject's most recent surgery.		Section 7.2.1
Corrected the volume of blood to be collected for native GLP-2.		Table 5
Removed references to subject assent as assent is not possible in a study of infants.		Section 7.1.1, Section 10.3.1
Clarified the definitions of the analysis sets.		Section 9.6
Clarified that an adjustment to enteral nutrition as appropriate is part of the PN/IV adjustment algorithm.		Figure A-1
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout protocol.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	Amendment Date 04 Dec 2018	Global
Description of Change		Section(s) Affected by Change
The fax number currently used to send the Shire Medical Monitor a copy of the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol is now retired; a copy of the form must be sent by email only. Updated emergency contact information to reflect the change of Shire medical monitor to [redacted], IQVIA back up medical support to [redacted], and IQVIA phone number for medical emergencies.		Emergency Contact Information
A single email address ([redacted]) is now used to report a Product Quality Complaint, independently from where it has originated.		Product Quality Complaints
Added the new secondary efficacy endpoint "Time to achieve enteral autonomy" and statistical methodology to be used.		Synopsis, Section 9.7.1.2, Section 9.7.2
Updated the information on the clinical studies with teduglutide in pediatric subjects to include the results of TED-C14-006.		Section 1.2
Clarified that teduglutide is the investigational product for this study.		Section 6.1
Updated the dose selection rationale with results from a simulation work using the previous population pharmacokinetic model. Based on the totality of clinical data, 0.05 mg/kg once daily is expected to provide comparable C_{max} concentrations in infants as compared to pediatric patients with SBS and was recommended as an evaluation		Section 6.2.5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	Amendment Date 04 Dec 2018	Global
Description of Change		Section(s) Affected by Change
dosing regimen in Study SHP633-301.		
Clarified that rescreening of subjects in the study will not be allowed. (Administrative amendment dated 03 Oct 2018)		Section 7.1.1
Clarifications were made to the definition of adverse events.		Section 8.1, Section 8.1.5, Section 8.2.4
Added heart failure with severe fluid overload, determined by the sponsor or investigator to be related to the investigational product, to the list of events leading to interruption of investigational product administration. This addition is in alignment with the warnings and special precautions listed in the investigator brochure.		Section 8.4
As recommended by the FDA, specified that if the DMC recommends termination of this pediatric study, the recommendations will be communicated to the relevant regulatory agencies within 7 calendar days.		Section 9.4
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout the protocol

Appendix 2 Guidelines for Nutritional Support Management During the Study

The nutritional support adjustment guidelines are designed to standardize management of parenteral and enteral nutritional support in this study. Adjustments to nutritional support should be considered at every scheduled clinic visit. Adjustments at phone visits may also be performed, but nutritional assessments at phone visits serve primarily to confirm that nutritional adjustments at prior clinic visits were tolerated.

All attempts should be made to follow the guidelines, but departure from the guidelines will not constitute a protocol deviation.

Clinical judgment is required within the algorithm. Each decision point requires integrating multiple sources of information into a yes/no decision. When individual data points are conflicting, the investigator must use their best judgment in the assessment.

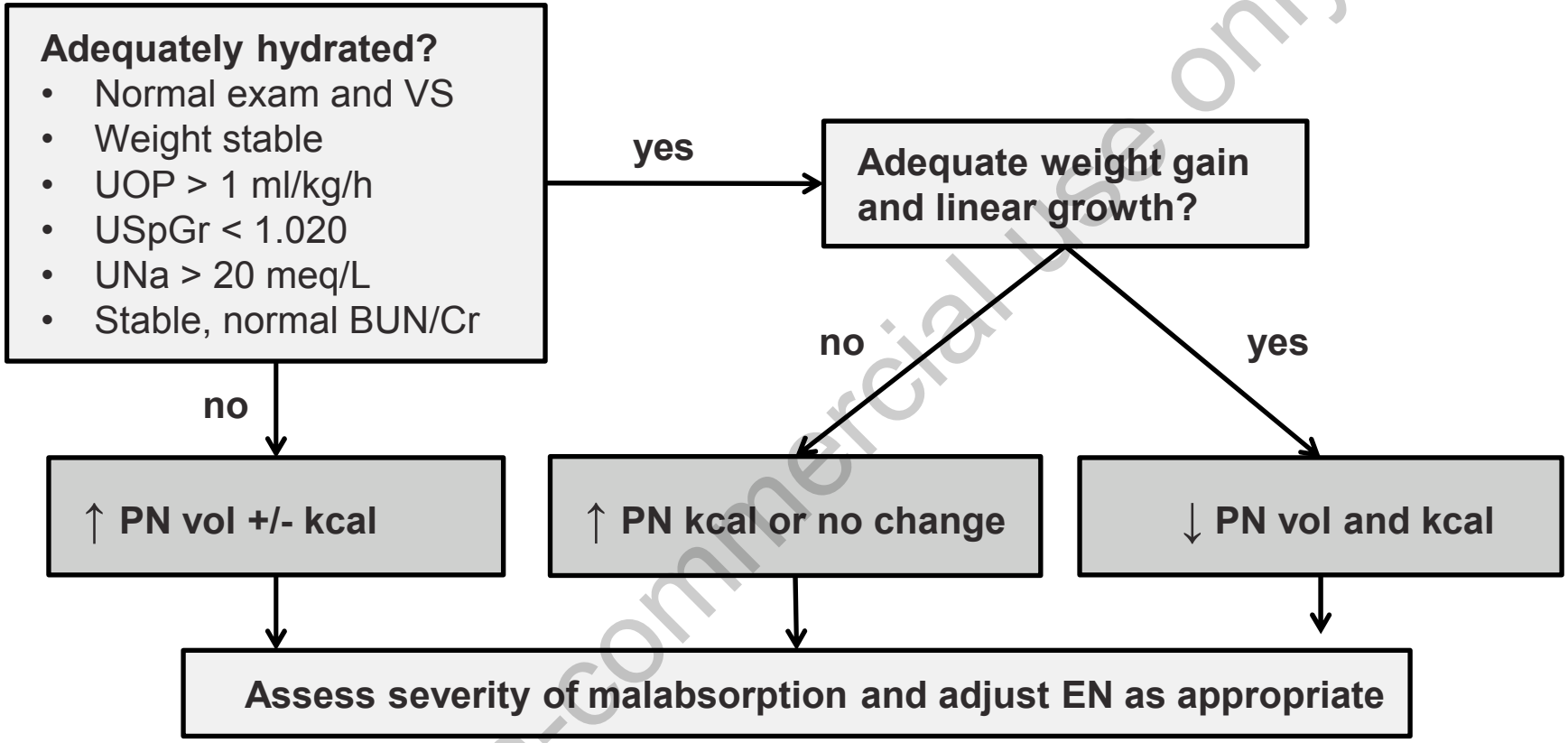
If intestinal adaptation is occurring, reductions in parenteral support volume and calories are expected to be in decrements of 5 to 10% relative to baseline values. Parenteral support components are at the discretion of the investigator, but care should be taken to balance carbohydrate, fat, and protein. Likewise, if intestinal adaptation is occurring, enteral nutrition volume and calories should be increased in increments of approximately 10% relative to baseline values.

Assessment of the severity of malabsorption may require estimation of stool output for children who have mixed stool and urine output.

Adjustments should be based on the actual nutritional support in volume and calories the subject infuses. Subjects should remain compliant with the nutritional support prescription in volume and calories during the study.

During the 48-hour output measurement period prior to the subject's scheduled visit, no further changes to the prescribed nutritional support should be made.

Figure A-1: Parenteral Nutrition/Intravenous Adjustment Algorithm for All Subjects



BUN=blood urea nitrogen; Cr=creatinine; PN=parenteral nutrition; UNa=urine sodium; UOP=urine output; USpGr=Urine specific gravity; VS=vital signs; vol=volume

PROTOCOL: SHP633-301

TITLE:	A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support
NUMBER	SHP633-301
PHASE	3
DRUG:	Teduglutide
INDICATION:	Short bowel syndrome
EUDRACT NO.:	2017-003606-40
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA
PROTOCOL HISTORY:	Original Protocol: 03 Oct 2017 Amendment 1: 18 Jan 2018 Amendment 1.1: 07 Aug 2018 (France-specific) Amendment 2.1: 04 Dec 2018 (France-specific) Amendment 3.1: 24 May 2019 (France-specific)

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	Date: [redacted]
[redacted], MD PhD [redacted], Global Clinical Development	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-301.

Title: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: _____
(please hand print or type) _____
_____

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the Shire Medical Monitor by e-mail at [redacted].

For protocol- or safety-related issues, the investigator must contact IQVIA Medical Support:

Primary Contact

[redacted], MD

[redacted]

Mobile: [redacted]

Phone: [redacted] (medical emergencies)

Email: [redacted]

Backup Contact

[redacted], MD, PhD

[redacted]

Mobile: [redacted]

Phone: [redacted] (medical emergencies)

Email: [redacted]

In addition, the investigator may also contact Shire:

[redacted], MD

Mobile Phone: [redacted]

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the E-mail address below to report the Product Quality Complaint:

[redacted]

Telephone numbers (provided for reference, if needed):

Shire (USA)
[redacted]

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3.1**	**Amendment Date** **24 May 2019**	**France-specific**
Description of Change and Rationale		**Section(s) Affected by Change**
Deleted Inclusion Criteria #6, Lack of terminal ileum and ileocecal valve, due to difficulties in enrollment.		Synopsis, Section 4.1
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout the protocol

See Appendix 1 for protocol history, including all amendments.

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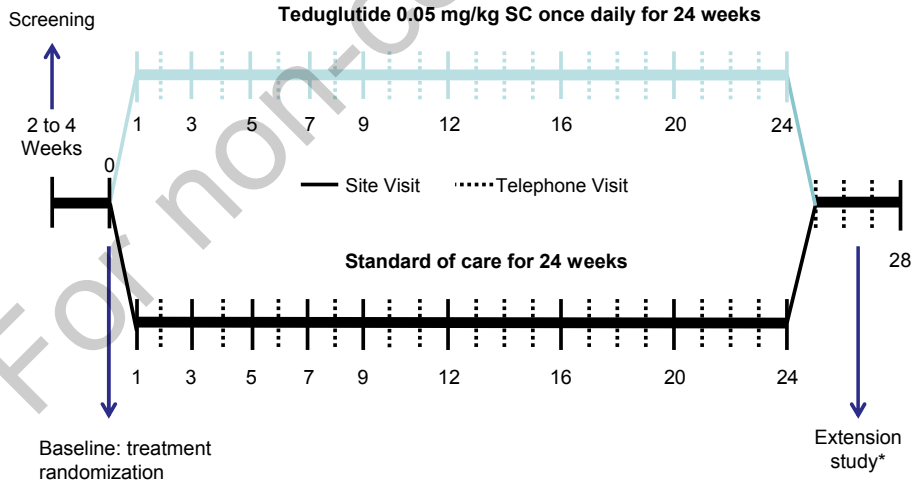
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
AUC_{ss}	area under the concentration-time curve at steady-state
$C_{max,ss}$	maximum plasma concentration at steady state
CRO	contract research organization
eCRF	electronic case report form
DMC	data monitoring committee
EDC	electronic data capture
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	glucagon-like peptide
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medicinal Journal Editors
I/O	oral fluid intake and urine output
IP	Investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PN	parenteral nutrition
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
SD	standard deviation
SOC	standard of care
ULN	upper limit of normal
US	United States

STUDY SYNOPSIS

Protocol number: SHP633-301	**Drug:** Teduglutide
Title of the study: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support	
Number of subjects (total and for each treatment arm): At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in a standard of care (SOC) comparator arm	
Investigator(s): Multicenter study	
Site(s) and Region(s): This study is planned to be conducted in approximately 5 to 10 sites globally.	
Study period (planned): 2017-2020	**Clinical phase:** 3
Objectives: The objectives of this clinical study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with short bowel syndrome (SBS) dependent on parenteral support.	
Investigational product, dose, and mode of administration: Teduglutide 0.05 mg/kg by subcutaneous (SC) injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm.	
Methodology: This is a randomized, multicenter, open-label study, consisting of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period.  * At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one "escape" criteria is met.	

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum 4 weeks). At the baseline visit (Week 0), subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for parenteral nutrition (PN) reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 or 12 (2 hours±10 minutes postdose).

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

Inclusion and Exclusion Criteria:

Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. This criteria was deleted.
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.
8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.
9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µl due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2-week period
13. More than 3 serious complications of intestinal failure (eg, catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.
19. Hypersensitivity to trace residues of tetracycline.

20. Signs of active severe or unstable, clinically significant hepatic impairment shown by any of the below laboratory test results at screening:

    a. Total bilirubin ≥2 x upper limit of normal (ULN)

    b. Aspartate aminotransferase (AST) ≥5 x ULN

    c. Alanine aminotransferase (ALT) ≥5 x ULN

    For subjects with Gilbert's disease:

    d. Indirect (unconjugated) bilirubin ≥2 x ULN

Maximum Duration of Subject Involvement in the Study:

The study consists of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

Endpoints:

Efficacy

Efficacy endpoints consist of the following:

Primary

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

Secondary

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by Week 24
- Time to achieve enteral autonomy
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to Week 24/EOT

Pharmacokinetics

The pharmacokinetic endpoint is plasma teduglutide concentration at nominal time point.

Safety

Safety endpoints consist of the following:

- Adverse events (AEs)
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

Health Economics and Outcomes Research

Health economics and outcomes research (HEOR) endpoints include the following:

- Cumulative number of hospitalization days during the study

Statistical Methods:

Efficacy

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm. Descriptive statistics will be used to summarize time to achievement of enteral autonomy by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

Pharmacokinetics

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.

Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg, number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, serious adverse events will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores; and descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

Health Economics and Outcomes Research

The HEOR endpoints will be summarized descriptively.

STUDY SCHEDULES

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X													
Eligibility	X	X												
Randomization		X												
Demographics	X													
SBS history	X													
Medical and surgical history	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight	X	X	X		X		X		X		X			X
Length and head circumference	X	X					X							X
UGI/SBFT	X													
Safety labs and urinalysis[b, c]	X	X[b]	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	(X)	X
PK sampling[a]		X							[X][d]					[X][d]
Antibodies to teduglutide[a,e]		X												X[e]
Native GLP-2[f]	X													
Provide intake and output diaries[g]	X	X	X		X		X		X		X			X
Review diaries and nutritional support		X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support as needed[h]		X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IP[a, i]		X	X		X		X		X		X			X

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Adjust IP dose[j]														X

EN=enteral nutrition; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PK=pharmacokinetics; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] Applicable to the teduglutide treatment arm only.

[b] At baseline, safety labs (Table 4) and PK can be separated by 1 day if blood volumes are limiting. Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline, and repeated if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity. Urine collection should be attempted, but inability to obtain urinalysis is not a protocol deviation.

[d] Subjects will have blood samples taken for teduglutide PK analysis predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the treatment period.

[e] Samples for antibody analysis will be drawn at the baseline and Week 12 visits. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.

[f] Blood samples for native GLP-2 should be collected postprandial. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

[i] The initial dose will be calculated based on body weight measured at baseline (Visit 0).

[j] The dose will be adjusted as needed, based on body weight measured at Week 12 visit.

Note: (X) denotes optional assessments; [X] denotes possible PK sampling time point (Refer to footnote “e”.)

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Visit type	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**
Study day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**175**	**182**	**189**	**196**
±window (days)	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight				X				X				X				X
Length and head circumference				X				X				X				X
Safety labs and urinalysis[b,c]	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X
Antibodies to teduglutide[d,e]																X
Native GLP-2[f]												X				
Provide intake and output diaries				X				X				X				
Review diaries and nutritional support[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adjust nutritional support as needed[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess follow-up period escape criteria[d]													X[i]	X[i]	X[i]	X
Dispense IP[d]				X				X								

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Visit type	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site
Study day	91	98	105	112	119	126	133	140	147	154	161	168	175	182	189	196
±window (days)	±3	±3	±3	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4

EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] At EOS subjects may enroll in an extension study, if subjects require treatment before the end of the 4-week follow-up they may enter the extension study immediately.

[b] Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR are tested if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity.

[d] Applicable to the teduglutide treatment arm only.

[e] Samples for antibody analysis will be drawn at the EOS (Week 28) visit.

[f] Blood samples for native GLP-2 should be collected postprandial. Blood samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.
Note: (X) denotes optional assessments.

[i] If a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.

1. BACKGROUND INFORMATION

1.1 Short Bowel Syndrome

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal diseases that result in major surgical resections of the small intestine (O'Keefe et al., 2006). Unlike the adult population, the majority of cases of SBS in pediatric subjects are due to congenital anomalies or catastrophic events that occur during infancy such as necrotizing enterocolitis, gastroschisis, intestinal atresia, midgut volvulus, or long-segment Hirschsprung disease (Beattie et al., 2010; Goulet and Ruemmele, 2006). A Canadian population-based study in neonates estimates an overall incidence of SBS to be 24.5 cases per 100,000 live births (Wales et al., 2004).

The small intestine is capable of remarkable adaptation, but excessive loss of absorptive surface area or specialized functions can lead to dependence on parenteral nutrition (PN)[1] fluids (O'Keefe et al., 2006). Although PN is life-sustaining in intestinal failure, it is associated with serious complications, including liver disease, life-threatening catheter-related blood stream infections, and central venous thrombosis (Beattie et al., 2010; Goulet and Ruemmele, 2006). Dependence on PN is also associated with reduced quality of life in both patients and caregivers and has an extremely high cost of care (Huisman-de Waal et al., 2007). About 30% of infants with SBS become independent of PN requirements within 12 months of the initial insult, and an additional 10% wean off PN within 24 months. After this time, linear intestinal growth slows. It is estimated that 42% to 86% of pediatric patients with SBS are able to become independent of PN within 1 to 3 years (Gonzalez-Hernandez et al., 2017; Khan et al., 2015; Squires et al., 2012). Nevertheless, despite optimal medical management, some children remain dependent on PN for many years (Squires et al., 2012). Infants who have less than 10% of expected small intestinal length for their gestational age have a low likelihood of ever achieving enteral autonomy (ie, independence from parenteral support). Providing the maximum tolerated amount of enteral nutrition (EN) has been the primary strategy to promote enteral adaptation (Spencer et al., 2005).

Accelerating the adaptive process and achieving enteral autonomy is an urgent goal for all patients with SBS who are dependent on PN (Khan et al., 2015; Squires et al., 2012). The adaptive process is in part controlled by glucagon-like peptide 2 (GLP-2), a 33 amino acid peptide hormone secreted from L-type enteroendocrine cells in the terminal ileum and colon in response to luminal nutrients and bile acids (Martin et al., 2006). The post-prandial plasma concentration of GLP-2 in infants with SBS correlates with length of the remaining small intestine (Sigalet et al., 2004). Infants who lack terminal ileum may have impaired adaptation due to inadequate production of GLP-2.

[1] For the purpose of the study the terms parenteral support (PS) and parenteral nutrition (PN) are used interchangeably.

1.2 Teduglutide

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$), approximately 2 hours in healthy adult subjects, 1.3 hours in adult SBS subjects, and 0.22 hours in pediatric SBS subjects, compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines (Tappenden et al., 2013; Thymann et al., 2014).

A Phase 3 study, TED-C13-003, has been completed in pediatric SBS subjects. In this study, teduglutide was administered to 3 cohorts of pediatric subjects from ages 1-17 years. Thirty-seven pediatric subjects received teduglutide at doses of 0.0125, 0.025, or 0.05 mg/kg/day for 12 weeks. Five additional pediatric subjects were enrolled in an observational standard of care (SOC) cohort. There were clear dose-dependent effects of teduglutide seen at the 0.025 and 0.05 mg/kg/day doses compared to SOC and the 0.0125 mg/kg/day dose. In the 0.025 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 37%, including complete independence from PN support in 1 subject, and a reduction of 3.94 hours per day infusion time. In the 0.05 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 39%, including complete independence from PN support in 3 subjects, and a reduction of 4.18 hours per day infusion time. Teduglutide was generally safe and well tolerated by pediatric subjects in all dosing cohorts. There were no deaths during the study and no treatment-emergent serious adverse events (SAEs) related to teduglutide were reported. No discontinuations from study were due to adverse events (AEs). Additional studies in pediatric patients with SBS are ongoing.

TED-C14-006 is a recently completed study of pediatric subjects through 17 years which included 2 treatment arms: a teduglutide treatment arm and a SOC treatment arm. Subjects in both arms participated in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the screening period, subjects chose into which arm to enroll. During the 24-week treatment period, subjects in the SOC treatment arm received standard medical therapy for SBS; while those in the teduglutide treatment arm received daily subcutaneous (SC) injections of teduglutide (study drug) in addition to standard medical therapy. The subjects enrolling in the teduglutide treatment arm were randomized 1:1 in a double-blinded manner into 2 parallel dose groups: 0.025 mg/kg/day or 0.05 mg/kg/day of teduglutide administered subcutaneously for 24 weeks. Compared to the SOC, treatment of pediatric subjects with SBS with teduglutide resulted in clinically meaningful reductions in PN/IV volume, calories, days per week, and hours per day. A total 10% of subjects who received teduglutide achieved enteral autonomy within 24 weeks despite prior dependence on PN/IV for several years. Teduglutide treatment also resulted in increases in EN volume and caloric intake as well as plasma citrulline.

Although the differences in efficacy between the 0.025 and 0.05 mg/kg dose groups were small, a consistently greater effect was seen in the 0.05 mg/kg dose in all efficacy parameters. The pharmacokinetic (PK) properties were well characterized in this population and were consistent with the prior 12 week pediatric study. Teduglutide was generally well tolerated by pediatric subjects with SBS. The safety profile was favorable and consistent with the prior pediatric study, the underlying disease, and previous experience with teduglutide in adult subjects with SBS.

Teduglutide (0.05 mg/kg/day) is currently approved for the treatment of adult patients with SBS in >30 countries. On 29 Jun 2016, the European Commission granted an extension of the Market Authorization for teduglutide for the treatment of patients aged 1 year and above with SBS.

Always refer to the latest version of the investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy and safety of teduglutide (SHP633).

2. OBJECTIVES

2.1 Rationale for the Study

There is no approved pharmacological therapy to improve intestinal adaptation in infants with SBS who are dependent on parenteral support. This study will evaluate whether teduglutide is safe and effective in this patient population.

2.2 Study Objectives

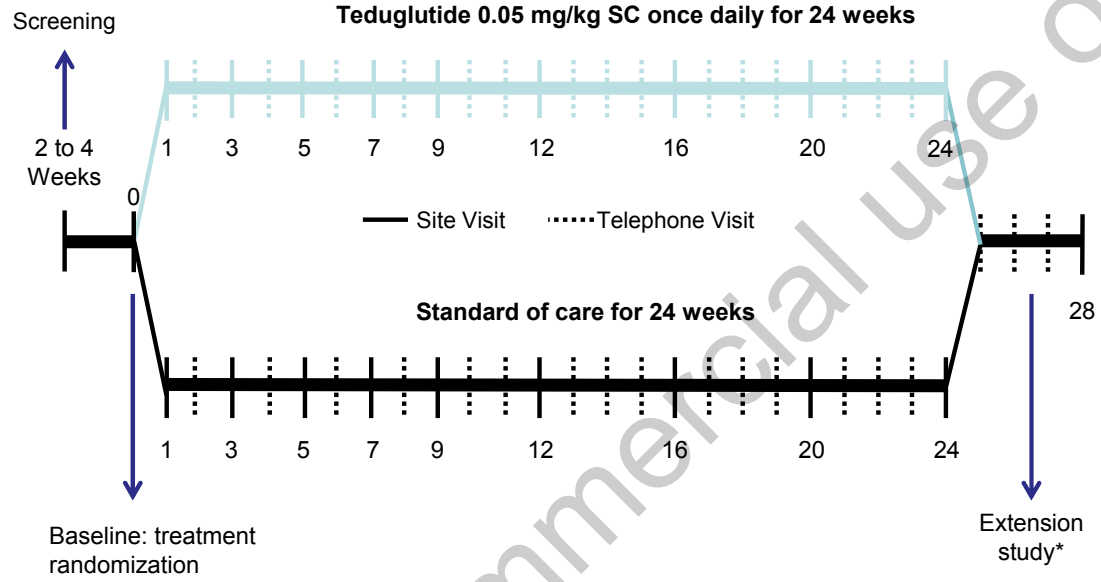
The objectives of this study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with SBS dependent on parenteral support.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a randomized, multicenter, open-label study, consisting of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. A schematic representation of the study design is presented in Figure 1.

Figure 1: Study Schematic



*At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one "escape" criteria is met.

3.1.1 Screening Period

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum: 4 weeks). The schedule of evaluations to be conducted during the Screening Period can be found in Table 1.

3.1.2 Treatment Period

At the baseline visit (Week 0), subjects will randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS, while those in the teduglutide arm will receive 0.05 mg/kg by SC injection once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28.

At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for PN reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability (Appendix 2). Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 or 12 (2 hours±10 minutes postdose).

The schedule of evaluations for the Treatment Period can be found in Table 1 (Visits -1 to 12) and Table 2 (Visits 13 to 28).

3.1.3 Follow-up Period

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product (IP) will be administered. At EOS, all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS visit if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

The schedule of evaluations for the Follow-up Period can be found in Table 2 (Visits 13 to 28).

3.2 Study Duration

The study consists of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

3.3 Sites and Regions

This study is planned to be conducted at approximately 5 to 10 sites globally.

4. STUDY POPULATION

At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in an SOC comparator arm.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. This criteria was deleted.
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.
8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.

9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µL due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2 week period.
13. More than 3 serious complications of intestinal failure (eg, catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.
19. Hypersensitivity to trace residues of tetracycline.
20. Signs of active severe or unstable, clinically significant hepatic impairment shown by any of the below laboratory test results at screening:
    a. Total bilirubin ≥2 x upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥5 x ULN
    c. Alanine aminotransferase (ALT) ≥5 x ULN

For subjects with Gilbert's disease:

    d. Indirect (unconjugated) bilirubin ≥2 x ULN

4.3 Reproductive Potential

Not applicable; this study will enroll infants.

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator should discuss withdrawal of a subject from investigational product with the medical monitor as soon as possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT/early termination are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period. Comments (spontaneous or elicited) or complaints pertaining to IP discontinuation made by the subject must be recorded in the source documents. The reason for discontinuation, the date and the total amount of investigational product administered must be recorded in the electronic case report form (eCRF) and source documents.

Subjects who discontinue will not be replaced.

4.4.1 Reasons for Discontinuation

The reason(s) for permanent discontinuation of treatment and/or withdrawal from the study must be determined by the investigator, and recorded in the subject's medical record and in the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document, and the most clinically relevant reason should be entered in the eCRF.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by parent/guardian
- Lack of efficacy
- Other

4.4.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact the parent(s)/guardian(s) of any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Medications and Procedures

Prior treatment includes all treatment and procedures (including but not limited to prescription treatments, herbal treatments, vitamins, non-pharmacological treatment, as appropriate) received within 14 days prior to the screening visit (Visit -1) (or pharmacokinetic equivalent of 5 half lives, whichever is longer, must be recorded on the appropriate eCRF page.

5.2 Concomitant Medications and Procedures

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins) and PN must be recorded from the first dose of investigational product and for the duration of the study in the appropriate sections of the eCRF. Any diagnostic, surgical or other therapeutic treatments received by a subject during the course of the study will also be recorded on the eCRF.

The mechanism of action of teduglutide may increase enteral absorption of oral drugs (eg, drugs used for management of SBS such as motility medication, opioids, psychotropics, metronidazole), so consideration should be given to modifying concomitant enteral medication regimens. Titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic index (eg, warfarin, digoxin, psychotropics) are given.

5.3 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.4 Prohibited Treatment

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the pretreatment visit (Table 3):

Table 3: Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pretreatment Visit
Teduglutide	Any
GLP-2, human growth hormone, or analogs of these hormones	6 months
Octreotide, GLP-1 analogs, and enteral glutamine	30 days

GLP=glucagon-like peptide

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

The investigational product is teduglutide, which will be provided in sterile, single-use 3 mL vials containing 1.25 mg teduglutide as a white lyophilized powder to be reconstituted before use with 0.5 mL sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the current investigator's brochure.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

All investigative study sites will be initially provided with sufficient investigational product to randomly assign a subject into the study (for either of the proposed treatment groups). Randomization will occur through an interactive response system. Random assignment of a subject will trigger replacement supplies for that investigative study site.

6.2.2 Allocation of Subjects to Treatment

Subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). The actual treatment given to individual subjects is determined by a randomization schedule.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined.

6.2.3 Dosing

The initial dose will be calculated based on body weight measured at baseline (Visit 0), and adjusted as needed, based on body weight measured at Week 12. No other adjustments to dose will be made during the teduglutide treatment period, unless discussed with the sponsor's medical monitor.

Following reconstitution, teduglutide will be administered by SC injection once daily (QD) into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used. Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later.

The subject should be dosed at approximately the same time each day. Consecutive doses should be separated by at least 12 hours. Each day, the injection site should be alternated.

Any subject who achieves complete independence from PN support at any time during the treatment period will continue to receive teduglutide treatment.

The first SC injection in teduglutide-naïve subjects should be administered under the supervision of the investigator or designee and the subject observed for hypersensitivity reactions for at least 4 hours during their initial dosing visit. The site of administration (arm, thigh, and abdomen) of the first teduglutide dose must be specified and recorded in the eCRF.

Detailed instructions for reconstitution and injection of the investigational product can be found in the Instructions for Use.

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.2.5 Dose Selection Rationale

Teduglutide is approved for adult and pediatric use in the EU at a dose of 0.05 mg/kg SC once daily. A completed 12-week dose finding study (TED-C13-003) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit-risk profile most meaningful at the 0.05 mg/kg/day dose (Carter et al., 2017).

Population pharmacokinetic modeling and simulations were conducted to determine the optimal dose to be used in pediatric subjects using data from 8 adult clinical studies including adult Phase 1 studies and Phases 2/3 studies as well as TED-C13-003 and suggested the same adult dose (0.05mg/kg) in pediatric subjects (aged between 1.67-14.7 years) (Marier et al., 2017).

To support dosing in the current age group, further PK simulation was conducted based on the population PK model previously established and a virtual population of 1000 pediatric patients created based on Centers for Disease Control (CDC) growth charts in the target age group (4 to 12 months) and taking into consideration body weights of pediatric patients with SBS enrolled in study TED-C13-003 and TED-C14-006 (approximately 15% lower than healthy subjects in the same age group). The model was customized by including a maturation function on clearance (CL/F) as a function of estimated glomerular filtration rate. Monte Carlo simulations for all age groups were performed according to the SC dosing regimens of 0.0125, 0.025 and 0.05 mg/kg every 24 hours. Rich concentration-time profiles were simulated with the customized population PK model to derive the exposure metrics area under the concentration curve at steady state (AUC_{ss}) and maximum concentration at steady state ($C_{max,ss}$). Exposure parameters in infant patients were compared to those derived in pediatric (1-17 years) and adult (≥18 years) patients with SBS using a Bayesian approach. Based on the clinical observations, C_{max} is considered to be associated with clinical responses. Following 0.05 mg/kg daily SC administration, the median $C_{max,ss}$ of teduglutide in neonate patients (24.9 ng/mL) was within 20% of that observed in the 2 to 4 and 4 to 6 years age groups (26.9 and 29.4 ng/mL, respectively); and approximately ~28% lower than that in adult patients with SBS. The median $C_{max,ss}$ of teduglutide in infant patients 4 to 12 months (41.9 ng/mL) following 0.05 mg/kg once daily was within 8% of that previously observed in adult patients with SBS (39.0 ng/mL, refer to the attached Simulation Report). In addition, individual simulated $C_{max,ss}$ values of teduglutide in infant patients 4 to 12 months (25.6 to 65.1 ng/mL) were contained within the range of $C_{max,ss}$ previously observed in pediatric patients 1 to 17 years (20.7 to 77.4 ng/mL). The clinical package in conjunction with C_{max} was considered to support teduglutide dose selection since AUC_{ss} was previously shown not to correlate with efficacy. Individual simulated AUC_{ss} values of teduglutide in infant patients 4 to 12 months (66.9 to 160 ng.h/mL) following 0.05 mg/kg once daily were contained within the range of AUC_{ss} values previously observed in pediatric patients 1 to 17 years (63.5 to 421 ng.h/mL). Based on the totality of clinical data, 0.05 mg/kg once daily is expected to provide comparable C_{max} concentrations in infants as compared to pediatric patients with SBS and was recommended as an evaluation dosing regimen in Study SHP633-301.

6.3 Labeling, Packaging, and Storage

6.3.1 Labeling

The investigational product will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of investigational product will be provided for this study. The vials will be labeled in accordance with applicable regulatory requirements.

Ancillary kits, containing supplies needed for the reconstitution and administration of the investigational product will also be provided and labeled in accordance with the applicable regulatory requirements.

All investigational product used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice.

6.3.2 Storage and Handling

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2-8°C (35.6-46.4°F) until dispensed to a subject. Once dispensed to a subject, the IP can be stored refrigerated or up to a controlled room temperature (acceptable range of 2-25°C, or 35.6-77°F). Parent/legal guardian will be instructed to keep the subject's IP and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the IP may be refrigerated. The IP is for single use only, and should be used within 3 hours following reconstitution.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels, as they are distributed.

6.4 Drug Accountability

Investigational product will not be dispatched to the study site until the sponsor or designee has received all required documents from the study site in accordance with applicable regulatory requirements and relevant standard operating procedures. Upon receipt, the study site's pharmacist or delegate is responsible for ensuring that all investigational product received at the site is inventoried and accounted for throughout the study. A copy of the shipping documents must be maintained for the investigator's records. Kits will be shipped to the site once the subject is screened.

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Investigational product kits will be dispensed at each of the applicable study visits at which the subject is required to be at the clinic. Each investigational product kit is sufficient for a treatment period of 1 week and enough kits will be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

Each subject will be given the investigational product according to the protocol. The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. All dispensed medication will be documented on the eCRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, subject returned investigational product, and empty/used investigational product packaging are to be sent to the sponsor or designee. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

Returned investigational product must be counted and verified by clinical site personnel and the sponsor (or study monitor). Shipment return forms, when used, must be signed prior to shipment from the site. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

The parent(s)/guardian(s) of subjects must be instructed to bring unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed and recorded at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging.

Subject compliance will be checked by site personnel at every visit by reviewing the subject diaries and asking the subject or the subject's parent or legally-authorized representative if they have administered the investigational product according to instructions. If any doses have been missed, the reason for missed dose should be documented in the subject's source documentation including, as applicable, the eCRF.

The investigator is responsible for contacting the sponsor or designee when the subject's daily investigational product dosing regimen is interrupted. Attempts should be made to contact the sponsor or designee prior to dose interruption. Reasons for dosage interruption may include but are not limited to hospitalization and AEs, a lapse in investigational product delivery, etc.

Subjects who have received 80% of the planned doses administered will be assessed as being compliant with the study protocol.

7. STUDY PROCEDURES

7.1 Study Schedule

Detailed study procedures and assessments to be performed for subjects throughout the study are outlined in the study schedules (Table 1 and Table 2) and must be referred to in conjunction with the instructions provided in this section.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period.

7.1.1 Screening

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the parent(s)/guardian(s) of the subject. The screening visit assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1. Rescreening will not be allowed.

7.1.2 Treatment Period

The randomized Treatment Period will comprise Weeks 1 to 24, during which all assessments will be performed as outlined in Table 1 and Table 2.

7.1.3 Follow-up Period

The Follow-up Period will comprise Weeks 25 to 28, during which all assessments will be performed as outlined in Table 2.

7.2 Study Evaluations and Procedures

7.2.1 Demographics and Other Baseline Characteristics

Demographics and Medical History

Demographic and/or other baseline variables obtained at the screening and/or baseline visits are listed below. Abnormal findings of clinical significance (if any) will be recorded as past medical history.

- Demography (including age, gestational age, sex, and race)
- Medical history (including surgical history)
- SBS history, including remnant anatomy

Upper Gastrointestinal Series with Small Bowel Follow-through

An upper GI contrast series with small bowel follow-through will be performed on all subjects during the screening period if one has not been done since the subject's last GI surgery.

It is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow-through performed since the subject's most recent surgery.

7.2.2 Efficacy Assessments

Subject Diaries

All available diary data will be reviewed by the investigator or their designee at each clinic and telephone visit to assess clinical status and opportunity for PN reduction and advance in feeds. Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

Intake Diary

Intake diaries will be used to collect and evaluate each subject's nutritional support. The parent/legally authorized representative/study site staff will complete the appropriate fields of the PN and EN sections of the intake diary daily throughout the study.

The following data will be captured in the intake diaries:

- Parenteral support volume and infusion duration
- Enteral nutrition (formula) including volume and calories

Site personnel will determine the actual PN and EN daily calories based on diary entries.

Output Diary

Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit; in addition, output should be recorded for subjects within 1 week of implementing a change in the PN prescription.

Urine data:

- Measure and record the weight of all urine-only diapers. Urine volume will be calculated using the following formula: 1 g (scale weight) = 1 mL or 1 cc
- At the discretion of the investigator, the parent or legal guardian/study site staff may be asked to collect the first void after the daily PN infusion to measure specific gravity

Stool data (includes diapers with mixed urine and stool):

- Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency (see Output diary). Stool volume will be calculated using the formula: 1 g (scale weight)=1 mL or 1 cc

All ostomy output volume should be recorded.

Native GLP-2

Blood samples for native GLP-2 should be collected postprandial. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

7.2.3 Safety Assessments

Laboratory Evaluations

Safety laboratory tests to be performed at site visits consist of clinical chemistry, hematology, and urinalysis and will be performed as outlined in the study plan (Table 1 and Table 2). Scheduled laboratory testing will be processed by a central lab. All laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the laboratory. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

During the Treatment Period, subjects will also have safety labs within approximately 5 to7 days after a PN adjustment. Safety labs performed after PN adjustment and between site visits will consist of clinical chemistry and urinalysis and may be processed by the central laboratory or a local laboratory. Local lab results are not required to be entered in the eCRFs; however, if the local lab results indicate any new clinically significant changes, they must be reported as an adverse event (see Section 8). Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

At baseline, blood samples for safety labs and PK can be separated by 1 day if blood volumes are limiting.

Safety labs at telephone visits will be collected at the discretion of the investigator.

For all subjects in the teduglutide treatment arm, prothrombin time (PT) and international normalized ratio (INR), tested at baseline, will be repeated if clinically indicated.

New clinically significant labs should be reported as AEs.

Close Monitoring Criteria Related To Liver Test Abnormalities:

The investigator should contact the medical monitor within 24 hours of their awareness if the subject develops any of the following changes in laboratory parameters:

- ALT or AST >5x ULN and >2x baseline value
- Total or direct bilirubin that is >2x baseline value or an absolute increase of ≥3 mg/dL (51.3 µmol/L)

If such changes are observed, the labs should be repeated along with an INR, and an inquiry should be made as to the presence of clinical symptoms consistent with new liver injury. The subject should be followed closely to determine the trajectory of the laboratory abnormalities and appropriate evaluations should be made, such as abdominal ultrasound with Doppler imaging to exclude vascular causes and biliary obstruction, consideration of sepsis, liver hypoperfusion, acute viral hepatitis (such as hepatitis A, EBV, or HSV), exposure to hepatotoxic medications, mitochondrial hepatopathy, or metabolic liver disease (such as hereditary fructose intolerance or arginosuccinate synthetase deficiency). Further evaluations can be performed at the discretion of the investigator in consultation with the Shire medical monitor.

The following clinical laboratory assessments will be performed according to the study schedules:

Table 4: List of Laboratory Tests

Biochemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bicarbonate
- Bilirubin (total and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- C-reactive protein
- Creatinine
- Estimated Glomerular Filtration Rate (Schwartz formula)
- Gamma-glutamyl transferase
- Glucose
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Triglycerides

Hematology[a]:
- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- Red blood cell morphology, if needed
- White blood cell count with differential

Coagulation[b]:
- Prothrombin time
- International normalized ratio

Urinalysis:
- Specific gravity
- Urine Sodium

[a] Hematology is not collected at Week 1 or at telephone visits.
[b] For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline and repeated only if clinically indicated.

Antibodies to Teduglutide

Blood samples will be drawn to test for antibodies to teduglutide. Samples will be taken before teduglutide administration at the screening visit (Visit -1) and at least 14 hours after the previous dose at Week 12 (Visit 12); samples may be drawn from a central line or peripheral access. One additional sample will be collected at the EOS 4 weeks after the EOT (ie, Week 28 or EOS).

Volume of Blood

Efforts will be made to minimize the amount of blood drawn from all pediatric subjects participating in this study. The volumes of blood to be drawn from each subject will vary depending on clinical status. Approximate volumes of blood to be drawn from each subject are shown in Table 5.

Table 5: Approximate Volume of Blood to be Drawn from Each Subject

Assessment	Sample Volume (mL)	No. Samples	Total Volume (mL)	Notes
Subjects Receiving Teduglutide Treatment				
Biochemistry	0.6	12	7.2	
Hematology	0.6	11	6.6	
Coagulation Parameters	0.6	1	0.6	PT and INR tested at baseline only, repeat while on study only if clinically indicated.
Antibodies	1.5	5	7.5	
Pharmacokinetics	1.5	4	6.0	Baseline: 3 timepoints Week 7: 1 timepoint OR Week 12: 1 timepoint
Native GLP-2	1.5	3	4.5	
Total mL:	**6.3**	**36**	**32.4**	
Subjects Receiving Standard of Care				
Biochemistry	0.6	12	7.2	
Hematology	0.6	11	6.6	
Native GLP-2	1.5	3	4.5	
Total mL:	**2.7**	**26**	**18.3**	

GLP=glucagon-like peptide; INR=international normalized ratio; PT=prothrombin time

Note: The amount of blood to be drawn for each assessment is an estimate. The amount of blood to be drawn may vary according to the instructions provided by the manufacturer or laboratory for an individual assessment. When more than 1 blood assessment is to be done at the time point/period, if they require the same type of tube, the assessments should be combined. Blood volume estimates do not include safety labs performed after PN adjustments.

Consistent with standard medical practice, efforts to minimize pain and discomfort during procedures such as peripheral venipuncture should be implemented as applicable. This may include oral sucrose solutions, a pacifier, distraction techniques, and the use of topical anesthetic such as EMLA.

Physical Examinations, Vital Signs, Weight, Length, and Head Circumference

Physical examinations will be performed according to the study schedules (Table 1 and Table 2). Any new clinically significant findings noted during physical examinations should be recorded on the appropriate AE page of the eCRF.

Vital signs will be measured according to the study schedules. Measurements will include systolic and diastolic blood pressure (mmHg), pulse (beats per minute), and body temperature (°C/°F). Blood pressure should be determined by the appropriate size cuff (using the same method, the same leg, and in the supine position throughout the study, when possible). Blood pressure measurements should be attempted as part of the vital signs, but lack of blood pressure results will not constitute a protocol deviation. New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Length and head circumference will be measured at selected visits. A height z-score, weight Z-score, and weight/length ratio will be calculated by the sponsor using the site-provided height and weight data collected at each site visit.

7.2.4 Pharmacokinetic Assessments

Subjects will have blood samples taken for teduglutide PK analysis predose, and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the treatment period. Blood for PK sampling should be collected via peripheral IV or venipuncture, not from a central line. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified.

7.2.5 Health Economics and Outcomes Research

Hospitalizations

Each hospitalization that occurs during the study will be recorded, including date of admission, date of discharge, reasons for hospitalization, discharge diagnosis, and discharge status.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, or a symptom is more severe or prolonged than expected given the diagnosis, then symptom(s) should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

AEs that are related to IP that are not resolved at EOS will be followed until the event resolves or stabilizes, as judged by the investigator.

Laboratory values, vital signs, and clinical findings at the scheduled physical examinations must be reported as AEs if the investigator considers the finding to be a clinically significant change from the baseline.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. It is assumed that some of the infants participating in this study may be hospitalized for planned surgery(ies) that will occur during their participation in the study. Such pre-planned, elective surgeries, do not need to be reported as SAEs for this protocol.

8.1.5 Clinical Laboratory and Other Safety Evaluations

An untoward change in the value of a clinical laboratory parameter, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. Clinical significance is defined as any abnormal finding that results in further clinical investigation(s), treatment(s), or the diagnosis of new or progression of established condition. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, or ECG values which were not present at the beginning of the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory value, vital sign, or ECG parameter is clinically significant and represents an AE.

8.1.6 Pregnancy

Not applicable.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.

- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Administration of a dose greater than the allocated dose of the study medication or at a frequency greater than the dosing interval specified by the protocol.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally-authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

All Adverse Events of Special Interest, as defined in Section 8.3, must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event even if the event does not fulfill seriousness criterion.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol, and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested). Fax or e-mail the completed form to the Shire Global Drug Safety Department. A copy of the completed Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the Shire medical monitor or designee using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3, and must be reported to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The Sponsor and/or Clinical Contract Research Organization (CRO) is responsible for notifying the relevant regulatory authorities, and US central Institutional Review Boards (IRBs)/EU central ethics committees (ECs), of related, unexpected SAEs.

In addition, the Clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP633 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

8.3 Adverse Events of Special Interest

An AE of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program and for which ongoing monitoring and immediate notification by the investigator to the sponsor is required.

The AEs of special interest that require expedited regulatory reporting include the following:

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the GI tract including the hepatobiliary system
- Tumor-promoting ability (eg, benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

For AEs of special interest, the sponsor must be informed within 24 hours of first awareness as per the SAE notification instructions described in Section 8.2.2 even if the event does not fulfill the seriousness criteria.

8.4 Dose Interruption Criteria

The investigator is responsible for contacting the sponsor/designee when the subject's teduglutide dosing regimen is interrupted. The length of dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

Investigational product must be interrupted if any of the following events occur:

- An adverse event of special interest (see Section 8.3)
- Intestinal obstruction
- Biliary obstruction
- Pancreatic duct obstruction
- Heart failure with severe fluid overload determined by the sponsor or investigator to be related to IP.

Investigational product must be permanently discontinued if any of the following events occur:

- Severe hypersensitivity, such as anaphylaxis, determined by the investigator to be related to IP.
- Any malignancy

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject' s visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Process

The study will be analyzed by the sponsor or designee. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, US) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the definitions and statistical methods for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

9.4 Planned Interim Analysis, and Data Monitoring Committee

No interim analyses is planned for this the study.

A data monitoring committee (DMC) will be involved in the management of this study. The DMC members will review the data approximately every 3 months according to the DMC Charter. The DMC review will include all cumulative safety data (ie, AEs, laboratory assessments, physical examinations, etc.) from study assessments through each cutoff period. Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of investigational product.

The DMC for this study will be conducted in accordance with the FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006).

The DMC will be an external, independent board comprised of physicians with relevant training. The DMC will be restricted to individuals free of significant conflicts of interest, including, but not limited to, financial, scientific, or regulatory in nature. The DMC will be governed by a Charter agreed to by members of the Board and the sponsor. Members of the Board may not be study investigators or be employed at the same institution as a study investigator, individuals employed by the sponsor, independent contractors hired by the sponsor, or members of regulatory agencies. The DMC may make recommendations to the sponsor regarding study aspects including stopping, modifying or continuing the study; however, the sponsor will have the final responsibility to determine whether the study should be modified or temporarily or permanently stopped. If the DMC recommends termination of this pediatric study, the recommendations will be communicated to the relevant regulatory agencies within 7 calendar days.

9.5 Sample Size Calculation and Power Considerations

The sample size is determined based on enrollment feasibility for this rare condition and the age of the study population.

9.6 Study Population

Intent to treat (ITT) population: All subjects randomized in the study.

Safety analysis population: The safety analysis set will contain all subjects who meet the following criteria:

- Teduglutide treatment arm: subjects who receive at least 1 dose of teduglutide and have undergone at least 1 post-baseline safety assessment; analyses will be performed according to dose group as appropriate.
- Standard of care treatment arm: subjects who have undergone at least 1 post-baseline safety assessment.

Per-protocol population: All subjects in the ITT population without any major protocol deviation that affects interpretation of efficacy results.

Pharmacokinetic analysis population: All subjects who received at least 1 dose of teduglutide and have at least 1 evaluable postdose PK concentration value.

9.7 Efficacy Analyses

9.7.1 Efficacy Endpoints

Efficacy endpoints consist of the following:

9.7.1.1 Primary Efficacy Endpoint

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

9.7.1.2 Secondary Efficacy Endpoints

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by Week 24
- Time to achieve enteral autonomy
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT

9.7.2 Method of Analysis-Efficacy Endpoints

Due to the limited size of the study population, descriptive statistics will be used with a goal of summarizing the sample. As such, no claims of significance will be made for any of the data. Continuous variables will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm. Descriptive statistics will be used to summarize time to achievement of enteral autonomy by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

9.8 Safety Analyses

9.8.1 Safety Endpoints

Safety endpoints consist of the following:

- Adverse events
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

9.8.2 Method of Analysis-Safety Endpoints

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg, number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, SAEs will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores, and descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

9.9 Health Economics and Outcomes Research Analyses

Health economics and outcomes research endpoints consist of the following:

- Cumulative number of hospitalization days during the study

Health economics and outcomes research endpoints will be summarized using descriptive statistics (number, mean and standard deviation) at nominal time points.

9.10 Pharmacokinetics Analyses

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points.

Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP.

This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly. The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator will be appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Electronic Case Report Forms

Electronic case report forms are supplied by the sponsor or designee and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data will be recorded directly onto the eCRF.

All data sent to the sponsor must be endorsed by the investigator.

The study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diaries, and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the parent/guardian agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent, where applicable, from the parent(s)/guardian(s) of all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject's legally authorized representative is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject's parent or guardian has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor/designee has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor/designee.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market teduglutide; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2 to 4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	03 Oct 2017	Global
Amendment 1	18 Jan 2018	Global
Amendment 1.1	07 Aug 2018	France-specific
Amendment 2.1	04 Dec 2018	France-specific
Amendment 3.1	24 May 2019	France-specific

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **18 Jan 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Updated emergency contact information to reflect the change of the Contract Research Organization's name.		Emergency Contact Information
Clarified the duration of the screening period and total time on study. Provided a clear definition of study completion. Updated the study schematic to reflect the study design changes.		Synopsis, Section 3.1, Section 3.2
Revised the telephone and clinic visit schedule to assure laboratory measurement could be collected without exceeding weekly/monthly total blood volume restrictions.		Synopsis, Table 1, Section 3.1.2
Moved the PK sampling from Week 6 to Week 7 so that the samples could be collected without exceeding weekly/monthly total blood volume restrictions. Clarified that blood for pharmacokinetic samples of postdose may be taken within ± 10 minutes of the time pre-specified.		Synopsis, Table 1, Section 3.1.2, Section 7.2.4, Table 5
Clarified that end jejunostomy or ileostomy are examples of small bowel ostomy rather than the stratification factors.		Synopsis, Section 3.1.2, Section 6.2.2
Clarified that all subjects regardless of treatment arm are eligible for the extension study.		Synopsis, Section 3.1.3
Clarified that if a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.		Synopsis, Table 2, Section 3.1.3, Section 6.2.3
Clarified that subjects must be 4 to 12 months corrected gestational age at screening.		Synopsis, Section 4.1
Changed dose adjustments to Week 12 rather than at every clinic visit to reduce site burden.		Synopsis, Table 1, Section 6.2.3
Clarified the definition of enteral autonomy.		Synopsis, Section 9.7.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **18 Jan 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Updated the pharmacokinetic endpoint and analysis to reflect that only descriptive statistics will be calculated on plasma teduglutide concentration values. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.		Synopsis, Section 9.10
Removed assessment of the 5-level EuroQol five dimensions questionnaire to reduce caregiver burden.		Synopsis, Table 1, Section 7.2.5, Section 9.9
Clarified that native GLP-2 samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.		Table 2, Section 7.2.2
Inserted a footnote to clarify that parenteral support and parenteral nutrition are used interchangeably.		Section 1.1
Removed the 5 mg vial of teduglutide as this size vial will not be supplied for this study.		Section 6.1
Clarified the procedures for assessing subject compliance.		Section 6.5
Specified that it is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow through performed since the subject's most recent surgery.		Section 7.2.1
Corrected the volume of blood to be collected for native GLP-2.		Table 5
Removed references to subject assent as assent is not possible in a study of infants.		Section 7.1.1, Section 10.3.1
Clarified the definitions of the analysis sets.		Section 9.6
Clarified that an adjustment to enteral nutrition as appropriate is part of the PN/IV adjustment algorithm.		Figure A-1
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout protocol.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1.1**	**Amendment Date** **07 Aug 2018**	**France-specific**
Description of Change and Rationale		**Section(s) Affected by Change**
The Shire contact was updated to [redacted].		Emergency Contact Information
Added an exclusion criterion for Gilbert's disease and liver failure based on the values of the transaminases and of total bilirubin as requested by Agence Nationale de Sécurité du Medicament et des Produits de Santé (ANSM).		Synopsis, Section 4.2
Added an exclusion criterion for hypersensitivity to trace residues of tetracycline to be consistent with the European Summary of Product Characteristics of teduglutide as requested by ANSM.		Synopsis, Section 4.2
Added text to specify that efforts to minimize pain and discomfort during procedures such as peripheral venipuncture will be implemented.		Section 7.2.3

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2.1**	**Amendment Date** **04 Dec 2018**	**France-specific**
Description of Change and Rationale		**Section(s) Affected by Change**
The fax number currently used to send the Shire Medical Monitor a copy of the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol is now retired; a copy of the form must be sent by email only. Updated emergency contact information to reflect the change of Shire medical monitor to [redacted], IQVIA back up medical support to [redacted], and IQVIA phone number for medical emergencies.		Emergency Contact Information
A single email address ([redacted]) is now used to report a Product Quality Complaint, independently from where it has originated.		Product Quality Complaints
Added the new secondary efficacy endpoint "Time to achieve enteral autonomy" and statistical methodology to be used.		Synopsis, Section 9.7.1.2, Section 9.7.2
Updated the information on the clinical studies with teduglutide in pediatric subjects to include the results of TED-C14-006.		Section 1.2
Clarified that teduglutide is the investigational product for this study.		Section 6.1
Updated the dose selection rationale with results from a simulation work using the previous population pharmacokinetic model. Based on the totality of clinical data, 0.05 mg/kg once daily is expected to provide comparable C_{max} concentrations in infants as compared to pediatric patients with SBS and was recommended as an evaluation dosing regimen in Study SHP633-301.		Section 6.2.5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2.1**	**Amendment Date** **04 Dec 2018**	**France-specific**
Description of Change and Rationale		**Section(s) Affected by Change**
Clarified that rescreening of subjects in the study will not be allowed. (Administrative amendment dated 03 Oct 2018)		Section 7.1.1
Clarifications were made to the definition of adverse events.		Section 8.1, Section 8.1.5, Section 8.2.4
Added heart failure with severe fluid overload, determined by the sponsor or investigator to be related to the investigational product, to the list of events leading to interruption of investigational product administration. This addition is in alignment with the warnings and special precautions listed in the investigator brochure.		Section 8.4
As recommended by the FDA, specified that if the DMC recommends termination of this pediatric study, the recommendations will be communicated to the relevant regulatory agencies within 7 calendar days.		Section 9.4
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout the protocol

Appendix 2 Guidelines for Nutritional Support Management During the Study

The nutritional support adjustment guidelines are designed to standardize management of parenteral and enteral nutritional support in this study. Adjustments to nutritional support should be considered at every scheduled clinic visit. Adjustments at phone visits may also be performed, but nutritional assessments at phone visits serve primarily to confirm that nutritional adjustments at prior clinic visits were tolerated.

All attempts should be made to follow the guidelines, but departure from the guidelines will not constitute a protocol deviation.

Clinical judgment is required within the algorithm. Each decision point requires integrating multiple sources of information into a yes/no decision. When individual data points are conflicting, the investigator must use their best judgment in the assessment.

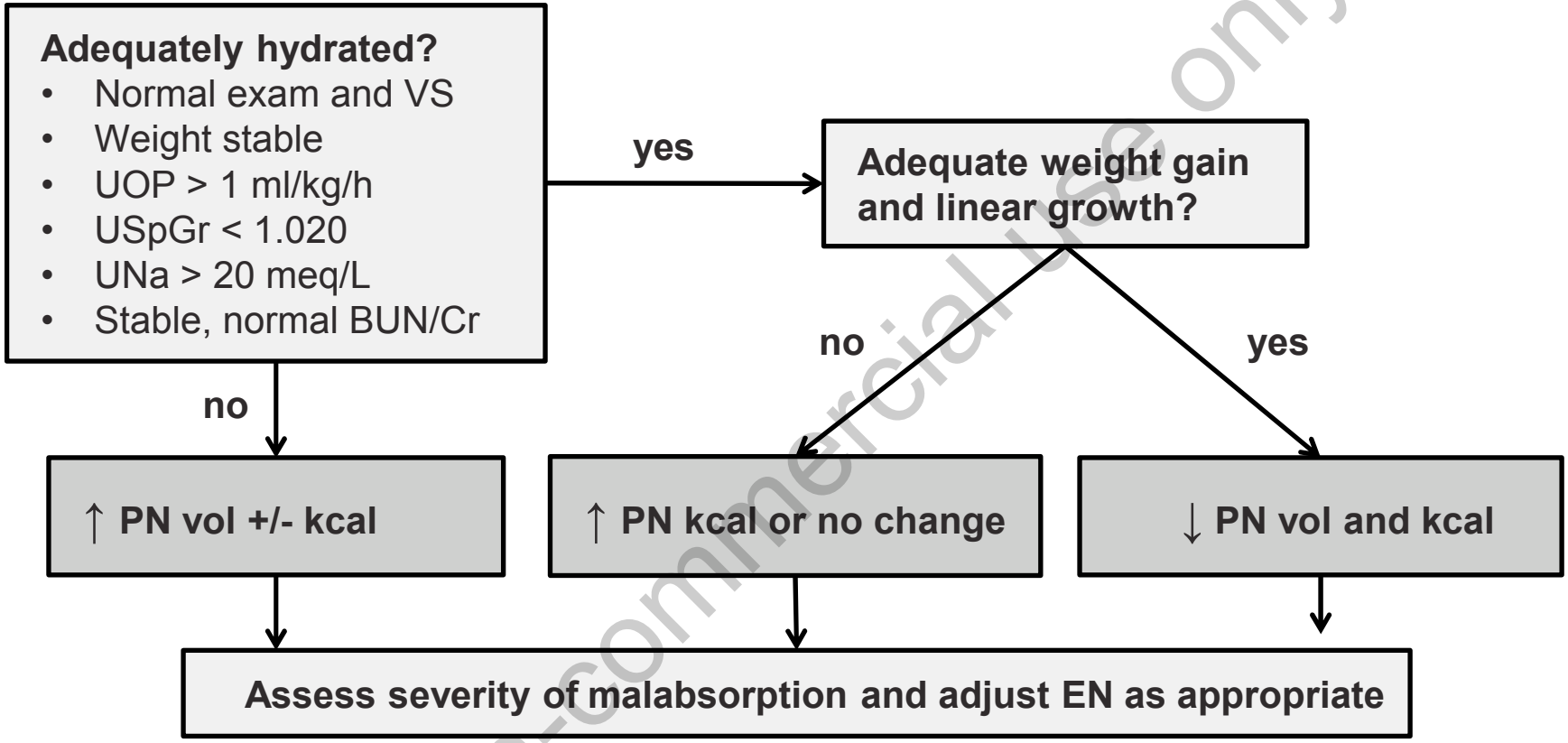
If intestinal adaptation is occurring, reductions in parenteral support volume and calories are expected to be in decrements of 5 to 10% relative to baseline values. Parenteral support components are at the discretion of the investigator, but care should be taken to balance carbohydrate, fat, and protein. Likewise, if intestinal adaptation is occurring, enteral nutrition volume and calories should be increased in increments of approximately 10% relative to baseline values.

Assessment of the severity of malabsorption may require estimation of stool output for children who have mixed stool and urine output.

Adjustments should be based on the actual nutritional support in volume and calories the subject infuses. Subjects should remain compliant with the nutritional support prescription in volume and calories during the study.

During the 48-hour output measurement period prior to the subject's scheduled visit, no further changes to the prescribed nutritional support should be made.

Figure A-1: Parenteral Nutrition/Intravenous Adjustment Algorithm for All Subjects



BUN=blood urea nitrogen; Cr=creatinine; PN=parenteral nutrition; UNa=urine sodium; UOP=urine output; USpGr=Urine specific gravity; VS=vital signs; vol=volume

Shire

Protocol Administrative Amendment
MEMORANDUM

To: SHP633-301 Trial Master File (TMF), SHP633-301 Study Sites
From: [redacted], MD
Date: 6 Sep 2019
Subject: Protocol Administrative Amendment: Change in Section 9.4 to include and Interim Analysis
EUDRACT NO: 2017-003606-40

Protocol Title: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support

Protocol Version: Protocol Amendment 3 dated 24May2019

The following Administrative Amendment is for Protocol SHP633-301, Protocol Amendment 3 dated 24May2019.

Administrative Change : Section 9.4 may be updated to include an Interim Analysis.

These changes are considered administrative in nature and do not compromise the scope, design, or integrity of the study or subject safety in any way. The revisions will be incorporated into any subsequent amendment to the protocol.

Copies of this letter shall be distributed to the Principal Investigators of the study and should be forwarded to the site Ethics Committees as necessary.

If you have further questions, please do not hesitate to contact your CRA or Shire directly.

I have reviewed the above Memorandum and am in agreement with the specified administrative clarifications.

Thank you,

[redacted]

[redacted], MD, PhD, FAAP

[redacted]

SHP633-301 Project Physician

[redacted]

Date

cc: SHP633-301 TMF Main Study File

PROTOCOL: SHP633-301

TITLE:	A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support
NUMBER	SHP633-301
PHASE	3
DRUG:	Teduglutide
INDICATION:	Short bowel syndrome
EUDRACT NO.:	2017-003606-40
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA
PROTOCOL HISTORY:	Original Protocol: 03 Oct 2017 Amendment 1: 18 Jan 2018 Amendment 2: 04 Dec 2018 Amendment 3: 24 May 2019 Amendment 4: 17 Dec 2019

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted]	**Date:** [redacted]
[redacted] MD PhD [redacted] Global Clinical Science	

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-301.

Title: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	_____ _____ _____

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the Shire Medical Monitor by e-mail at [redacted].

For protocol- or safety-related issues, the investigator must contact IQVIA Medical Support:

Primary Contact	**Backup Contact**
[redacted], MD	[redacted], MD, PhD
[redacted]	[redacted]
Mobile: [redacted]	Mobile: [redacted]
Phone: [redacted] (medical emergencies)	Phone: [redacted] (medical emergencies)
Email: [redacted]	Email: [redacted]

In addition, the investigator may also contact Shire:

[redacted], MD

Mobile Phone: [redacted]

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the E-mail address below to report the Product Quality Complaint:

[redacted]

Telephone numbers (provided for reference, if needed):

Shire (USA)
[redacted]

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4**	**Amendment Date** **17 Dec 2019**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Clarified that subjects may enroll in an extension study at end of study (EOS) if that study is open to enrollment at the time of the SHP633-301 EOS.		Synopsis, Table 2, Section 3.1, Section 3.1.3, Section 6.2.3
Clarified when and how parenteral nutrition prescriptions are to be recorded.		Table 1, Table 2, Section 7.2.2
Clarified that at baseline safety labs and PK samples will be separated by 1 day.		Synopsis, Table 1, Table 5, Section 7.2.4
PT/INR measurements should be performed at screening for all subjects instead of baseline for teduglutide-treated subjects.		Table 1, Section 7.2.3, Table 4, Table 5
Specified that C-reactive will not be collected at screening for all subjects and will not be collected at any visit for subjects who weigh <7 kg.		Table 1, Table 4, Table 5
Removed the optional PK measurement at Week 12. Postbaseline PK samples should be performed at Week 7.		Table 1, Section 3.1.2, Table 5
Specified that the predose PK sample will not be collected from subjects who weigh <7 kg.		Table 1, Section 7.2.3, Table 5
Clarified that hematology laboratories are not collected at Week 1. Specified that hematology will not be collected at screening for subjects who weigh <7 kg.		Table 1, Section 7.2.3, Table 4, Table 5
Simplified the language describing the population PK modeling and simulations in previous studies.		Section 6.2.5
Updated to allow 1 rescreening attempt to aide in enrollment.		Section 7.1.1
Clarified information to be collected for the pharmacokinetic assessments.		Section 7.2.4
Interim analysis will be conducted for regulatory submissions, as needed. Analyses will be descriptive in nature. No formal comparisons are planned, and no hypotheses will be formally tested. Due to the open-label nature of this study, personnel involved in conducting the interim analyses will have access to treatment assignments.		Section 9.4
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout the protocol

See Appendix 1 for protocol history, including all amendments.

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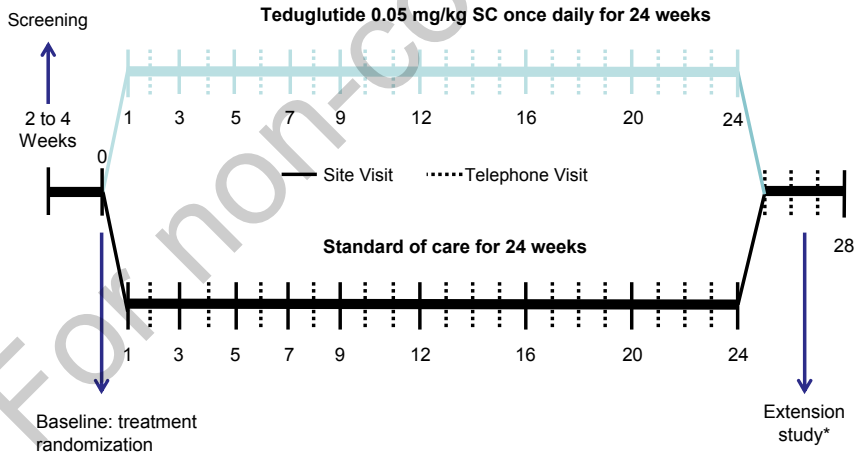
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
AUC_{ss}	area under the concentration-time curve at steady-state
$C_{max,ss}$	maximum plasma concentration at steady state
CRO	contract research organization
eCRF	electronic case report form
DMC	data monitoring committee
EDC	electronic data capture
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	glucagon-like peptide
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medicinal Journal Editors
I/O	oral fluid intake and urine output
IP	Investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PN	parenteral nutrition
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
SD	standard deviation
SOC	standard of care
ULN	upper limit of normal
US	United States

STUDY SYNOPSIS

Protocol number: SHP633-301	**Drug:** Teduglutide
Title of the study: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support	
Number of subjects (total and for each treatment arm): At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in a standard of care (SOC) comparator arm	
Investigator(s): Multicenter study	
Site(s) and Region(s): This study is planned to be conducted in approximately 5 to 10 sites globally.	
Study period (planned): 2017-2020	**Clinical phase:** 3
Objectives: The objectives of this clinical study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with short bowel syndrome (SBS) dependent on parenteral support.	
Investigational product, dose, and mode of administration: Teduglutide 0.05 mg/kg by subcutaneous (SC) injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm.	
Methodology: This is a randomized, multicenter, open-label study, consisting of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period.  * At EOS all subjects regardless of treatment arm may enroll in an extension study if that study is open to enrollment at the time of the SHP633-301 EOS that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one "escape" criteria is met.	

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum 4 weeks). At the baseline visit (Week 0), subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for parenteral nutrition (PN) reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 (2 hours±10 minutes postdose). At baseline, safety labs and PK will be separated by 1 day.

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study if that study is open to enrollment at the time of the SHP633-301 EOS that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

Inclusion and Exclusion Criteria:

Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length *Z*-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. This criteria was deleted.
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.
8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.
9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µl due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2-week period
13. More than 3 serious complications of intestinal failure (eg, catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

Maximum Duration of Subject Involvement in the Study:

The study consists of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

Endpoints:

Efficacy

Efficacy endpoints consist of the following:

Primary

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

Secondary

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by week 24
- Time to achieve enteral autonomy
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to Week 24/EOT

Pharmacokinetics

The pharmacokinetic endpoint is plasma teduglutide concentration at nominal time points.

Safety

Safety endpoints consist of the following:

- Adverse events (AEs)
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

Health Economics and Outcomes Research

Health economics and outcomes research (HEOR) endpoints include the following:

- Cumulative number of hospitalization days during the study

Statistical Methods:

Efficacy

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm. Descriptive statistics will be used to summarize time to achievement of enteral autonomy by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

Pharmacokinetics

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and will be reported separately.

Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg, number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, serious adverse events will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores; and descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

Health Economics and Outcomes Research

The HEOR endpoints will be summarized descriptively.

STUDY SCHEDULES

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X													
Eligibility	X	X												
Randomization		X												
Demographics	X													
SBS history	X													
Medical and surgical history	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight	X	X	X		X		X		X		X			X
Length and head circumference	X	X					X							X
UGI/SBFT	X													
Safety labs and urinalysis[b, c]	X	X[b]	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	(X)	X
PK sampling[a]		X							[X][d]					
Antibodies to teduglutide[a,e]		X												X[e]
Native GLP-2[f]	X													
Provide intake and output diaries[g]	X	X	X		X		X		X		X			X
Review diaries and nutritional support		X	X	X	X	X	X	X	X	X	X	X	X	X
Record PN prescription and adjust nutritional support as needed[h]		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Dispense IP[a, i]		X	X		X		X		X		X			X
Adjust IP dose[j]														X

EN=enteral nutrition; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PK=pharmacokinetics; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] Applicable to the teduglutide treatment arm only.

[b] At baseline, safety labs (Table 4) and PK will be separated by 1 day. Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR will be tested at screening, and repeated if clinically indicated. Hematology is not collected at Week 1 or at telephone visits. Hematology will not be collected at screening for subjects who weigh <7 kg. C-reactive will not be collected at screening for all subjects and will not be collected at any visit for subjects who weigh <7 kg.

[c] Urinalysis will consist of urine sodium and specific gravity. Urine collection should be attempted, but inability to obtain urinalysis is not a protocol deviation.

[d] Subjects will have blood samples taken for teduglutide PK analysis predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). The predose sample will not be collected from subjects who weigh <7 kg. Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) of the treatment period.

[e] Samples for antibody analysis will be drawn at the baseline and Week 12 visits. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.

[f] Blood samples for native GLP-2 should be collected postprandial. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

[i] The initial dose will be calculated based on body weight measured at baseline (Visit 0).

[j] The dose will be adjusted as needed, based on body weight measured at Week 12 visit.

Note: (X) denotes optional assessments.

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Visit type	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**
Study day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**175**	**182**	**189**	**196**
±window (days)	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight				X				X				X				X
Length and head circumference				X				X				X				X
Safety labs and urinalysis[b,c]	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X
Antibodies to teduglutide[d,e]																X
Native GLP-2[f]												X				
Provide intake and output diaries				X				X				X				
Review diaries and nutritional support[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record PN prescription and adjust nutritional support as needed[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess follow-up period escape criteria[d]													X[i]	X[i]	X[i]	X
Dispense IP[d]				X				X								

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Visit type	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site
Study day	91	98	105	112	119	126	133	140	147	154	161	168	175	182	189	196
±window (days)	±3	±3	±3	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4

EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] At EOS subjects may enroll in an extension study if that study is open to enrollment at the time of the SHP633-301 EOS; if subjects require treatment before the end of the 4-week follow-up they may enter the extension study immediately.

[b] Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR are tested if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity.

[d] Applicable to the teduglutide treatment arm only.

[e] Samples for antibody analysis will be drawn at the EOS (Week 28) visit.

[f] Blood samples for native GLP-2 should be collected postprandial. Blood samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

[i] If a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.

Note: (X) denotes optional assessments.

1. BACKGROUND INFORMATION

1.1 Short Bowel Syndrome

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal diseases that result in major surgical resections of the small intestine (O'Keefe et al., 2006). Unlike the adult population, the majority of cases of SBS in pediatric subjects are due to congenital anomalies or catastrophic events that occur during infancy such as necrotizing enterocolitis, gastroschisis, intestinal atresia, midgut volvulus, or long-segment Hirschsprung disease (Beattie et al., 2010; Goulet and Ruemmele, 2006). A Canadian population-based study in neonates estimates an overall incidence of SBS to be 24.5 cases per 100,000 live births (Wales et al., 2004).

The small intestine is capable of remarkable adaptation, but excessive loss of absorptive surface area or specialized functions can lead to dependence on parenteral nutrition (PN)[1] fluids (O'Keefe et al., 2006). Although PN is life-sustaining in intestinal failure, it is associated with serious complications, including liver disease, life-threatening catheter-related blood stream infections, and central venous thrombosis (Beattie et al., 2010; Goulet and Ruemmele, 2006). Dependence on PN is also associated with reduced quality of life in both patients and caregivers and has an extremely high cost of care (Huisman-de Waal et al., 2007). About 30% of infants with SBS become independent of PN requirements within 12 months of the initial insult, and an additional 10% wean off PN within 24 months. After this time, linear intestinal growth slows. It is estimated that 42% to 86% of pediatric patients with SBS are able to become independent of PN within 1 to 3 years (Gonzalez-Hernandez et al., 2017; Khan et al., 2015; Squires et al., 2012). Nevertheless, despite optimal medical management, some children remain dependent on PN for many years (Squires et al., 2012). Infants who have less than 10% of expected small intestinal length for their gestational age have a low likelihood of ever achieving enteral autonomy (ie, independence from parenteral support). Providing the maximum tolerated amount of enteral nutrition (EN) has been the primary strategy to promote enteral adaptation (Spencer et al., 2005).

Accelerating the adaptive process and achieving enteral autonomy is an urgent goal for all patients with SBS who are dependent on PN (Khan et al., 2015; Squires et al., 2012). The adaptive process is in part controlled by glucagon-like peptide 2 (GLP-2), a 33 amino acid peptide hormone secreted from L-type enteroendocrine cells in the terminal ileum and colon in response to luminal nutrients and bile acids (Martin et al., 2006). The post-prandial plasma concentration of GLP-2 in infants with SBS correlates with length of the remaining small intestine (Sigalet et al., 2004). Infants who lack terminal ileum may have impaired adaptation due to inadequate production of GLP-2.

[1] For the purpose of the study the terms parenteral support (PS) and parenteral nutrition (PN) are used interchangeably.

1.2 Teduglutide

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$), approximately 2 hours in healthy adult subjects, 1.3 hours in adult SBS subjects, and 0.22 hours in pediatric SBS subjects, compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines (Tappenden et al., 2013; Thymann et al., 2014).

A Phase 3 study, TED-C13-003, has been completed in pediatric SBS subjects. In this study, teduglutide was administered to 3 cohorts of pediatric subjects from ages 1-17 years. Thirty-seven pediatric subjects received teduglutide at doses of 0.0125, 0.025, or 0.05 mg/kg/day for 12 weeks. Five additional pediatric subjects were enrolled in an observational standard of care (SOC) cohort. There were clear dose-dependent effects of teduglutide seen at the 0.025 and 0.05 mg/kg/day doses compared to SOC and the 0.0125 mg/kg/day dose. In the 0.025 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 37%, including complete independence from PN support in 1 subject, and a reduction of 3.94 hours per day infusion time. In the 0.05 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 39%, including complete independence from PN support in 3 subjects, and a reduction of 4.18 hours per day infusion time. Teduglutide was generally safe and well tolerated by pediatric subjects in all dosing cohorts. There were no deaths during the study and no treatment-emergent serious adverse events (SAEs) related to teduglutide were reported. No discontinuations from study were due to adverse events (AEs). Additional studies in pediatric patients with SBS are ongoing.

TED-C14-006 is a recently completed study of pediatric subjects through 17 years which included 2 treatment arms: a teduglutide treatment arm and a SOC treatment arm. Subjects in both arms participated in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the screening period, subjects chose into which arm to enroll. During the 24-week treatment period, subjects in the SOC treatment arm received standard medical therapy for SBS; while those in the teduglutide treatment arm received daily subcutaneous (SC) injections of teduglutide (study drug) in addition to standard medical therapy. The subjects enrolling in the teduglutide treatment arm were randomized 1:1 in a double-blinded manner into 2 parallel dose groups: 0.025 mg/kg/day or 0.05 mg/kg/day of teduglutide administered subcutaneously for 24 weeks. Compared to the SOC, treatment of pediatric subjects with SBS with teduglutide resulted in clinically meaningful reductions in PN volume, calories, days per week, and hours per day. A total 10% of subjects who received teduglutide achieved enteral autonomy within 24 weeks despite prior dependence on PN for several years. Teduglutide treatment also resulted in increases in EN volume and caloric intake as well as plasma citrulline. Although the differences in efficacy between the 0.025 and 0.05 mg/kg dose groups were small, a consistently greater effect was seen in the 0.05 mg/kg dose in all efficacy parameters.

The pharmacokinetic (PK) properties were well characterized in this population and were consistent with the prior 12 week pediatric study. Teduglutide was generally well tolerated by pediatric subjects with SBS. The safety profile was favorable and consistent with the prior pediatric study, the underlying disease, and previous experience with teduglutide in adult subjects with SBS.

Teduglutide (0.05 mg/kg/day) is currently approved for the treatment of adult patients with SBS in >30 countries. On 29 Jun 2016, the European Commission granted an extension of the Market Authorization for teduglutide for the treatment of patients aged 1 year and above with SBS.

Always refer to the latest version of the investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy and safety of teduglutide (SHP633).

2. OBJECTIVES

2.1 Rationale for the Study

There is no approved pharmacological therapy to improve intestinal adaptation in infants with SBS who are dependent on parenteral support. This study will evaluate whether teduglutide is safe and effective in this patient population.

2.2 Study Objectives

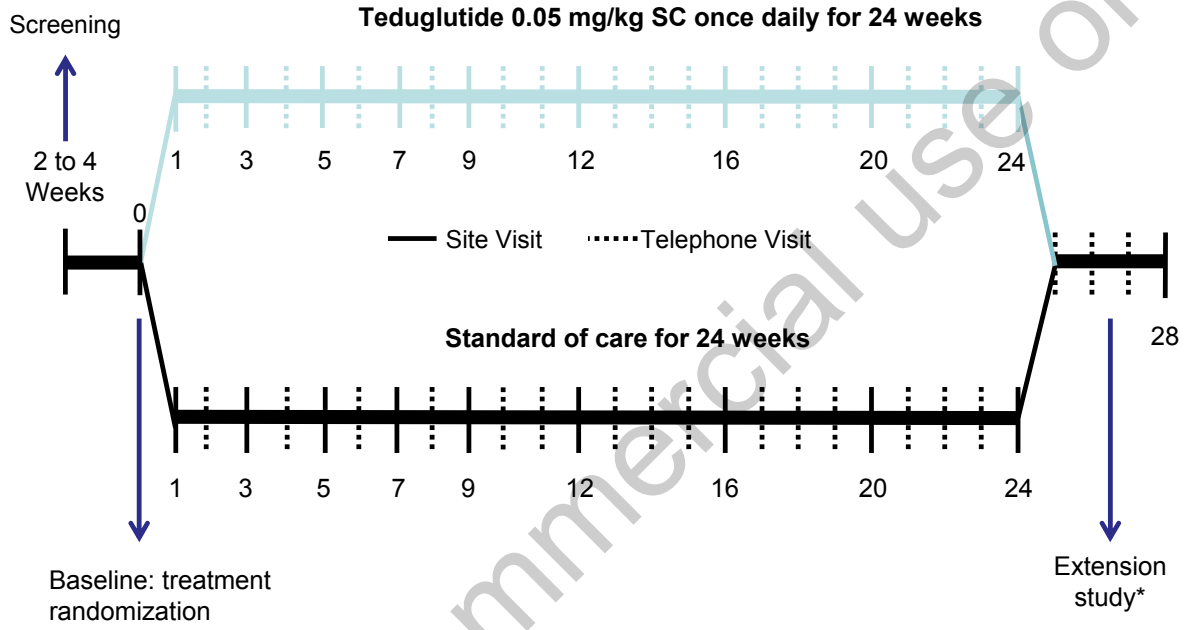
The objectives of this study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with SBS dependent on parenteral support.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a randomized, multicenter, open-label study, consisting of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. A schematic representation of the study design is presented in Figure 1.

Figure 1: Study Schematic



*At EOS all subjects regardless of treatment arm may enroll in an extension study if that study is open to enrollment at the time of the SHP633-301 EOS that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one "escape" criteria is met.

3.1.1 Screening Period

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum: 4 weeks). The schedule of evaluations to be conducted during the Screening Period can be found in Table 1.

3.1.2 Treatment Period

At the baseline visit (Week 0), subjects will randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS, while those in the teduglutide arm will receive 0.05 mg/kg by SC injection once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits.

Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for PN reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability (Appendix 2). Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour±10 minutes and 4 hours±10 minutes postdose) and at Week 7 (2 hours±10 minutes postdose).

The schedule of evaluations for the Treatment Period can be found in Table 1 (Visits -1 to 12) and Table 2 (Visits 13 to 28).

3.1.3 Follow-up Period

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product (IP) will be administered. At EOS, all subjects regardless of treatment arm may enroll in an extension study if that study is open to enrollment at the time of the SHP633-301 EOS that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS visit if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

The schedule of evaluations for the Follow-up Period can be found in Table 2 (Visits 13 to 28).

3.2 Study Duration

The study consists of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

3.3 Sites and Regions

This study is planned to be conducted at approximately 5 to 10 sites globally.

4. STUDY POPULATION

At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in an SOC comparator arm.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. This criteria was deleted.
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.

8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.
9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µL due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2 week period.
13. More than 3 serious complications of intestinal failure (eg, catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.

4.3 Reproductive Potential

Not applicable; this study will enroll infants.

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator should discuss withdrawal of a subject from investigational product with the medical monitor as soon as possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT/early termination are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period. Comments (spontaneous or elicited) or complaints pertaining to IP discontinuation made by the subject must be recorded in the source documents. The reason for discontinuation, the date and the total amount of investigational product administered must be recorded in the electronic case report form (eCRF) and source documents.

Subjects who discontinue will not be replaced.

4.4.1 Reasons for Discontinuation

The reason(s) for permanent discontinuation of treatment and/or withdrawal from the study must be determined by the investigator, and recorded in the subject's medical record and in the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document, and the most clinically relevant reason should be entered in the eCRF.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by parent/guardian
- Lack of efficacy
- Other

4.4.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact the parent(s)/guardian(s) of any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Medications and Procedures

Prior treatment includes all treatment and procedures (including but not limited to prescription treatments, herbal treatments, vitamins, non-pharmacological treatment, as appropriate) received within 14 days prior to the screening visit (Visit -1) (or pharmacokinetic equivalent of 5 half lives, whichever is longer, must be recorded on the appropriate eCRF page.

5.2 Concomitant Medications and Procedures

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins) and PN must be recorded from the first dose of investigational product and for the duration of the study in the appropriate sections of the eCRF. Any diagnostic, surgical or other therapeutic treatments received by a subject during the course of the study will also be recorded on the eCRF.

The mechanism of action of teduglutide may increase enteral absorption of oral drugs (eg, drugs used for management of SBS such as motility medication, opioids, psychotropics, metronidazole), so consideration should be given to modifying concomitant enteral medication regimens. Titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic index (eg, warfarin, digoxin, psychotropics) are given.

5.3 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.4 Prohibited Treatment

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the pretreatment visit (Table 3):

Table 3: Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pretreatment Visit
Teduglutide	Any
GLP-2, human growth hormone, or analogs of these hormones	6 months
Octreotide, GLP-1 analogs, and enteral glutamine	30 days

GLP=glucagon-like peptide

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

The investigational product is teduglutide, which will be provided in sterile, single-use 3 mL vials containing 1.25 mg teduglutide as a white lyophilized powder to be reconstituted before use with 0.5 mL sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the current investigator's brochure.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

All investigative study sites will be initially provided with sufficient investigational product to randomly assign a subject into the study (for either of the proposed treatment groups). Randomization will occur through an interactive response system. Random assignment of a subject will trigger replacement supplies for that investigative study site.

6.2.2 Allocation of Subjects to Treatment

Subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). The actual treatment given to individual subjects is determined by a randomization schedule.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined.

6.2.3 Dosing

The initial dose will be calculated based on body weight measured at baseline (Visit 0), and adjusted as needed, based on body weight measured at Week 12. No other adjustments to dose will be made during the teduglutide treatment period, unless discussed with the sponsor's medical monitor.

Following reconstitution, teduglutide will be administered by SC injection once daily (QD) into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used. Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later.

The subject should be dosed at approximately the same time each day. Consecutive doses should be separated by at least 12 hours. Each day, the injection site should be alternated.

Any subject who achieves complete independence from PN support at any time during the treatment period will continue to receive teduglutide treatment.

The first SC injection in teduglutide-naïve subjects should be administered under the supervision of the investigator or designee and the subject observed for hypersensitivity reactions for at least 4 hours during their initial dosing visit. The site of administration (arm, thigh, and abdomen) of the first teduglutide dose must be specified and recorded in the eCRF.

Detailed instructions for reconstitution and injection of the investigational product can be found in the Instructions for Use.

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study if that study is open to enrollment at the time of the SHP633-301 EOS that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.2.5 Dose Selection Rationale

Teduglutide is approved for adult and pediatric use in the EU at a dose of 0.05 mg/kg SC once daily. A completed 12-week dose finding study (TED-C13-003) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit-risk profile most meaningful at the 0.05 mg/kg/day dose (Carter et al., 2017).

Population pharmacokinetic modeling and simulations were conducted using data from 8 adult clinical studies including adult Phase 1 studies and Phases 2/3 studies as well as study TED-C13-003 and suggested that the same adult dose (0.05mg/kg) be used in pediatric subjects (aged between 1.67-14.7 years) (Marier et al., 2017).

To support dosing in the current age group, further PK simulation was conducted based on the population PK model previously established and a virtual population of 1000 pediatric patients created based on Centers for Disease Control (CDC) growth charts in the target age group (4 to 12 months) and taking into consideration body weights of pediatric patients with SBS enrolled in study TED-C13-003 and TED-C14-006 (approximately 15% lower than healthy subjects in the same age group). The model was customized by including a maturation function on clearance (CL/F) as a function of estimated glomerular filtration rate. Monte Carlo simulations for all age groups were performed according to the SC dosing regimens of 0.0125, 0.025 and 0.05 mg/kg every 24 hours. Rich concentration-time profiles were simulated with the customized population PK model to derive the exposure metrics area under the concentration curve at steady state (AUC_{ss}) and maximum concentration at steady state ($C_{max,ss}$). Exposure parameters in infant patients were compared to those derived in pediatric (1-17 years) and adult (≥18 years) patients with SBS using a Bayesian approach. Based on the clinical observations, C_{max} is considered to be associated with clinical responses. Following 0.05 mg/kg daily SC administration, the median $C_{max,ss}$ of teduglutide in neonate patients (24.9 ng/mL) was within 20% of that observed in the 2 to 4 and 4 to 6 years age groups (26.9 and 29.4 ng/mL, respectively); and approximately ~28% lower than that in adult patients with SBS. The median $C_{max,ss}$ of teduglutide in infant patients 4 to 12 months (41.9 ng/mL) following 0.05 mg/kg once daily was within 8% of that previously observed in adult patients with SBS (39.0 ng/mL, refer to the attached Simulation Report). In addition, individual simulated $C_{max,ss}$ values of teduglutide in infant patients 4 to 12 months (25.6 to 65.1 ng/mL) were contained within the range of $C_{max,ss}$ previously observed in pediatric patients 1 to 17 years (20.7 to 77.4 ng/mL). The clinical package in conjunction with C_{max} was considered to support teduglutide dose selection since AUC_{ss} was previously shown not to correlate with efficacy. Individual simulated AUC_{ss} values of teduglutide in infant patients 4 to 12 months (66.9 to 160 ng.h/mL) following 0.05 mg/kg once daily were contained within the range of AUC_{ss} values previously observed in pediatric patients 1 to 17 years (63.5 to 421 ng.h/mL). Based on the totality of clinical data, 0.05 mg/kg once daily is expected to provide comparable C_{max} concentrations in infants as compared to pediatric patients with SBS and was recommended as an evaluation dosing regimen in Study SHP633-301.

6.3 Labeling, Packaging, and Storage

6.3.1 Labeling

The investigational product will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of investigational product will be provided for this study. The vials will be labeled in accordance with applicable regulatory requirements.

Ancillary kits, containing supplies needed for the reconstitution and administration of the investigational product will also be provided and labeled in accordance with the applicable regulatory requirements.

All investigational product used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice.

6.3.2 Storage and Handling

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2-8°C (35.6-46.4°F) until dispensed to a subject. Once dispensed to a subject, the IP can be stored refrigerated or up to a controlled room temperature (acceptable range of 2-25°C, or 35.6-77°F). Parent/legal guardian will be instructed to keep the subject's IP and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the IP may be refrigerated. The IP is for single use only, and should be used within 3 hours following reconstitution.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels, as they are distributed.

6.4 Drug Accountability

Investigational product will not be dispatched to the study site until the sponsor or designee has received all required documents from the study site in accordance with applicable regulatory requirements and relevant standard operating procedures. Upon receipt, the study site's pharmacist or delegate is responsible for ensuring that all investigational product received at the site is inventoried and accounted for throughout the study. A copy of the shipping documents must be maintained for the investigator's records. Kits will be shipped to the site once the subject is screened.

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Investigational product kits will be dispensed at each of the applicable study visits at which the subject is required to be at the clinic. Each investigational product kit is sufficient for a treatment period of 1 week and enough kits will be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

Each subject will be given the investigational product according to the protocol. The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. All dispensed medication will be documented on the eCRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, subject returned investigational product, and empty/used investigational product packaging are to be sent to the sponsor or designee. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

Returned investigational product must be counted and verified by clinical site personnel and the sponsor (or study monitor). Shipment return forms, when used, must be signed prior to shipment from the site. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

The parent(s)/guardian(s) of subjects must be instructed to bring unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed and recorded at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging.

Subject compliance will be checked by site personnel at every visit by reviewing the subject diaries and asking the subject or the subject's parent or legally-authorized representative if they have administered the investigational product according to instructions. If any doses have been missed, the reason for missed dose should be documented in the subject's source documentation including, as applicable, the eCRF.

The investigator is responsible for contacting the sponsor or designee when the subject's daily investigational product dosing regimen is interrupted. Attempts should be made to contact the sponsor or designee prior to dose interruption. Reasons for dosage interruption may include but are not limited to hospitalization and AEs, a lapse in investigational product delivery, etc.

Subjects who have received 80% of the planned doses administered will be assessed as being compliant with the study protocol.

7. STUDY PROCEDURES

7.1 Study Schedule

Detailed study procedures and assessments to be performed for subjects throughout the study are outlined in the study schedules (Table 1 and Table 2) and must be referred to in conjunction with the instructions provided in this section.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period.

7.1.1 Screening

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the parent(s)/guardian(s) of the subject. The screening visit assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1.

Subjects will be designated as a screen failure if they fail to meet all inclusion criteria and/or meet any of the exclusion criteria. Screen failures will not be administered investigational product.

At the discretion of the investigator, subjects who fail screening may be rescreened one time with prior sponsor approval. In the event of rescreening, the subject should be reconsented, a new subject number assigned, and all screening procedures (except UGI/SBFT if performed within 2 months prior to rescreening) should be repeated.

7.1.2 Treatment Period

The randomized Treatment Period will comprise Weeks 1 to 24, during which all assessments will be performed as outlined in Table 1 and Table 2.

7.1.3 Follow-up Period

The Follow-up Period will comprise Weeks 25 to 28, during which all assessments will be performed as outlined in Table 2.

7.2 Study Evaluations and Procedures

7.2.1 Demographics and Other Baseline Characteristics

Demographics and Medical History

Demographic and/or other baseline variables obtained at the screening and/or baseline visits are listed below. Abnormal findings of clinical significance (if any) will be recorded as past medical history.

- Demography (including age, gestational age, sex, and race)

- Medical history (including surgical history)
- SBS history, including remnant anatomy

Upper Gastrointestinal Series with Small Bowel Follow-through

An upper GI contrast series with small bowel follow-through will be performed on all subjects during the screening period if one has not been done since the subject's last GI surgery.

It is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow-through performed since the subject's most recent surgery.

7.2.2 Efficacy Assessments

Subject Diaries

All available diary data will be reviewed by the investigator or their designee at each clinic and telephone visit to assess clinical status and opportunity for PN reduction and advance in feeds. Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

Intake Diary

Intake diaries will be used to collect and evaluate each subject's nutritional support. The parent/legally authorized representative/study site staff will complete the appropriate fields of the PN and EN sections of the intake diary daily throughout the study.

The following data will be captured in the intake diaries:

- Parenteral support volume and infusion duration
- Enteral nutrition (formula) including volume and calories

Site personnel will determine the actual PN and EN daily calories based on diary entries.

Output Diary

Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit; in addition, output should be recorded for subjects within 1 week of implementing a change in the PN prescription.

Urine data:

- Measure and record the weight of all urine-only diapers. Urine volume will be calculated using the following formula: 1 g (scale weight)=1 mL or 1 cc
- At the discretion of the investigator, the parent or legal guardian/study site staff may be asked to collect the first void after the daily PN infusion to measure specific gravity

Stool data (includes diapers with mixed urine and stool):

- Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency (see Output diary). Stool volume will be calculated using the formula: 1 g (scale weight)=1 mL or 1 cc

All ostomy output volume should be recorded.

Prescribed Parenteral Nutrition

The prescribed PN weekly total volume and days per week will be recorded. Changes in PN prescription that reflect changes in the subject's intestinal absorption are recorded.

Temporary adjustments to PN that last less than 72 hours should be recorded as concomitant medications, not a PN adjustments. Examples include fluid resuscitation during treatment of sepsis or acute gastroenteritis, and modification of PS due to interruption of entral venous access.

Parenteral nutrition prescriptions that last more than 72 hours should be recorded as PN adjustments. Examples include recurrent replacement of fluid losses, titration of PN due to changes in intestinal absorptive function, and discontinuation of PN due to achievement of enteral autonomy.

Native GLP-2

Blood samples for native GLP-2 should be collected postprandial. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

7.2.3 Safety Assessments

Laboratory Evaluations

Safety laboratory tests to be performed at site visits consist of clinical chemistry, hematology, and urinalysis and will be performed as outlined in the study plan (Table 1 and Table 2). Scheduled laboratory testing will be processed by a central lab. All laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the laboratory. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

During the Treatment Period, subjects will also have safety labs within approximately 5 to7 days after a PN adjustment. Safety labs performed after PN adjustment and between site visits will consist of clinical chemistry and urinalysis and may be processed by the central laboratory or a local laboratory.

Local lab results are not required to be entered in the eCRFs; however, if the local lab results indicate any new clinically significant changes, they must be reported as an adverse event (see Section 8). Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

At baseline, blood samples for safety labs and PK will be separated by 1 day. The predose sample will not be collected from subjects who weigh <7 kg.

Safety labs at telephone visits will be collected at the discretion of the investigator.

Hematology will not be collected at Week 1 or at telephone visits. Hematology will not be collected at screening for subjects <7 kg.

For all subjects, prothrombin time (PT) and international normalized ratio (INR), tested at screening, will be repeated if clinically indicated.

New clinically significant labs should be reported as AEs.

Close Monitoring Criteria Related To Liver Test Abnormalities:

The investigator should contact the medical monitor within 24 hours of their awareness if the subject develops any of the following changes in laboratory parameters:

- ALT or AST >5x ULN and >2x baseline value
- Total or direct bilirubin that is >2x baseline value or an absolute increase of ≥3 mg/dL (51.3 µmol/L)

If such changes are observed, the labs should be repeated along with an INR, and an inquiry should be made as to the presence of clinical symptoms consistent with new liver injury. The subject should be followed closely to determine the trajectory of the laboratory abnormalities and appropriate evaluations should be made, such as abdominal ultrasound with Doppler imaging to exclude vascular causes and biliary obstruction, consideration of sepsis, liver hypoperfusion, acute viral hepatitis (such as hepatitis A, EBV, or HSV), exposure to hepatotoxic medications, mitochondrial hepatopathy, or metabolic liver disease (such as hereditary fructose intolerance or arginosuccinate synthetase deficiency). Further evaluations can be performed at the discretion of the investigator in consultation with the Shire medical monitor.

The following clinical laboratory assessments will be performed according to the study schedules:

Table 4: List of Laboratory Tests

Biochemistry:

- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bicarbonate
- Bilirubin (total and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- C-reactive protein[c]
- Creatinine
- Estimated Glomerular Filtration Rate (Schwartz formula)
- Gamma-glutamyl transferase
- Glucose
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Triglycerides

Hematology[a]:

- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- Red blood cell morphology, if needed
- White blood cell count with differential

Coagulation[b]:

- Prothrombin time
- International normalized ratio

Urinalysis:

- Specific gravity
- Urine Sodium

[a] Hematology will not be collected at Week 1 or at telephone visits. Hematology will not be collected at screening for subjects <7 kg.

[b] For all subjects, PT and INR will be tested at screening and repeated only if clinically indicated.

[c] C-reactive protein will not be collected at screening for all subjects and will not be collected at any visit for subjects <7 kg.

Antibodies to Teduglutide

Blood samples will be drawn to test for antibodies to teduglutide. Samples will be taken before teduglutide administration at the screening visit (Visit -1) and at least 14 hours after the previous dose at Week 12 (Visit 12); samples may be drawn from a central line or peripheral access. One additional sample will be collected at the EOS 4 weeks after the EOT (ie, Week 28 or EOS).

Volume of Blood

Efforts will be made to minimize the amount of blood drawn from all pediatric subjects participating in this study. The volumes of blood to be drawn from each subject will vary depending on clinical status. Approximate volumes of blood to be drawn from each subject are shown in Table 5.

Table 5: Approximate Volume of Blood to be Drawn from Each Subject

Assessment	Sample Volume (mL)	No. Samples for Subjects > 7kg	Total Volume (mL)
Subjects Receiving Teduglutide Treatment			
Biochemistry (not including CRP)	1.1	12	13.2
CRP[a]	1.1	11	12.1
Hematology[b]	1.2	11	13.2
Coagulation Parameters[c]	1.4	1	1.4
Antibodies	2.0	3	6.0
Pharmacokinetics[d]	2.0	4	8.0
Native GLP-2[e]	1.5	2	3
Total mL:			**56.9**
Subjects Receiving Standard of Care			
Biochemistry (not including CRP)	1.1	12	13.2
CRP[a]	1.1	11	12.1
Hematology[b]	1.2	11	13.2
Coagulation Parameters[c]	1.4	1	1.4
Native GLP-2 [e]	1.5	2	3.0
Total mL:			**42.9**

CRP=C-reactive protein; GLP=glucagon-like peptide; INR=international normalized ratio; PT=prothrombin time

[a] C-reactive will not be collected at screening for all subjects and will not be collected at any visit for subjects <7 kg.

[b] Hematology will not be collected at Week 1 or at telephone visits. Hematology will not be collected at screening for subjects <7 kg.

[c] PT and INR tested at screening only, repeat while on study only if clinically indicated.

[d] At baseline, safety labs and PK will be separated by 1 day. Baseline: 3 timepoints; The predose sample will not be collected from subjects who weigh <7 kg. Week 7: 1 timepoint.

[e] Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

Note: The amount of blood to be drawn for each assessment is an estimate. Blood volume estimates do not include safety labs performed after PN adjustments.

Physical Examinations, Vital Signs, Weight, Length, and Head Circumference

Physical examinations will be performed according to the study schedules (Table 1 and Table 2). Any new clinically significant findings noted during physical examinations should be recorded on the appropriate AE page of the eCRF.

Vital signs will be measured according to the study schedules. Measurements will include systolic and diastolic blood pressure (mmHg), pulse (beats per minute), and body temperature (°C/°F). Blood pressure should be determined by the appropriate size cuff (using the same method, the same leg, and in the supine position throughout the study, when possible).

Blood pressure measurements should be attempted as part of the vital signs, but lack of blood pressure results will not constitute a protocol deviation. New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Length and head circumference will be measured at selected visits. A height z-score, weight Z-score, and weight/length ratio will be calculated by the sponsor using the site-provided height and weight data collected at each site visit.

7.2.4 Pharmacokinetic Assessments

Subjects will have blood samples taken for teduglutide PK analysis predose, and 1 hour±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). At baseline, safety labs and PK will be separated by 1 day. Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) of the treatment period. Blood for PK sampling should be collected via peripheral IV or venipuncture, not from a central line. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified as well as the exact date and time of the sample.

7.2.5 Health Economics and Outcomes Research

Hospitalizations

Each hospitalization that occurs during the study will be recorded, including date of admission, date of discharge, reasons for hospitalization, discharge diagnosis, and discharge status.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, or a symptom is more severe or prolonged than expected given the diagnosis, then symptom(s) should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

AEs that are related to IP that are not resolved at EOS will be followed until the event resolves or stabilizes, as judged by the investigator.

Laboratory values, vital signs, and clinical findings at the scheduled physical examinations must be reported as AEs if the investigator considers the finding to be a clinically significant change from the baseline.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. It is assumed that some of the infants participating in this study may be hospitalized for planned surgery(ies) that will occur during their participation in the study. Such pre-planned, elective surgeries, do not need to be reported as SAEs for this protocol.

8.1.5 Clinical Laboratory and Other Safety Evaluations

An untoward change in the value of a clinical laboratory parameter, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. Clinical significance is defined as any abnormal finding that results in further clinical investigation(s), treatment(s), or the diagnosis of new or progression of established condition. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, or ECG values which were not present at the beginning of the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory value, vital sign, or ECG parameter is clinically significant and represents an AE.

8.1.6 Pregnancy

Not applicable.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.

- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Administration of a dose greater than the allocated dose of the study medication or at a frequency greater than the dosing interval specified by the protocol.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally-authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

All Adverse Events of Special Interest, as defined in Section 8.3, must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event even if the event does not fulfill seriousness criterion.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol, and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested). Fax or e-mail the completed form to the Shire Global Drug Safety Department. A copy of the completed Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the Shire medical monitor or designee using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3, and must be reported to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The Sponsor and/or Clinical Contract Research Organization (CRO) is responsible for notifying the relevant regulatory authorities, and US central Institutional Review Boards (IRBs)/EU central ethics committees (ECs), of related, unexpected SAEs.

In addition, the Clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP633 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

8.3 Adverse Events of Special Interest

An AE of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program and for which ongoing monitoring and immediate notification by the investigator to the sponsor is required.

The AEs of special interest that require expedited regulatory reporting include the following:

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the GI tract including the hepatobiliary system
- Tumor-promoting ability (eg, benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

For AEs of special interest, the sponsor must be informed within 24 hours of first awareness as per the SAE notification instructions described in Section 8.2.2 even if the event does not fulfill the seriousness criteria.

8.4 Dose Interruption Criteria

The investigator is responsible for contacting the sponsor/designee when the subject's teduglutide dosing regimen is interrupted. The length of dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

Investigational product must be interrupted if any of the following events occur:

- An adverse event of special interest (see Section 8.3)
- Intestinal obstruction
- Biliary obstruction
- Pancreatic duct obstruction
- Heart failure with severe fluid overload determined by the sponsor or investigator to be related to IP.

Investigational product must be permanently discontinued if any of the following events occur:

- Severe hypersensitivity, such as anaphylaxis, determined by the investigator to be related to IP.
- Any malignancy

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Process

The study will be analyzed by the sponsor or designee. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, US) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the definitions and statistical methods for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

9.4 Planned Interim Analysis, and Data Monitoring Committee

Interim analysis will be conducted for regulatory submissions, as needed. Analyses will be descriptive in nature. No formal comparisons are planned, and no hypotheses will be formally tested. Due to the open-label nature of this study, personnel involved in conducting the interim analyses will have access to treatment assignments.

A data monitoring committee (DMC) will be involved in the management of this study. The DMC members will review the data approximately every 3 months according to the DMC Charter. The DMC review will include all cumulative safety data (ie, AEs, laboratory assessments, physical examinations, etc.) from study assessments through each cutoff period.

Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of investigational product.

The DMC for this study will be conducted in accordance with the FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006).

The DMC will be an external, independent board comprised of physicians with relevant training. The DMC will be restricted to individuals free of significant conflicts of interest, including, but not limited to, financial, scientific, or regulatory in nature. The DMC will be governed by a Charter agreed to by members of the Board and the sponsor. Members of the Board may not be study investigators or be employed at the same institution as a study investigator, individuals employed by the sponsor, independent contractors hired by the sponsor, or members of regulatory agencies. The DMC may make recommendations to the sponsor regarding study aspects including stopping, modifying or continuing the study; however, the sponsor will have the final responsibility to determine whether the study should be modified or temporarily or permanently stopped. If the DMC recommends termination of this pediatric study, the recommendations will be communicated to the relevant regulatory agencies within 7 calendar days.

9.5 Sample Size Calculation and Power Considerations

The sample size is determined based on enrollment feasibility for this rare condition and the age of the study population.

9.6 Study Population

Intent to treat (ITT) population: All subjects randomized in the study.

Safety analysis population: The safety analysis set will contain all subjects who meet the following criteria:

- Teduglutide treatment arm: subjects who receive at least 1 dose of teduglutide and have undergone at least 1 post-baseline safety assessment; analyses will be performed according to dose group as appropriate.
- Standard of care treatment arm: subjects who have undergone at least 1 post-baseline safety assessment.

Per-protocol population: All subjects in the ITT population without any major protocol deviation that affects interpretation of efficacy results.

Pharmacokinetic analysis population: All subjects who received at least 1 dose of teduglutide and have at least 1 evaluable postdose PK concentration value.

9.7 Efficacy Analyses

9.7.1 Efficacy Endpoints

Efficacy endpoints consist of the following:

9.7.1.1 Primary Efficacy Endpoint

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

9.7.1.2 Secondary Efficacy Endpoints

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by Week 24
- Time to achieve enteral autonomy
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT

9.7.2 Method of Analysis-Efficacy Endpoints

Due to the limited size of the study population, descriptive statistics will be used with a goal of summarizing the sample. As such, no claims of significance will be made for any of the data. Continuous variables will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm. Descriptive statistics will be used to summarize time to achievement of enteral autonomy by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

9.8 Safety Analyses

9.8.1 Safety Endpoints

Safety endpoints consist of the following:

- Adverse events
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

9.8.2 Method of Analysis-Safety Endpoints

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg, number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, SAEs will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores, and descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

9.9 Health Economics and Outcomes Research Analyses

Health economics and outcomes research endpoints consist of the following:

- Cumulative number of hospitalization days during the study

Health economics and outcomes research endpoints will be summarized using descriptive statistics (number, mean and standard deviation) at nominal time points.

9.10 Pharmacokinetics Analyses

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points.

Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and will be reported separately.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP.

This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly. The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator will be appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Electronic Case Report Forms

Electronic case report forms are supplied by the sponsor or designee and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data will be recorded directly onto the eCRF.

All data sent to the sponsor must be endorsed by the investigator.

The study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diaries, and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the parent/guardian agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent, where applicable, from the parent(s)/guardian(s) of all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject's legally authorized representative is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject's parent or guardian has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor/designee has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor/designee.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study.

These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market teduglutide; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2 to 4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	03 Oct 2017	Global
Amendment 1	18 Jan 2018	Global
Amendment 2	04 Dec 2018	Global
Amendment 3	24 May 2019	Global
Amendment 4	17 Dec 2019	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date 18 Jan 2018**	**Global**
Description of Change		**Section(s) Affected by Change**
Updated emergency contact information to reflect the change of the Contract Research Organization's name.		Emergency Contact Information
Clarified the duration of the screening period and total time on study. Provided a clear definition of study completion. Updated the study schematic to reflect the study design changes.		Synopsis, Section 3.1.1, Section 3.2
Revised the telephone and clinic visit schedule to assure laboratory measurement could be collected without exceeding weekly/monthly total blood volume restrictions.		Synopsis, Table 1, Section 3.1.2
Moved the PK sampling from Week 6 to Week 7 so that the samples could be collected without exceeding weekly/monthly total blood volume restrictions. Clarified that blood for pharmacokinetic samples of postdose may be taken within ±10 minutes of the time pre-specified.		Synopsis, Table 1, Section 3.1.2, Section 7.2.4, Table 5
Clarified that end jejunostomy or ileostomy are examples of small bowel ostomy rather than the stratification factors.		Synopsis, Section 3.1.2, Section 6.2.2
Clarified that all subjects regardless of treatment arm are eligible for the extension study.		Synopsis, Section 3.1.3
Clarified that if a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.		Synopsis, Table 2, Section 3.1.3, Section 6.2.3
Clarified that subjects must be 4 to 12 months corrected gestational age at screening.		Synopsis, Section 4.1
Changed dose adjustments to Week 12 rather than at every clinic visit to reduce site burden.		Synopsis, Table 1, Section 6.2.3
Clarified the definition of enteral autonomy.		Synopsis, Section 9.7.2
Updated the pharmacokinetic endpoint and analysis to reflect that only descriptive statistics will be calculated on plasma teduglutide concentration values. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.		Synopsis, Section 9.10
Removed assessment of the 5-level EuroQol five dimensions questionnaire to reduce caregiver burden.		Synopsis, Table 1, Section 7.2.5, Section 9.9

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date 18 Jan 2018**	**Global**
Description of Change		**Section(s) Affected by Change**
Clarified that native GLP-2 samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.		Table 2, Section 7.2.2
Inserted a footnote to clarify that parenteral support and parenteral nutrition are used interchangeably.		Section 1.1
Removed the 5 mg vial of teduglutide as this size vial will not be supplied for this study.		Section 6.1
Clarified the procedures for assessing subject compliance.		Section 6.5
Specified that it is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow through performed since the subject's most recent surgery.		Section 7.2.1
Corrected the volume of blood to be collected for native GLP-2.		Table 5
Removed references to subject assent as assent is not possible in a study of infants.		Section 7.1.1, Section 10.3.1
Clarified the definitions of the analysis sets.		Section 9.6
Clarified that an adjustment to enteral nutrition as appropriate is part of the PN adjustment algorithm.		Figure A-1
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout protocol.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	**Amendment Date 04 Dec 2018**	**Global**
Description of Change		**Section(s) Affected by Change**
The fax number currently used to send the Shire Medical Monitor a copy of the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol is now retired; a copy of the form must be sent by email only. Updated emergency contact information to reflect the change of Shire medical monitor to [redacted], IQVIA back up medical support to [redacted], and IQVIA phone number for medical emergencies.		Emergency Contact Information
A single email address ([redacted]) is now used to report a Product Quality Complaint, independently from where it has originated.		Product Quality Complaints
Added the new secondary efficacy endpoint "Time to achieve enteral autonomy" and statistical methodology to be used.		Synopsis, Section 9.7.1.2, Section 9.7.2
Updated the information on the clinical studies with teduglutide in pediatric subjects to include the results of TED-C14-006.		Section 1.2
Clarified that teduglutide is the investigational product for this study.		Section 6.1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2**	**Amendment Date** **04 Dec 2018**	**Global**
Description of Change		**Section(s) Affected by Change**
Updated the dose selection rationale with results from a simulation work using the previous population pharmacokinetic model. Based on the totality of clinical data, 0.05 mg/kg once daily is expected to provide comparable C_{max} concentrations in infants as compared to pediatric patients with SBS and was recommended as an evaluation dosing regimen in Study SHP633-301.		Section 6.2.5
Clarified that rescreening of subjects in the study will not be allowed. (Administrative amendment dated 03 Oct 2018)		Section 7.1.1
Clarifications were made to the definition of adverse events.		Section 8.1, Section 8.1.5, Section 8.2.4
Added heart failure with severe fluid overload, determined by the sponsor or investigator to be related to the investigational product, to the list of events leading to interruption of investigational product administration. This addition is in alignment with the warnings and special precautions listed in the investigator brochure.		Section 8.4
As recommended by the FDA, specified that if the DMC recommends termination of this pediatric study, the recommendations will be communicated to the relevant regulatory agencies within 7 calendar days.		Section 9.4
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout the protocol

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3**	**Amendment Date** **24 May 2019**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Deleted Inclusion Criteria #6, Lack of terminal ileum and ileocecal valve, due to difficulties in enrollment.		Synopsis, Section 4.1
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout the protocol

Appendix 2 Guidelines for Nutritional Support Management During the Study

The nutritional support adjustment guidelines are designed to standardize management of parenteral and enteral nutritional support in this study. Adjustments to nutritional support should be considered at every scheduled clinic visit. Adjustments at phone visits may also be performed, but nutritional assessments at phone visits serve primarily to confirm that nutritional adjustments at prior clinic visits were tolerated.

All attempts should be made to follow the guidelines, but departure from the guidelines will not constitute a protocol deviation.

Clinical judgment is required within the algorithm. Each decision point requires integrating multiple sources of information into a yes/no decision. When individual data points are conflicting, the investigator must use their best judgment in the assessment.

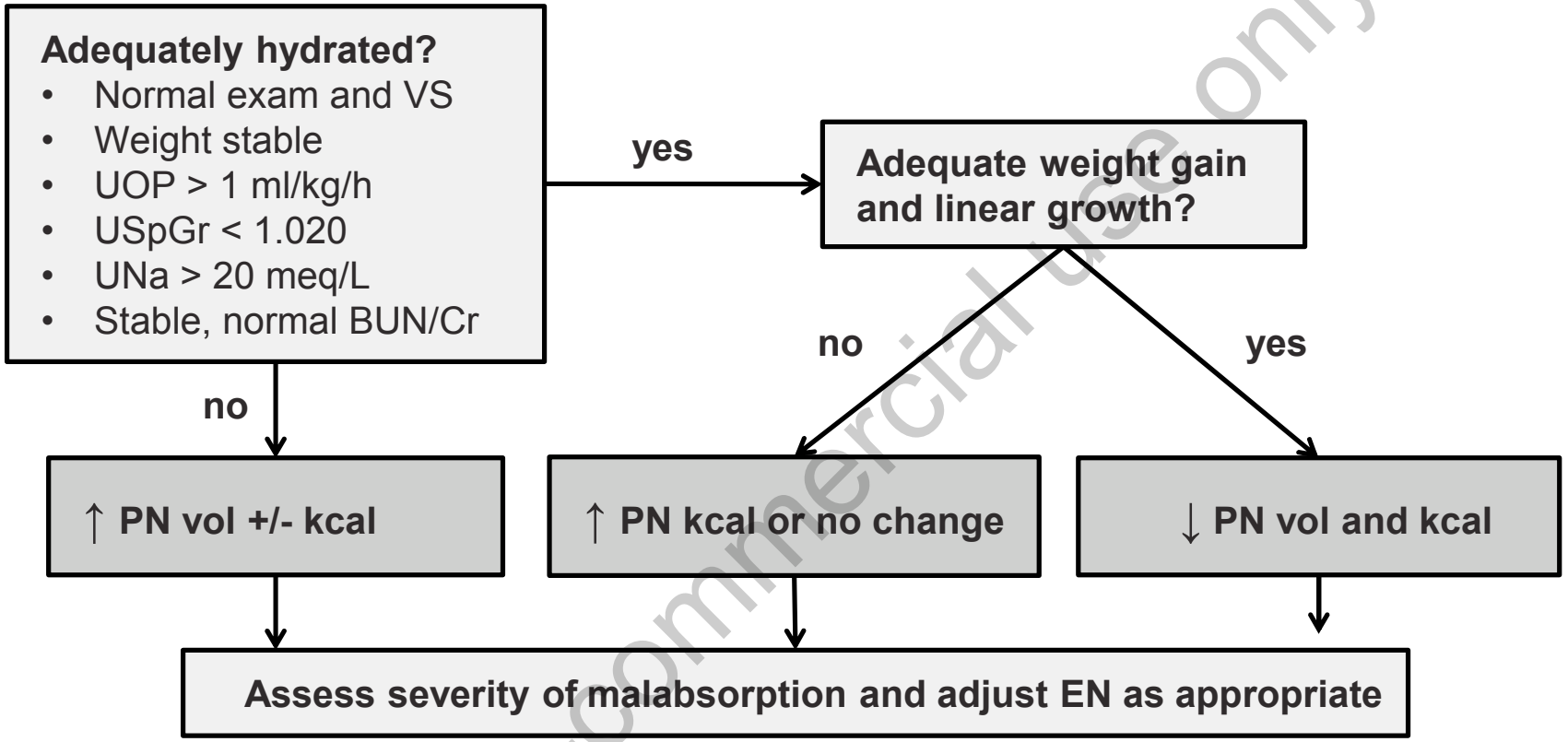
If intestinal adaptation is occurring, reductions in parenteral support volume and calories are expected to be in decrements of 5 to 10% relative to baseline values. Parenteral support components are at the discretion of the investigator, but care should be taken to balance carbohydrate, fat, and protein. Likewise, if intestinal adaptation is occurring, enteral nutrition volume and calories should be increased in increments of approximately 10% relative to baseline values.

Assessment of the severity of malabsorption may require estimation of stool output for children who have mixed stool and urine output.

Adjustments should be based on the actual nutritional support in volume and calories the subject infuses. Subjects should remain compliant with the nutritional support prescription in volume and calories during the study.

During the 48-hour output measurement period prior to the subject's scheduled visit, no further changes to the prescribed nutritional support should be made.

Figure A-1: Parenteral Nutrition/Intravenous Adjustment Algorithm for All Subjects



BUN=blood urea nitrogen; Cr=creatinine; PN=parenteral nutrition; UNa=urine sodium; UOP=urine output; USpGr=Urine specific gravity; VS=vital signs; vol=volume

PROTOCOL: SHP633-301

TITLE:	A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support
NUMBER	SHP633-301
PHASE	3
DRUG:	Teduglutide
INDICATION:	Short bowel syndrome
EUDRACT NO.:	2017-003606-40
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way Lexington, MA 02421 USA
PROTOCOL HISTORY:	Original Protocol: 03 Oct 2017 Amendment 1: 18 Jan 2018 Amendment 1.1: 07 Aug 2018 (France-specific) Amendment 2.1: 04 Dec 2018 (France-specific) Amendment 3.1: 24 May 2019 (France-specific) Amendment 4.1: 17 Dec 2019 (France-specific)

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

Signature: [redacted] **Date:** [redacted]

[redacted] MD PhD
[redacted] Global Clinical Science

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-301.

Title: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines on Good Clinical Practice (GCP) and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: _____
(please hand print or type) _____
_____
_____

Signature: _____ **Date:** _____

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol within 24 hours to the Shire Global Drug Safety Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the Shire Medical Monitor by e-mail at [redacted].

For protocol- or safety-related issues, the investigator must contact IQVIA Medical Support:

Primary Contact	**Backup Contact**
[redacted], MD	[redacted], MD, PhD
[redacted]	[redacted]
Mobile: [redacted]	Mobile: [redacted]
Phone: [redacted] (medical emergencies)	Phone: [redacted] (medical emergencies)
Email: [redacted]	Email: [redacted]

In addition, the investigator may also contact Shire:

[redacted], MD

Mobile Phone: [redacted]

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints to Shire within 24 hours. This includes any instances wherein the quality or performance of a Shire product (marketed or investigational) does not meet expectations (eg, inadequate or faulty closure, product contamination) or that the product did not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products). For instructions on reporting AEs related to product complaints, see Section 8.

Please use the E-mail address below to report the Product Quality Complaint:

[redacted]

Telephone numbers (provided for reference, if needed):

Shire (USA)
[redacted]

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **4.1**	**Amendment Date** **17 Dec 2019**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Clarified that subjects may enroll in an extension study at end of study (EOS) if that study is open to enrollment at the time of the SHP633-301 EOS.		Synopsis, Table 2, Section 3.1, Section 3.1.3, Section 6.2.3
Clarified when and how parenteral nutrition prescriptions are to be recorded.		Table 1, Table 2, Section 7.2.2
Clarified that at baseline safety labs and PK samples will be separated by 1 day.		Synopsis, Table 1, Table 5, Section 7.2.4
PT/INR measurements should be performed at screening for all subjects instead of baseline for teduglutide-treated subjects.		Table 1, Section 7.2.3, Table 4, Table 5
Specified that C-reactive will not be collected at screening for all subjects and will not be collected at any visit for subjects who weigh <7 kg.		Table 1, Table 4, Table 5
Removed the optional PK measurement at Week 12. Postbaseline PK samples should be performed at Week 7.		Table 1, Section 3.1.2, Table 5
Specified that the predose PK sample will not be collected from subjects who weigh <7 kg.		Table 1, Section 7.2.3, Table 5
Clarified that hematology laboratories are not collected at Week 1. Specified that hematology will not be collected at screening for subjects who weigh <7 kg.		Table 1, Section 7.2.3, Table 4, Table 5
Simplified the language describing the population PK modeling and simulations in previous studies.		Section 6.2.5
Updated to allow 1 rescreening attempt to aide in enrollment.		Section 7.1.1
Clarified information to be collected for the pharmacokinetic assessments.		Section 7.2.4
Interim analysis will be conducted for regulatory submissions, as needed. Analyses will be descriptive in nature. No formal comparisons are planned, and no hypotheses will be formally tested. Due to the open-label nature of this study, personnel involved in conducting the interim analyses will have access to treatment assignments.		Section 9.4
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout the protocol

See Appendix 1 for protocol history, including all amendments.

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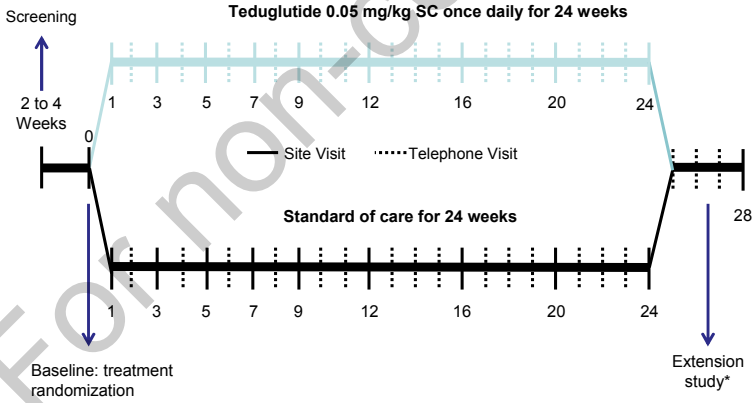
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	adverse event
AUC_{ss}	area under the concentration-time curve at steady-state
$C_{max,ss}$	maximum plasma concentration at steady state
CRO	contract research organization
eCRF	electronic case report form
DMC	data monitoring committee
EDC	electronic data capture
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	glucagon-like peptide
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medicinal Journal Editors
I/O	oral fluid intake and urine output
IP	Investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
PK	pharmacokinetics
PN	parenteral nutrition
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
SD	standard deviation
SOC	standard of care
ULN	upper limit of normal
US	United States

STUDY SYNOPSIS

Protocol number: SHP633-301	**Drug:** Teduglutide
Title of the study: A Randomized, Open-label, 24-Week Safety, Efficacy, and Pharmacokinetic Study of Teduglutide in Infants 4 to 12 Months of Age with Short Bowel Syndrome Who are Dependent on Parenteral Support	
Number of subjects (total and for each treatment arm): At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in a standard of care (SOC) comparator arm	
Investigator(s): Multicenter study	
Site(s) and Region(s): This study is planned to be conducted in approximately 5 to 10 sites globally.	
Study period (planned): 2017-2020	**Clinical phase:** 3
Objectives: The objectives of this clinical study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with short bowel syndrome (SBS) dependent on parenteral support.	
Investigational product, dose, and mode of administration: Teduglutide 0.05 mg/kg by subcutaneous (SC) injection once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm.	
Methodology: This is a randomized, multicenter, open-label study, consisting of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period.  * At EOS all subjects regardless of treatment arm may enroll in an extension study if that study is open to enrollment at the time of the SHP633-301 EOS that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one "escape" criteria is met.	

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum 4 weeks). At the baseline visit (Week 0), subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for parenteral nutrition (PN) reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 or 12 (2 hours±10 minutes postdose). At baseline, safety labs and PK will be separated by 1 day.

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study if that study is open to enrollment at the time of the SHP633-301 EOS that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

Inclusion and Exclusion Criteria:

Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. This criteria was deleted.
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.
8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.
9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/µl due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 µmol/L) over a 2-week period
13. More than 3 serious complications of intestinal failure (eg, catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.
19. Hypersensitivity to trace residues of tetracycline.

20. Signs of active severe or unstable, clinically significant hepatic impairment shown by any of the below laboratory test results at screening:

    a. Total bilirubin ≥2 x upper limit of normal (ULN)

    b. Aspartate aminotransferase (AST) ≥5 x ULN

    c. Alanine aminotransferase (ALT) ≥5 x ULN

    For subjects with Gilbert's disease:

    d. Indirect (unconjugated) bilirubin ≥2 x ULN

Maximum Duration of Subject Involvement in the Study:

The study consists of a 2 to 4 week screening period, a 24-week treatment period, and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

Endpoints:

Efficacy

Efficacy endpoints consist of the following:

Primary

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

Secondary

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by Week 24
- Time to achieve enteral autonomy
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to Week 24/EOT

Pharmacokinetics

The pharmacokinetic endpoint is plasma teduglutide concentration at nominal time points.

Safety

Safety endpoints consist of the following:

- Adverse events (AEs)
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

Health Economics and Outcomes Research

Health economics and outcomes research (HEOR) endpoints include the following:

- Cumulative number of hospitalization days during the study

Statistical Methods:

Efficacy

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm. Descriptive statistics will be used to summarize time to achievement of enteral autonomy by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

Pharmacokinetics

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and will be reported separately.

Safety

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg, number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, serious adverse events will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores; and descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

Health Economics and Outcomes Research

The HEOR endpoints will be summarized descriptively.

STUDY SCHEDULES

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Informed consent	X													
Eligibility	X	X												
Randomization		X												
Demographics	X													
SBS history	X													
Medical and surgical history	X													
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight	X	X	X		X		X		X		X			X
Length and head circumference	X	X					X							X
UGI/SBFT	X													
Safety labs and urinalysis[b, c]	X	X[b]	X	(X)	X	(X)	X	(X)	X	(X)	X	(X)	(X)	X
PK sampling[a]		X							[X][d]					
Antibodies to teduglutide[a,e]		X												X[e]
Native GLP-2[f]	X													
Provide intake and output diaries[g]	X	X	X		X		X		X		X			X
Review diaries and nutritional support		X	X	X	X	X	X	X	X	X	X	X	X	X
Record PN prescription and adjust nutritional support as needed[h]		X	X	X	X	X	X	X	X	X	X	X	X	X

Table 1: Study Schedule: Visits -1 to 12

Procedures	Screening	Baseline (Week 0)	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12
Visit number	**-1**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Visit type	**Site**	**Site**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Site**	**Tel**	**Tel**	**Site**
Study day	**-14**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**	**70**	**77**	**84**
±window (days)	**-2 weeks**		**±2**	**±2**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Dispense IP[a, i]		X	X		X		X		X		X			X
Adjust IP dose[j]														X

EN=enteral nutrition; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PK=pharmacokinetics; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] Applicable to the teduglutide treatment arm only.

[b] At baseline, safety labs (Table 4) and PK will be separated by 1 day. Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR will be tested at screening, and repeated if clinically indicated. Hematology is not collected at Week 1 or at telephone visits. Hematology will not be collected at screening for subjects who weigh <7 kg. C-reactive will not be collected at screening for all subjects and will not be collected at any visit for subjects who weigh <7 kg.

[c] Urinalysis will consist of urine sodium and specific gravity. Urine collection should be attempted, but inability to obtain urinalysis is not a protocol deviation.

[d] Subjects will have blood samples taken for teduglutide PK analysis predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). The predose sample will not be collected from subjects who weigh <7 kg. Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) of the treatment period.

[e] Samples for antibody analysis will be drawn at the baseline and Week 12 visits. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.

[f] Blood samples for native GLP-2 should be collected postprandial. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

[i] The initial dose will be calculated based on body weight measured at baseline (Visit 0).

[j] The dose will be adjusted as needed, based on body weight measured at Week 12 visit.

Note: (X) denotes optional assessments.

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27**	**28**
Visit type	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**	**Tel**	**Tel**	**Tel**	**Site**
Study day	**91**	**98**	**105**	**112**	**119**	**126**	**133**	**140**	**147**	**154**	**161**	**168**	**175**	**182**	**189**	**196**
±window (days)	**±3**	**±3**	**±3**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**	**±4**
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hospitalizations	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination, vital signs, weight				X				X				X				X
Length and head circumference				X				X				X				X
Safety labs and urinalysis[b,c]	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X	(X)	(X)	(X)	X
Antibodies to teduglutide[d,e]																X
Native GLP-2[f]												X				
Provide intake and output diaries				X				X				X				
Review diaries and nutritional support[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record PN prescription and adjust nutritional support as needed[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Assess follow-up period escape criteria[d]													X[i]	X[i]	X[i]	X
Dispense IP[d]				X				X								

Table 2: Study Schedule: Visits 13-28

Procedures	Week 13	Week 14	Week 15	Week 16	Week 17	Week 18	Week 19	Week 20	Week 21	Week 22	Week 23	Week 24 (EOT/ET)	Week 25	Week 26	Week 27	Week 28 (EOS)[a]
Visit number	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Visit type	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site	Tel	Tel	Tel	Site
Study day	91	98	105	112	119	126	133	140	147	154	161	168	175	182	189	196
±window (days)	±3	±3	±3	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4	±4

EN=enteral nutrition; EOS=end of study; EOT=end of treatment; ET=early termination; GLP-2=glucagon-like peptide 2; INR=international normalized ratio; IP=investigational product; PN=parenteral nutrition; PT=prothrombin time; UGI/SBFT=upper GI series with small bowel follow-through

[a] At EOS subjects may enroll in an extension study if that study is open to enrollment at the time of the SHP633-301 EOS; if subjects require treatment before the end of the 4-week follow-up they may enter the extension study immediately.

[b] Safety labs at telephone visits will be collected at the discretion of the investigator. For all subjects in the teduglutide treatment arm, PT and INR are tested if clinically indicated.

[c] Urinalysis will consist of urine sodium and specific gravity.

[d] Applicable to the teduglutide treatment arm only.

[e] Samples for antibody analysis will be drawn at the EOS (Week 28) visit.

[f] Blood samples for native GLP-2 should be collected postprandial. Blood samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

[g] Intake diaries will collect actual PN volume and hours per day and EN volume and calories. Intake diaries should be completed daily throughout the study. Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit, and within 1 week of implementing a change in the PN prescription.

[h] Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

[i] If a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.

Note: (X) denotes optional assessments.

1. BACKGROUND INFORMATION

1.1 Short Bowel Syndrome

Short bowel syndrome (SBS) is a rare disorder resulting from congenital abnormalities or severe intestinal diseases that result in major surgical resections of the small intestine (O'Keefe et al., 2006). Unlike the adult population, the majority of cases of SBS in pediatric subjects are due to congenital anomalies or catastrophic events that occur during infancy such as necrotizing enterocolitis, gastroschisis, intestinal atresia, midgut volvulus, or long-segment Hirschsprung disease (Beattie et al., 2010; Goulet and Ruemmele, 2006). A Canadian population-based study in neonates estimates an overall incidence of SBS to be 24.5 cases per 100,000 live births (Wales et al., 2004).

The small intestine is capable of remarkable adaptation, but excessive loss of absorptive surface area or specialized functions can lead to dependence on parenteral nutrition (PN)[1] fluids (O'Keefe et al., 2006). Although PN is life-sustaining in intestinal failure, it is associated with serious complications, including liver disease, life-threatening catheter-related blood stream infections, and central venous thrombosis (Beattie et al., 2010; Goulet and Ruemmele, 2006). Dependence on PN is also associated with reduced quality of life in both patients and caregivers and has an extremely high cost of care (Huisman-de Waal et al., 2007). About 30% of infants with SBS become independent of PN requirements within 12 months of the initial insult, and an additional 10% wean off PN within 24 months. After this time, linear intestinal growth slows. It is estimated that 42% to 86% of pediatric patients with SBS are able to become independent of PN within 1 to 3 years (Gonzalez-Hernandez et al., 2017; Khan et al., 2015; Squires et al., 2012). Nevertheless, despite optimal medical management, some children remain dependent on PN for many years (Squires et al., 2012). Infants who have less than 10% of expected small intestinal length for their gestational age have a low likelihood of ever achieving enteral autonomy (ie, independence from parenteral support). Providing the maximum tolerated amount of enteral nutrition (EN) has been the primary strategy to promote enteral adaptation (Spencer et al., 2005).

Accelerating the adaptive process and achieving enteral autonomy is an urgent goal for all patients with SBS who are dependent on PN (Khan et al., 2015; Squires et al., 2012). The adaptive process is in part controlled by glucagon-like peptide 2 (GLP-2), a 33 amino acid peptide hormone secreted from L-type enteroendocrine cells in the terminal ileum and colon in response to luminal nutrients and bile acids (Martin et al., 2006). The post-prandial plasma concentration of GLP-2 in infants with SBS correlates with length of the remaining small intestine (Sigalet et al., 2004). Infants who lack terminal ileum may have impaired adaptation due to inadequate production of GLP-2.

[1] For the purpose of the study the terms parenteral support (PS) and parenteral nutrition (PN) are used interchangeably.

1.2 Teduglutide

Teduglutide is a novel, recombinant analog of naturally occurring human GLP-2 that regulates the functional and structural integrity of the cells lining the gastrointestinal (GI) tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$), approximately 2 hours in healthy adult subjects, 1.3 hours in adult SBS subjects, and 0.22 hours in pediatric SBS subjects, compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines (Tappenden et al., 2013; Thymann et al., 2014).

A Phase 3 study, TED-C13-003, has been completed in pediatric SBS subjects. In this study, teduglutide was administered to 3 cohorts of pediatric subjects from ages 1-17 years. Thirty-seven pediatric subjects received teduglutide at doses of 0.0125, 0.025, or 0.05 mg/kg/day for 12 weeks. Five additional pediatric subjects were enrolled in an observational standard of care (SOC) cohort. There were clear dose-dependent effects of teduglutide seen at the 0.025 and 0.05 mg/kg/day doses compared to SOC and the 0.0125 mg/kg/day dose. In the 0.025 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 37%, including complete independence from PN support in 1 subject, and a reduction of 3.94 hours per day infusion time. In the 0.05 mg/kg/day cohort there was a reduction in PN volume at Week 12 of 39%, including complete independence from PN support in 3 subjects, and a reduction of 4.18 hours per day infusion time. Teduglutide was generally safe and well tolerated by pediatric subjects in all dosing cohorts. There were no deaths during the study and no treatment-emergent serious adverse events (SAEs) related to teduglutide were reported. No discontinuations from study were due to adverse events (AEs). Additional studies in pediatric patients with SBS are ongoing.

TED-C14-006 is a recently completed study of pediatric subjects through 17 years which included 2 treatment arms: a teduglutide treatment arm and a SOC treatment arm. Subjects in both arms participated in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the screening period, subjects chose into which arm to enroll. During the 24-week treatment period, subjects in the SOC treatment arm received standard medical therapy for SBS; while those in the teduglutide treatment arm received daily subcutaneous (SC) injections of teduglutide (study drug) in addition to standard medical therapy. The subjects enrolling in the teduglutide treatment arm were randomized 1:1 in a double-blinded manner into 2 parallel dose groups: 0.025 mg/kg/day or 0.05 mg/kg/day of teduglutide administered subcutaneously for 24 weeks. Compared to the SOC, treatment of pediatric subjects with SBS with teduglutide resulted in clinically meaningful reductions in PN volume, calories, days per week, and hours per day. A total 10% of subjects who received teduglutide achieved enteral autonomy within 24 weeks despite prior dependence on PN for several years. Teduglutide treatment also resulted in increases in EN volume and caloric intake as well as plasma citrulline.

Although the differences in efficacy between the 0.025 and 0.05 mg/kg dose groups were small, a consistently greater effect was seen in the 0.05 mg/kg dose in all efficacy parameters. The pharmacokinetic (PK) properties were well characterized in this population and were consistent with the prior 12 week pediatric study. Teduglutide was generally well tolerated by pediatric subjects with SBS. The safety profile was favorable and consistent with the prior pediatric study, the underlying disease, and previous experience with teduglutide in adult subjects with SBS.

Teduglutide (0.05 mg/kg/day) is currently approved for the treatment of adult patients with SBS in >30 countries. On 29 Jun 2016, the European Commission granted an extension of the Market Authorization for teduglutide for the treatment of patients aged 1 year and above with SBS.

Always refer to the latest version of the investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy and safety of teduglutide (SHP633).

2. OBJECTIVES

2.1 Rationale for the Study

There is no approved pharmacological therapy to improve intestinal adaptation in infants with SBS who are dependent on parenteral support. This study will evaluate whether teduglutide is safe and effective in this patient population.

2.2 Study Objectives

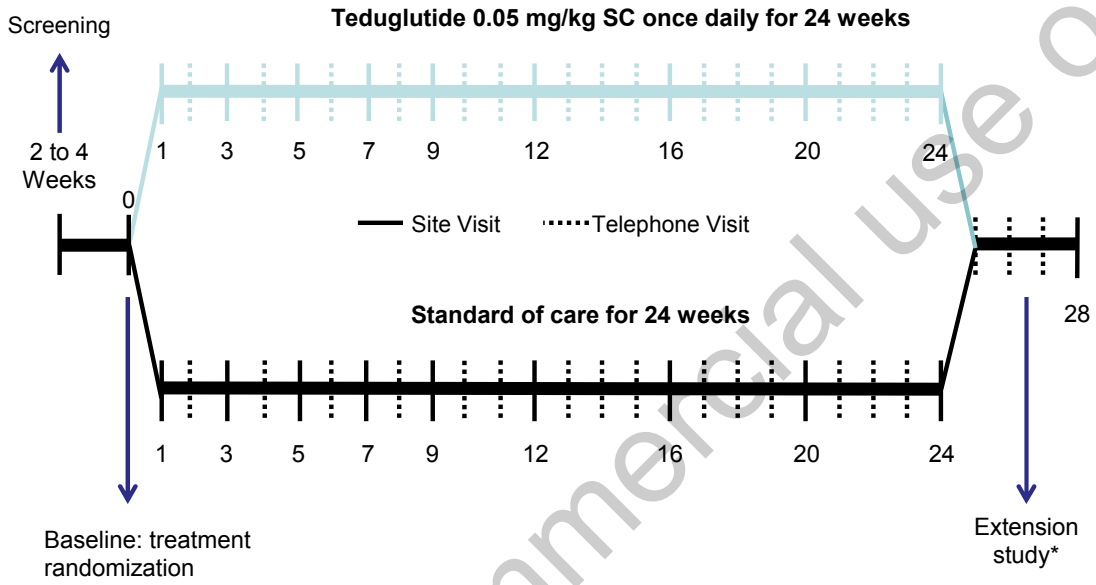
The objectives of this study are to evaluate the safety, efficacy/pharmacodynamics and pharmacokinetics (PK) of teduglutide treatment in infants with SBS dependent on parenteral support.

3. STUDY DESIGN

3.1 Study Design and Flow Chart

This is a randomized, multicenter, open-label study, consisting of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. A schematic representation of the study design is presented in Figure 1.

Figure 1: Study Schematic



*At EOS all subjects regardless of treatment arm may enroll in an extension study if that study is open to enrollment at the time of the SHP633-301 EOS that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one "escape" criteria is met.

3.1.1 Screening Period

Study eligibility will be confirmed during the screening period (minimum: 2 weeks; maximum: 4 weeks). The schedule of evaluations to be conducted during the Screening Period can be found in Table 1.

3.1.2 Treatment Period

At the baseline visit (Week 0), subjects will randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS, while those in the teduglutide arm will receive 0.05 mg/kg by SC injection once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28.

At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. To maintain consistency across centers, guidance and training will be provided to help sites follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) related to decisions for PN reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability (Appendix 2). Deviations from the guidelines are not considered a protocol deviation.

Sparse PK sampling, in the teduglutide treatment arm only, will occur at baseline (predose and 1 hour ±10 minutes and 4 hours ±10 minutes postdose) and at Week 7 (2 hours±10 minutes postdose).

The schedule of evaluations for the Treatment Period can be found in Table 1 (Visits -1 to 12) and Table 2 (Visits 13 to 28).

3.1.3 Follow-up Period

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product (IP) will be administered. At EOS, all subjects regardless of treatment arm may enroll in an extension study if that study is open to enrollment at the time of the SHP633-301 EOS that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS visit if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following discontinuation of teduglutide.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

The schedule of evaluations for the Follow-up Period can be found in Table 2 (Visits 13 to 28).

3.2 Study Duration

The study consists of a 2 to 4-week screening period, a 24-week treatment period and a 4-week follow-up period. The maximum duration of participation for each subject is 32 weeks.

Study completion is defined as the last subject, last visit. This is the visit date at which the last subject on the study has his or her last follow-up visit on the study (whether during the 24-week treatment period or the 4-week follow-up period).

3.3 Sites and Regions

This study is planned to be conducted at approximately 5 to 10 sites globally.

4. STUDY POPULATION

At least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in an SOC comparator arm.

4.1 Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below:

1. Informed consent by the parent or legal guardian.
2. Male or female infant 4 to 12 months corrected gestational age at screening.
3. Weight at least 5 kg and weight-for-length Z-score greater than -2 at screening and baseline.
4. Short bowel syndrome with dependence on parenteral support to provide at least 50% of fluid or caloric needs.
5. Stable PN requirements for at least 1 month prior to screening, defined as a ≤10% change in the weight-normalized parenteral total fluid and caloric intake, despite attempts to wean PN, notwithstanding transient instability for events such as sepsis or interruption of central venous access.
6. This criteria was deleted.
7. Parent or legal guardian understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.2 Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Previous treatment with teduglutide.
2. Intestinal malabsorption due to a genetic condition, such as cystic fibrosis, microvillus inclusion disease, etc.
3. Severe, known dysmotility syndrome, such as pseudo-obstruction or persistent, severe, active gastroschisis-related dysmotility, that is the primary contributing factor to feeding intolerance and inability to reduce parenteral support, prior to screening. Dysmotility is defined as severe if it is expected to limit the advancement of enteral feeding.
4. Inability to advance oral or enteral feeding due to lack of access to the gut, such as oral aversion in the absence of a feeding tube.
5. Intestinal obstruction or clinically significant intestinal stenosis.
6. Major gastrointestinal surgical intervention, such as serial transverse enteroplasty or major intestinal resection or anastomosis, within 3 months prior to screening or planned during the study period.
7. Unstable cardiac disease.
8. Renal dysfunction, defined as estimated glomerular filtration rate <50 mL/min/1.73 m^2.

9. Biliary obstruction, stenosis, or malformation.
10. Clinically significant pancreatic disease.
11. Severe hepatic dysfunction or portal hypertension, defined by at least 2 of the following parameters:
    a. International normalized ratio (INR) >1.5 not corrected with parenteral vitamin K
    b. Platelet count <100×10^3/μL due to portal hypertension
    c. Presence of clinically significant gastric or esophageal varices
    d. Documented cirrhosis
12. Persistent cholestasis defined as conjugated bilirubin >4 mg/dL (>68 μmol/L) over a 2 week period.
13. More than 3 serious complications of intestinal failure (eg, catheter-associated bloodstream infections, interruption of nutrition due to feeding intolerance, catheter-associated thrombosis, severe fluid or electrolyte disturbances) within 1 month prior to or during screening.
14. A history of cancer or a known cancer predisposition syndrome, such as juvenile polyposis or Beckwith-Wiedemann syndrome, or first degree relative with early onset of gastrointestinal cancer (including hepatobiliary and pancreatic cancers).
15. Concurrent treatment with glucagon-like peptide-1 (GLP-1); glucagon-like peptide-2 (GLP-2); insulin-like growth factor-1 (IGF-1); growth hormone, somatostatin, or analogs of these hormones; or glutamine.
16. Participation in a clinical study using an experimental drug within 3 months or 5.5 half-lives of the experimental drug, whichever is longer.
17. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
18. Any condition, disease, illness, or circumstance that, in the investigator's opinion, puts the subject at any undue risk, prevents completion of the study, or interferes with analysis of the study results.
19. Hypersensitivity to trace residues of tetracycline.
20. Signs of active severe or unstable, clinically significant hepatic impairment shown by any of the below laboratory test results at screening:
    a. Total bilirubin ≥2 x upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥5 x ULN
    c. Alanine aminotransferase (ALT) ≥5 x ULN

For subjects with Gilbert's disease:

    d. Indirect (unconjugated) bilirubin ≥2 x ULN
    Reproductive Potential

Not applicable; this study will enroll infants.

4.3 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator should discuss withdrawal of a subject from investigational product with the medical monitor as soon as possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT/early termination are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period. Comments (spontaneous or elicited) or complaints pertaining to IP discontinuation made by the subject must be recorded in the source documents. The reason for discontinuation, the date and the total amount of investigational product administered must be recorded in the electronic case report form (eCRF) and source documents.

Subjects who discontinue will not be replaced.

4.3.1 Reasons for Discontinuation

The reason(s) for permanent discontinuation of treatment and/or withdrawal from the study must be determined by the investigator, and recorded in the subject's medical record and in the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document, and the most clinically relevant reason should be entered in the eCRF.

Reasons for discontinuation include, but are not limited to:

- Adverse event
- Death
- Lost to follow-up
- Physician decision
- Protocol deviation
- Study terminated by sponsor
- Withdrawal by parent/guardian
- Lack of efficacy
- Other

4.3.2 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact the parent(s)/guardian(s) of any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

5.1 Prior Medications and Procedures

Prior treatment includes all treatment and procedures (including but not limited to prescription treatments, herbal treatments, vitamins, non-pharmacological treatment, as appropriate) received within 14 days prior to the screening visit (Visit -1) (or pharmacokinetic equivalent of 5 half lives, whichever is longer, must be recorded on the appropriate eCRF page.

5.2 Concomitant Medications and Procedures

The administration of all medications including concomitant medications (including prescription and nonprescription medications, dietary and nutritional supplements, and vitamins) and PN must be recorded from the first dose of investigational product and for the duration of the study in the appropriate sections of the eCRF. Any diagnostic, surgical or other therapeutic treatments received by a subject during the course of the study will also be recorded on the eCRF.

The mechanism of action of teduglutide may increase enteral absorption of oral drugs (eg, drugs used for management of SBS such as motility medication, opioids, psychotropics, metronidazole), so consideration should be given to modifying concomitant enteral medication regimens. Titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic index (eg, warfarin, digoxin, psychotropics) are given.

5.3 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.4 Prohibited Treatment

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the pretreatment visit (Table 3):

Table 3: Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pretreatment Visit
Teduglutide	Any
GLP-2, human growth hormone, or analogs of these hormones	6 months
Octreotide, GLP-1 analogs, and enteral glutamine	30 days

GLP=glucagon-like peptide

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide arm will receive 0.05 mg/kg SC once daily in addition to standard medical therapy.

The investigational product is teduglutide, which will be provided in sterile, single-use 3 mL vials containing 1.25 mg teduglutide as a white lyophilized powder to be reconstituted before use with 0.5 mL sterile water for injection. In addition to the active ingredient (teduglutide), each vial of teduglutide contains L-histidine, mannitol, monobasic sodium phosphate monohydrate, and dibasic sodium phosphate as excipients. Additional information is provided in the current investigator's brochure.

6.2 Administration of Investigational Product

6.2.1 Interactive Response Technology for Investigational Product Management

All investigative study sites will be initially provided with sufficient investigational product to randomly assign a subject into the study (for either of the proposed treatment groups). Randomization will occur through an interactive response system. Random assignment of a subject will trigger replacement supplies for that investigative study site.

6.2.2 Allocation of Subjects to Treatment

Subjects will be randomized 1:1 to the teduglutide or SOC treatment arm. Randomization will be stratified according to the presence of a small bowel ostomy (eg, end jejunostomy or ileostomy). The actual treatment given to individual subjects is determined by a randomization schedule.

Subject numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), the subject number is assigned to subjects according to the sequence of presentation for study participation.

The randomization number represents a unique number corresponding to investigational product allocated to the subject, once eligibility has been determined.

6.2.3 Dosing

The initial dose will be calculated based on body weight measured at baseline (Visit 0), and adjusted as needed, based on body weight measured at Week 12. No other adjustments to dose will be made during the teduglutide treatment period, unless discussed with the sponsor's medical monitor.

Following reconstitution, teduglutide will be administered by SC injection once daily (QD) into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma should not be used. Teduglutide should be used as soon as possible after reconstitution, but no more than 3 hours later.

The subject should be dosed at approximately the same time each day. Consecutive doses should be separated by at least 12 hours. Each day, the injection site should be alternated.

Any subject who achieves complete independence from PN support at any time during the treatment period will continue to receive teduglutide treatment.

The first SC injection in teduglutide-naïve subjects should be administered under the supervision of the investigator or designee and the subject observed for hypersensitivity reactions for at least 4 hours during their initial dosing visit. The site of administration (arm, thigh, and abdomen) of the first teduglutide dose must be specified and recorded in the eCRF.

Detailed instructions for reconstitution and injection of the investigational product can be found in the Instructions for Use.

At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/EOS) during which time subjects will receive standard medical therapy, but no investigational product will be administered. At EOS all subjects regardless of treatment arm may enroll in an extension study if that study is open to enrollment at the time of the SHP633-301 EOS that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one of the following "escape" criteria is met:

1. Increasing PN requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated EN following teduglutide discontinuation.
3. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
4. Severe diarrhea related to teduglutide discontinuation.

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.2.5 Dose Selection Rationale

Teduglutide is approved for adult and pediatric use in the EU at a dose of 0.05 mg/kg SC once daily. A completed 12-week dose finding study (TED-C13-003) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit-risk profile most meaningful at the 0.05 mg/kg/day dose (Carter et al., 2017).

Population pharmacokinetic modeling and simulations were conducted using data from 8 adult clinical studies including adult Phase 1 studies and Phases 2/3 studies as well as study TED-C13-003 and suggested that the same adult dose (0.05mg/kg) be used in pediatric subjects (aged between 1.67-14.7 years) (Marier et al., 2017).

To support dosing in the current age group, further PK simulation was conducted based on the population PK model previously established and a virtual population of 1000 pediatric patients created based on Centers for Disease Control (CDC) growth charts in the target age group (4 to 12 months) and taking into consideration body weights of pediatric patients with SBS enrolled in study TED-C13-003 and TED-C14-006 (approximately 15% lower than healthy subjects in the same age group). The model was customized by including a maturation function on clearance (CL/F) as a function of estimated glomerular filtration rate. Monte Carlo simulations for all age groups were performed according to the SC dosing regimens of 0.0125, 0.025 and 0.05 mg/kg every 24 hours. Rich concentration-time profiles were simulated with the customized population PK model to derive the exposure metrics area under the concentration curve at steady state (AUC_{ss}) and maximum concentration at steady state ($C_{max,ss}$). Exposure parameters in infant patients were compared to those derived in pediatric (1-17 years) and adult (≥18 years) patients with SBS using a Bayesian approach. Based on the clinical observations, C_{max} is considered to be associated with clinical responses. Following 0.05 mg/kg daily SC administration, the median $C_{max,ss}$ of teduglutide in neonate patients (24.9 ng/mL) was within 20% of that observed in the 2 to 4 and 4 to 6 years age groups (26.9 and 29.4 ng/mL, respectively); and approximately ~28% lower than that in adult patients with SBS. The median $C_{max,ss}$ of teduglutide in infant patients 4 to 12 months (41.9 ng/mL) following 0.05 mg/kg once daily was within 8% of that previously observed in adult patients with SBS (39.0 ng/mL, refer to the attached Simulation Report). In addition, individual simulated $C_{max,ss}$ values of teduglutide in infant patients 4 to 12 months (25.6 to 65.1 ng/mL) were contained within the range of $C_{max,ss}$ previously observed in pediatric patients 1 to 17 years (20.7 to 77.4 ng/mL). The clinical package in conjunction with C_{max} was considered to support teduglutide dose selection since AUC_{ss} was previously shown not to correlate with efficacy. Individual simulated AUC_{ss} values of teduglutide in infant patients 4 to 12 months (66.9 to 160 ng.h/mL) following 0.05 mg/kg once daily were contained within the range of AUC_{ss} values previously observed in pediatric patients 1 to 17 years (63.5 to 421 ng.h/mL). Based on the totality of clinical data, 0.05 mg/kg once daily is expected to provide comparable C_{max} concentrations in infants as compared to pediatric patients with SBS and was recommended as an evaluation dosing regimen in Study SHP633-301.

6.3 Labeling, Packaging, and Storage

6.3.1 Labeling

The investigational product will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of investigational product will be provided for this study. The vials will be labeled in accordance with applicable regulatory requirements.

Ancillary kits, containing supplies needed for the reconstitution and administration of the investigational product will also be provided and labeled in accordance with the applicable regulatory requirements.

All investigational product used in this study will be manufactured, tested, labeled, and released according to current legal requirements and Good Manufacturing Practice.

6.3.2 Storage and Handling

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Investigational product must be kept in a locked area with access restricted to specific study personnel. Investigational product will be stored refrigerated at a temperature between 2-8°C (35.6-46.4°F) until dispensed to a subject. Once dispensed to a subject, the IP can be stored refrigerated or up to a controlled room temperature (acceptable range of 2-25°C, or 35.6-77°F). Parent/legal guardian will be instructed to keep the subject's IP and sterile water diluent at controlled room temperature. If there are concerns that the controlled room temperature cannot be maintained, the IP may be refrigerated. The IP is for single use only, and should be used within 3 hours following reconstitution.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

Investigational products are distributed by the pharmacy or nominated member of the study team. The pharmacist/nominated team member will enter the unique subject identifier on the investigational product bottle/carton labels, as they are distributed.

6.4 Drug Accountability

Investigational product will not be dispatched to the study site until the sponsor or designee has received all required documents from the study site in accordance with applicable regulatory requirements and relevant standard operating procedures. Upon receipt, the study site's pharmacist or delegate is responsible for ensuring that all investigational product received at the site is inventoried and accounted for throughout the study. A copy of the shipping documents must be maintained for the investigator's records. Kits will be shipped to the site once the subject is screened.

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Investigational product kits will be dispensed at each of the applicable study visits at which the subject is required to be at the clinic. Each investigational product kit is sufficient for a treatment period of 1 week and enough kits will be supplied to cover the period until the next planned study visit. Additional study kits will be provided as necessary.

Each subject will be given the investigational product according to the protocol. The investigator is to keep a current record of the inventory and dispensing of all clinical supplies. All dispensed medication will be documented on the eCRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records.

At the end of the study, or as instructed by the sponsor, all unused stock, subject returned investigational product, and empty/used investigational product packaging are to be sent to the sponsor or designee. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

Returned investigational product must be counted and verified by clinical site personnel and the sponsor (or study monitor). Shipment return forms, when used, must be signed prior to shipment from the site. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational product must comply with local, state, and national laws.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

The parent(s)/guardian(s) of subjects must be instructed to bring unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed and recorded at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging.

Subject compliance will be checked by site personnel at every visit by reviewing the subject diaries and asking the subject or the subject's parent or legally-authorized representative if they have administered the investigational product according to instructions. If any doses have been missed, the reason for missed dose should be documented in the subject's source documentation including, as applicable, the eCRF.

The investigator is responsible for contacting the sponsor or designee when the subject's daily investigational product dosing regimen is interrupted. Attempts should be made to contact the sponsor or designee prior to dose interruption. Reasons for dosage interruption may include but are not limited to hospitalization and AEs, a lapse in investigational product delivery, etc.

Subjects who have received 80% of the planned doses administered will be assessed as being compliant with the study protocol.

7. STUDY PROCEDURES

7.1 Study Schedule

Detailed study procedures and assessments to be performed for subjects throughout the study are outlined in the study schedules (Table 1 and Table 2) and must be referred to in conjunction with the instructions provided in this section.

If investigational product is discontinued, regardless of the reason, the evaluations listed for Week 24/EOT are to be performed as completely as possible. Whenever possible, all discontinued subjects should also undergo the protocol-specified 4-week Follow-up Period.

7.1.1 Screening

Prior to performing any study-related procedures (including those related to screening), the investigator or his/her designee must obtain written informed consent from the parent(s)/guardian(s) of the subject. The screening visit assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1.

Subjects will be designated as a screen failure if they fail to meet all inclusion criteria and/or meet any of the exclusion criteria. Screen failures will not be administered investigational product.

At the discretion of the investigator, subjects who fail screening may be rescreened one time with prior sponsor approval. In the event of rescreening, the subject should be reconsented, a new subject number assigned, and all screening procedures (except UGI/SBFT if performed within 2 months prior to rescreening) should be repeated.

7.1.2 Treatment Period

The randomized Treatment Period will comprise Weeks 1 to 24, during which all assessments will be performed as outlined in Table 1 and Table 2.

7.1.3 Follow-up Period

The Follow-up Period will comprise Weeks 25 to 28, during which all assessments will be performed as outlined in Table 2.

7.2 Study Evaluations and Procedures

7.2.1 Demographics and Other Baseline Characteristics

Demographics and Medical History

Demographic and/or other baseline variables obtained at the screening and/or baseline visits are listed below. Abnormal findings of clinical significance (if any) will be recorded as past medical history.

- Demography (including age, gestational age, sex, and race)

- Medical history (including surgical history)
- SBS history, including remnant anatomy

Upper Gastrointestinal Series with Small Bowel Follow-through

An upper GI contrast series with small bowel follow-through will be performed on all subjects during the screening period if one has not been done since the subject's last GI surgery.

It is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow-through performed since the subject's most recent surgery.

7.2.2 Efficacy Assessments

Subject Diaries

All available diary data will be reviewed by the investigator or their designee at each clinic and telephone visit to assess clinical status and opportunity for PN reduction and advance in feeds. Parenteral support adjustments should be made after review of the intake and output diaries and the safety lab data according to the guidance for nutrition support adjustment provided in Appendix 2.

Intake Diary

Intake diaries will be used to collect and evaluate each subject's nutritional support. The parent/legally authorized representative/study site staff will complete the appropriate fields of the PN and EN sections of the intake diary daily throughout the study.

The following data will be captured in the intake diaries:

- Parenteral support volume and infusion duration
- Enteral nutrition (formula) including volume and calories

Site personnel will determine the actual PN and EN daily calories based on diary entries.

Output Diary

Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit; in addition, output should be recorded for subjects within 1 week of implementing a change in the PN prescription.

Urine data:

- Measure and record the weight of all urine-only diapers. Urine volume will be calculated using the following formula: 1 g (scale weight)=1 mL or 1 cc
- At the discretion of the investigator, the parent or legal guardian/study site staff may be asked to collect the first void after the daily PN infusion to measure specific gravity

Stool data (includes diapers with mixed urine and stool):

- Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency (see Output diary). Stool volume will be calculated using the formula: 1 g (scale weight)=1 mL or 1 cc

All ostomy output volume should be recorded.

Prescribed Parenteral Nutrition

The prescribed PN weekly total volume and days per week will be recorded. Changes in PN prescription that reflect changes in the subject's intestinal absorption are recorded.

Temporary adjustments to PN that last less than 72 hours should be recorded as concomitant medications, not a PN adjustments. Examples include fluid resuscitation during treatment of sepsis or acute gastroenteritis, and modification of PS due to interruption of entral venous access.

Parenteral nutrition prescriptions that last more than 72 hours should be recorded as PN adjustments. Examples include recurrent replacement of fluid losses, titration of PN due to changes in intestinal absorptive function, and discontinuation of PN due to achievement of enteral autonomy.

Native GLP-2

Blood samples for native GLP-2 should be collected postprandial. Blood samples while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose. Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

7.2.3 Safety Assessments

Laboratory Evaluations

Safety laboratory tests to be performed at site visits consist of clinical chemistry, hematology, and urinalysis and will be performed as outlined in the study plan (Table 1 and Table 2). Scheduled laboratory testing will be processed by a central lab. All laboratory assays will be performed according to the central laboratory's normal procedures. Reference ranges are to be supplied by the laboratory. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, may, at the discretion of the investigator or sponsor, be repeated as soon as possible until confirmed, explained, or resolved.

During the Treatment Period, subjects will also have safety labs within approximately 5 to 7 days after a PN adjustment. Safety labs performed after PN adjustment and between site visits will consist of clinical chemistry and urinalysis and may be processed by the central laboratory or a local laboratory.

Local lab results are not required to be entered in the eCRFs; however, if the local lab results indicate any new clinically significant changes, they must be reported as an adverse event (see Section 8). Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

At baseline, blood samples for safety labs and PK will be separated by 1 day. The predose sample will not be collected from subjects who weigh <7 kg.

Safety labs at telephone visits will be collected at the discretion of the investigator.

Hematology will not be collected at Week 1 or at telephone visits. Hematology will not be collected at screening for subjects <7 kg.

For all subjects, prothrombin time (PT) and international normalized ratio (INR), tested at screening, will be repeated if clinically indicated.

New clinically significant labs should be reported as AEs.

Close Monitoring Criteria Related To Liver Test Abnormalities:

The investigator should contact the medical monitor within 24 hours of their awareness if the subject develops any of the following changes in laboratory parameters:

- ALT or AST >5x ULN and >2x baseline value
- Total or direct bilirubin that is >2x baseline value or an absolute increase of ≥3 mg/dL (51.3 µmol/L)

If such changes are observed, the labs should be repeated along with an INR, and an inquiry should be made as to the presence of clinical symptoms consistent with new liver injury. The subject should be followed closely to determine the trajectory of the laboratory abnormalities and appropriate evaluations should be made, such as abdominal ultrasound with Doppler imaging to exclude vascular causes and biliary obstruction, consideration of sepsis, liver hypoperfusion, acute viral hepatitis (such as hepatitis A, EBV, or HSV), exposure to hepatotoxic medications, mitochondrial hepatopathy, or metabolic liver disease (such as hereditary fructose intolerance or arginosuccinate synthetase deficiency). Further evaluations can be performed at the discretion of the investigator in consultation with the Shire medical monitor.

The following clinical laboratory assessments will be performed according to the study schedules:

Table 4: List of Laboratory Tests

Biochemistry:

- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bicarbonate
- Bilirubin (total and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- C-reactive protein[c]
- Creatinine
- Estimated Glomerular Filtration Rate (Schwartz formula)
- Gamma-glutamyl transferase
- Glucose
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Triglycerides

Hematology[a]:

- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- Red blood cell morphology, if needed
- White blood cell count with differential

Coagulation[b]:

- Prothrombin time
- International normalized ratio

Urinalysis:

- Specific gravity
- Urine Sodium

[a] Hematology will not be collected at Week 1 or at telephone visits. Hematology will not be collected at screening for subjects <7 kg.
[b] For all subjects in the teduglutide treatment arm, PT and INR will be tested at baseline and repeated only if clinically indicated.
[c] C-reactive protein will not be collected at screening for all subjects and will not be collected at any visit for subjects <7 kg.

Antibodies to Teduglutide

Blood samples will be drawn to test for antibodies to teduglutide. Samples will be taken before teduglutide administration at the screening visit (Visit -1) and at least 14 hours after the previous dose at Week 12 (Visit 12); samples may be drawn from a central line or peripheral access. One additional sample will be collected at the EOS 4 weeks after the EOT (ie, Week 28 or EOS).

Volume of Blood

Efforts will be made to minimize the amount of blood drawn from all pediatric subjects participating in this study. The volumes of blood to be drawn from each subject will vary depending on clinical status. Approximate volumes of blood to be drawn from each subject are shown in Table 5.

Table 5: Approximate Volume of Blood to be Drawn from Each Subject

Assessment	Sample Volume (mL)	No. Samples for Subjects >7 kg	Total Volume (mL)
Subjects Receiving Teduglutide Treatment			
Biochemistry (not including CRP)	1.1	12	13.2
CRP[a]	1.1	11	12.1
Hematology[b]	1.2	11	13.2
Coagulation Parameters[c]	1.4	1	1.4
Antibodies	2.0	3	6.0
Pharmacokinetics[d]	2.0	4	8.0
Native GLP-2[e]	1.5	2	3.0
Total mL:			**56.9**
Subjects Receiving Standard of Care			
Biochemistry (not including CRP)	1.1	12	13.2
CRP[a]	1.1	11	12.1
Hematology[b]	1.2	11	13.2
Coagulation Parameters[c]	1.4	1	1.4
Native GLP-2 [e]	1.5	2	3.0
Total mL:			**42.9**

CRP=C-reactive protein; GLP=glucagon-like peptide; INR=international normalized ratio; PT=prothrombin time

[a] C-reactive will not be collected at screening for all subjects and will not be collected at any visit for subjects <7 kg.

[b] Hematology will not be collected at Week 1 or at telephone visits. Hematology will not be collected at screening for subjects <7 kg.

[c] PT and INR tested at screening only, repeat while on study only if clinically indicated.

[d] At baseline, safety labs and PK will be separated by 1 day. Baseline: 3 timepoints; The predose sample will not be collected from subjects who weigh <7 kg. Week 7: 1 timepoint.

[e] Native GLP-2 may not be collected in some subjects if blood volumes are limiting based on subject weight or at investigator discretion based on weekly/monthly total volume.

Note: The amount of blood to be drawn for each assessment is an estimate. Blood volume estimates do not include safety labs performed after PN adjustments.

Consistent with standard medical practice, efforts to minimize pain and discomfort during procedures such as peripheral venipuncture should be implemented as applicable. This may include oral sucrose solutions, a pacifier, distraction techniques, and the use of topical anesthetic such as EMLA.

Physical Examinations, Vital Signs, Weight, Length, and Head Circumference

Physical examinations will be performed according to the study schedules (Table 1 and Table 2). Any new clinically significant findings noted during physical examinations should be recorded on the appropriate AE page of the eCRF.

Vital signs will be measured according to the study schedules. Measurements will include systolic and diastolic blood pressure (mmHg), pulse (beats per minute), and body temperature (°C/°F). Blood pressure should be determined by the appropriate size cuff (using the same method, the same leg, and in the supine position throughout the study, when possible). Blood pressure measurements should be attempted as part of the vital signs, but lack of blood pressure results will not constitute a protocol deviation. New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Length and head circumference will be measured at selected visits. A height z-score, weight Z-score, and weight/length ratio will be calculated by the sponsor using the site-provided height and weight data collected at each site visit.

7.2.4 Pharmacokinetic Assessments

Subjects will have blood samples taken for teduglutide PK analysis predose, and 1 hour ±10 minutes and 4 hours ±10 minutes postdose at baseline (Visit 0). At baseline, safety labs and PK will be separated by 1 day. Subjects also will have blood samples taken for teduglutide PK analysis 2 hours ±10 minutes postdose at Week 7 (Visit 7) or Week 12 (Visit 12) of the treatment period. Blood for PK sampling should be collected via peripheral IV or venipuncture, not from a central line. The site of teduglutide administration prior to PK blood draws (arm, thigh, abdomen) must be specified as well as the exact date and time of the sample.

7.2.5 Health Economics and Outcomes Research

Hospitalizations

Each hospitalization that occurs during the study will be recorded, including date of admission, date of discharge, reasons for hospitalization, discharge diagnosis, and discharge status.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, or a symptom is more severe or prolonged than expected given the diagnosis, then symptom(s) should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must make the assessment of relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

AEs that are related to IP that are not resolved at EOS will be followed until the event resolves or stabilizes, as judged by the investigator.

Laboratory values, vital signs, and clinical findings at the scheduled physical examinations must be reported as AEs if the investigator considers the finding to be a clinically significant change from the baseline.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved with Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE. It is assumed that some of the infants participating in this study may be hospitalized for planned surgery(ies) that will occur during their participation in the study. Such pre-planned, elective surgeries, do not need to be reported as SAEs for this protocol.

8.1.5 Clinical Laboratory and Other Safety Evaluations

An untoward change in the value of a clinical laboratory parameter, vital sign measure, or ECG assessment can represent an AE if the change is clinically relevant or if, during administration of investigational product, a shift of a parameter is observed from a value in the normative range to a value that is outside the normal range and considered clinically significant, or a further waning of an already clinically significant value. Clinical significance is defined as any abnormal finding that results in further clinical investigation(s), treatment(s), or the diagnosis of new or progression of established condition. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing administration or after the end of administration with the investigational product, and the range of variation of the respective parameter within its reference range, should also be considered.

If, at the end of the treatment phase, there are abnormal clinical laboratory (such as hematology panel or clinical chemistry panel), vital sign, or ECG values which were not present at the beginning of the pretreatment evaluation observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease or expected disease evolution) is found for the abnormal values.

The investigator should assess, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory value, vital sign, or ECG parameter is clinically significant and represents an AE.

8.1.6 Pregnancy

Not applicable.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- **Abuse** – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society.

- **Misuse** – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol).
- **Overdose** – Administration of a dose greater than the allocated dose of the study medication or at a frequency greater than the dosing interval specified by the protocol.
- **Medication Error** – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation.

The administration and/or use of an expired investigational product should be considered as a reportable medication error.

All investigational product provided to pediatric subjects should be supervised by the parent/legally-authorized representative/caregiver.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigator brochure which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

All Adverse Events of Special Interest, as defined in Section 8.3, must be reported by the investigator to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event even if the event does not fulfill seriousness criterion.

The investigator must complete, sign, and date the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by Protocol, and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested). Fax or e-mail the completed form to the Shire Global Drug Safety Department. A copy of the completed Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol (and any applicable follow-up reports) must also be sent to the Shire medical monitor or designee using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A SAE is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term 'life-threatening' in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to investigational product) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3, and must be reported to the Shire Global Drug Safety Department and the Shire Medical Monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered “related” to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Drug Safety Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the informed consent form, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The Sponsor and/or Clinical Contract Research Organization (CRO) is responsible for notifying the relevant regulatory authorities, and US central Institutional Review Boards (IRBs)/EU central ethics committees (ECs), of related, unexpected SAEs.

In addition, the Clinical CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP633 program.

The investigator is responsible for notifying the local IRB, local EC, or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

8.3 Adverse Events of Special Interest

An AE of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program and for which ongoing monitoring and immediate notification by the investigator to the sponsor is required.

The AEs of special interest that require expedited regulatory reporting include the following:

- Growth of pre-existing polyps of the colon
- Benign neoplasia of the GI tract including the hepatobiliary system
- Tumor-promoting ability (eg, benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

For AEs of special interest, the sponsor must be informed within 24 hours of first awareness as per the SAE notification instructions described in Section 8.2.2 even if the event does not fulfill the seriousness criteria.

8.4 Dose Interruption Criteria

The investigator is responsible for contacting the sponsor/designee when the subject's teduglutide dosing regimen is interrupted. The length of dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

Investigational product must be interrupted if any of the following events occur:

- An adverse event of special interest (see Section 8.3)
- Intestinal obstruction
- Biliary obstruction
- Pancreatic duct obstruction
- Heart failure with severe fluid overload determined by the sponsor or investigator to be related to IP.

Investigational product must be permanently discontinued if any of the following events occur:

- Severe hypersensitivity, such as anaphylaxis, determined by the investigator to be related to IP.
- Any malignancy

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. Once a subject is randomized, it is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Statistical Analysis Process

The study will be analyzed by the sponsor or designee. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, US) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the definitions and statistical methods for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, investigational product exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

9.4 Planned Interim Analysis, and Data Monitoring Committee

Interim analysis will be conducted for regulatory submissions, as needed. Analyses will be descriptive in nature. No formal comparisons are planned and no hypotheses will be formally tested. Due to the open-label nature of this study, personnel involved in conducting the interim analyses will have access to treatment assignments.

A data monitoring committee (DMC) will be involved in the management of this study. The DMC members will review the data approximately every 3 months according to the DMC Charter. The DMC review will include all cumulative safety data (ie, AEs, laboratory assessments, physical examinations, etc.) from study assessments through each cutoff period.

Further details regarding the DMC can be found in the DMC charter, which will be available prior to the administration of investigational product.

The DMC for this study will be conducted in accordance with the FDA Guidance for Clinical Trial Sponsors: Establishment and Operation of Clinical Trial Data Monitoring Committees (March 2006).

The DMC will be an external, independent board comprised of physicians with relevant training. The DMC will be restricted to individuals free of significant conflicts of interest, including, but not limited to, financial, scientific, or regulatory in nature. The DMC will be governed by a Charter agreed to by members of the Board and the sponsor. Members of the Board may not be study investigators or be employed at the same institution as a study investigator, individuals employed by the sponsor, independent contractors hired by the sponsor, or members of regulatory agencies. The DMC may make recommendations to the sponsor regarding study aspects including stopping, modifying or continuing the study; however, the sponsor will have the final responsibility to determine whether the study should be modified or temporarily or permanently stopped. If the DMC recommends termination of this pediatric study, the recommendations will be communicated to the relevant regulatory agencies within 7 calendar days.

9.5 Sample Size Calculation and Power Considerations

The sample size is determined based on enrollment feasibility for this rare condition and the age of the study population.

9.6 Study Population

Intent to treat (ITT) population: All subjects randomized in the study.

Safety analysis population: The safety analysis set will contain all subjects who meet the following criteria:

- Teduglutide treatment arm: subjects who receive at least 1 dose of teduglutide and have undergone at least 1 post-baseline safety assessment; analyses will be performed according to dose group as appropriate.
- Standard of care treatment arm: subjects who have undergone at least 1 post-baseline safety assessment.

Per-protocol population: All subjects in the ITT population without any major protocol deviation that affects interpretation of efficacy results.

Pharmacokinetic analysis population: All subjects who received at least 1 dose of teduglutide and have at least 1 evaluable postdose PK concentration value.

9.7 Efficacy Analyses

9.7.1 Efficacy Endpoints

Efficacy endpoints consist of the following:

9.7.1.1 Primary Efficacy Endpoint

- Reduction in weight-normalized PN fluid volume by at least 20% from baseline at Week 24/EOT

9.7.1.2 Secondary Efficacy Endpoints

- Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by Week 24
- Time to achieve enteral autonomy
- Change in weight-normalized parenteral fluid volume from baseline to each visit
- Change in weight-normalized parenteral calories from baseline to each visit
- Change in weight-normalized enteral fluid volume from baseline to each visit
- Change in weight-normalized enteral caloric intake from baseline to each visit
- Increase in weight-normalized enteral fluid intake by at least 20% from baseline to week 24/EOT
- Increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT

9.7.2 Method of Analysis-Efficacy Endpoints

Due to the limited size of the study population, descriptive statistics will be used with a goal of summarizing the sample. As such, no claims of significance will be made for any of the data. Continuous variables will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

Analyses of weekly PN support will be based on 2 data sources: the subject diary data (also referred to as actual data) and the investigator prescribed data.

The number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized average daily PN volume at Week 24/EOT and the number and percentage of subjects who achieve at least a 20% reduction from baseline in weight-normalized parenteral calories at Week 24/EOT will be summarized by treatment arm.

During the treatment period, a subject will be considered to have achieved enteral autonomy (completely weaned off PN) at a given visit if the investigator prescribes no PN at that visit and for the remainder of the treatment period, and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period. During the follow-up period, a subject will be considered to have achieved enteral autonomy at a given visit if the investigator prescribes no PN at that visit and for the remainder of the follow-up period and there is no use of PN recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period. The number and percentage of subjects who achieve enteral autonomy at each scheduled visit, as well as at EOT, will be summarized by treatment arm. Descriptive statistics will be used to summarize time to achievement of enteral autonomy by treatment arm.

The absolute and percent change in weight-normalized weekly PN volume, parenteral calories, enteral fluid volume, and enteral caloric intake, from baseline to each scheduled visit, as well as at EOT, will be summarized by treatment arm using descriptive statistics.

The number and percentage of subjects who demonstrate an increase in weight-normalized enteral fluid intake by at least 20% from baseline to Week 24/EOT and the number and percentage of subjects who demonstrate an increase in weight-normalized enteral caloric intake by at least 20% from baseline to week 24/EOT will be summarized by treatment arm.

9.8 Safety Analyses

9.8.1 Safety Endpoints

Safety endpoints consist of the following:

- Adverse events
- Physical examinations
- Vital signs
- Weight, length, head circumference, and weight-for-length Z-scores (corrected for gestational age)
- Laboratory safety data (biochemistry and hematology)
- Urine output
- Stool (including mixed) output
- Antibodies to teduglutide

9.8.2 Method of Analysis-Safety Endpoints

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent AEs will be summarized by system organ class and preferred term using descriptive statistics (eg, number and percentage of subjects). Adverse events will be summarized by severity and relationship to treatment. In addition, SAEs will also be tabulated by overall and treatment-related events. AEs leading to treatment discontinuation and death will also be summarized.

For laboratory tests; vital signs; urine and stool output; weight, length, and head circumference Z-scores, and descriptive statistics (eg, n, mean, standard deviation, median, minimum and maximum values, and the number and percentage of subjects in specified categories) will be used to summarize the absolute values and change from baseline at each visit.

The number and percentage of subjects classified as having antibodies to teduglutide will be used to summarize the presence of antibodies.

9.9 Health Economics and Outcomes Research Analyses

Health economics and outcomes research endpoints consist of the following:

- Cumulative number of hospitalization days during the study

Health economics and outcomes research endpoints will be summarized using descriptive statistics (number, mean and standard deviation) at nominal time points.

9.10 Pharmacokinetics Analyses

Plasma concentrations will be summarized using descriptive statistics (number, mean, standard deviation, geometric mean, coefficient of variation, minimum, median, and maximum) at nominal time points.

Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and will be reported separately.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, ICH, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third-party vendor (eg, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH Good Clinical Practice (GCP) Guideline E6 (1996), EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current GCP and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Indemnity/Liability and Insurance

The sponsor of this research adheres to the recommendations of the Association of British Pharmaceutical Industry Guidelines. If appropriate, a copy of the indemnity document is supplied to the investigator before study initiation, per local country guidelines.

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of the study. An insurance certificate is supplied as necessary.

10.1.3 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.4 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP.

This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance. The sponsor will provide the ECs with a copy of the same summary.

10.1.5 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly. The sponsor will make an end-of-study declaration to the relevant competent authority as required by Article 10 (c) of Directive 2001/20/EC.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator will be appointed to review the final clinical study report for multicenter studies. Agreement with the final clinical study report is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Electronic Case Report Forms

Electronic case report forms are supplied by the sponsor or designee and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the investigator or designee as stated in the site delegation log. All data will have separate source documentation; no data will be recorded directly onto the eCRF.

All data sent to the sponsor must be endorsed by the investigator.

The study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries are sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, subject diaries, and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor; the respective national, local, or foreign regulatory authorities; the IRB/EC; and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the parent/guardian agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc). Non-study site personnel will not disclose any personal information or personal medical information.

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US FDA, EMA, UK Medicines and Healthcare products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the European Medicines Agency (EMA), the Medicines and Healthcare products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent, where applicable, from the parent(s)/guardian(s) of all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject's legally authorized representative is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject's parent or guardian has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject's legally authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form that was reviewed by the IRB/EC and received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

For sites outside the EU, it is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

The applicant for an EC opinion can be the sponsor or investigator for sites within the EU; for multicenter studies, the applicant can be the coordinating principal investigator or sponsor, according to national provisions.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor/designee has received written IRB/EC approval of and copies of revised documents.

For sites outside the EU, the investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; this can be done by the sponsor or investigator for sites within the EU, or for multicenter studies, it can be done by the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the sponsor/designee.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market teduglutide; national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (eg, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

Study Results/Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2 to 4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must, however, acknowledge in the publication the limitations of the single site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors (ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

11. REFERENCES

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12. APPENDICES

Appendix 1 Protocol History

Document	Date	Global/Country/Site Specific
Original Protocol	03 Oct 2017	Global
Amendment 1	18 Jan 2018	Global
Amendment 1.1	07 Aug 2018	France-specific
Amendment 2.1	04 Dec 2018	France-specific
Amendment 3.1	24 May 2019	France-specific
Amendment 4.1	17 Dec 2019	France-specific

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date 18 Jan 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Updated emergency contact information to reflect the change of the Contract Research Organization's name.		Emergency Contact Information
Clarified the duration of the screening period and total time on study. Provided a clear definition of study completion. Updated the study schematic to reflect the study design changes.		Synopsis, Section 3.1, Section 3.2
Revised the telephone and clinic visit schedule to assure laboratory measurement could be collected without exceeding weekly/monthly total blood volume restrictions.		Synopsis, Table 1, Section 3.1.2
Moved the PK sampling from Week 6 to Week 7 so that the samples could be collected without exceeding weekly/monthly total blood volume restrictions. Clarified that blood for pharmacokinetic samples of postdose may be taken within ± 10 minutes of the time pre-specified.		Synopsis, Table 1, Section 3.1.2, Section 7.2.4, Table 5
Clarified that end jejunostomy or ileostomy are examples of small bowel ostomy rather than the stratification factors.		Synopsis, Section 3.1.2, Section 6.2.2
Clarified that all subjects regardless of treatment arm are eligible for the extension study.		Synopsis, Section 3.1.3
Clarified that if a subject treated with teduglutide meets the escape criteria, the assessments scheduled for the EOS visit should be conducted.		Synopsis, Table 2, Section 3.1.3, Section 6.2.3
Clarified that subjects must be 4 to 12 months corrected gestational age at screening.		Synopsis, Section 4.1
Changed dose adjustments to Week 12 rather than at every clinic visit to reduce site burden.		Synopsis, Table 1, Section 6.2.3
Clarified the definition of enteral autonomy.		Synopsis, Section 9.7.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1**	**Amendment Date** **18 Jan 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Updated the pharmacokinetic endpoint and analysis to reflect that only descriptive statistics will be calculated on plasma teduglutide concentration values. Pharmacokinetic parameters will be estimated using a population PK modeling approach as appropriate and reported separately.		Synopsis, Section 9.10
Removed assessment of the 5-level EuroQol five dimensions questionnaire to reduce caregiver burden.		Synopsis, Table 1, Section 7.2.5, Section 9.9
Clarified that native GLP-2 samples drawn while subjects are receiving teduglutide should be drawn at least 14 hours after the previous dose.		Table 2, Section 7.2.2
Inserted a footnote to clarify that parenteral support and parenteral nutrition are used interchangeably.		Section 1.1
Removed the 5 mg vial of teduglutide as this size vial will not be supplied for this study.		Section 6.1
Clarified the procedures for assessing subject compliance.		Section 6.5
Specified that it is acceptable to only enroll subjects who have already had an upper GI series with small bowel follow through performed since the subject's most recent surgery.		Section 7.2.1
Corrected the volume of blood to be collected for native GLP-2.		Table 5
Removed references to subject assent as assent is not possible in a study of infants.		Section 7.1.1, Section 10.3.1
Clarified the definitions of the analysis sets.		Section 9.6
Clarified that an adjustment to enteral nutrition as appropriate is part of the PN/IV adjustment algorithm.		Figure A-1
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout protocol.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **1.1**	**Amendment Date** **07 Aug 2018**	**France-specific**
Description of Change and Rationale		**Section(s) Affected by Change**
The Shire contact was updated to [redacted].		Emergency Contact Information
Added an exclusion criterion for Gilbert's disease and liver failure based on the values of the transaminases and of total bilirubin as requested by Agence Nationale de Sécurité du Medicament et des Produits de Santé (ANSM).		Synopsis, Section 4.2
Added an exclusion criterion for hypersensitivity to trace residues of tetracycline to be consistent with the European Summary of Product Characteristics of teduglutide as requested by ANSM.		Synopsis, Section 4.2
Added text to specify that efforts to minimize pain and discomfort during procedures such as peripheral venipuncture will be implemented.		Section 7.2.3

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2.1**	**Amendment Date** **04 Dec 2018**	**France-specific**
Description of Change and Rationale		**Section(s) Affected by Change**
The fax number currently used to send the Shire Medical Monitor a copy of the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by Protocol is now retired; a copy of the form must be sent by email only. Updated emergency contact information to reflect the change of Shire medical monitor to [redacted], IQVIA back up medical support to [redacted], and IQVIA phone number for medical emergencies.		Emergency Contact Information
A single email address ([redacted]) is now used to report a Product Quality Complaint, independently from where it has originated.		Product Quality Complaints
Added the new secondary efficacy endpoint "Time to achieve enteral autonomy" and statistical methodology to be used.		Synopsis, Section 9.7.1.2, Section 9.7.2
Updated the information on the clinical studies with teduglutide in pediatric subjects to include the results of TED-C14-006.		Section 1.2
Clarified that teduglutide is the investigational product for this study.		Section 6.1
Updated the dose selection rationale with results from a simulation work using the previous population pharmacokinetic model. Based on the totality of clinical data, 0.05 mg/kg once daily is expected to provide comparable C_{max} concentrations in infants as compared to pediatric patients with SBS and was recommended as an evaluation dosing regimen in Study SHP633-301.		Section 6.2.5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **2.1**	**Amendment Date** **04 Dec 2018**	**France-specific**
Description of Change and Rationale		**Section(s) Affected by Change**
Clarified that rescreening of subjects in the study will not be allowed. (Administrative amendment dated 03 Oct 2018)		Section 7.1.1
Clarifications were made to the definition of adverse events.		Section 8.1, Section 8.1.5, Section 8.2.4
Added heart failure with severe fluid overload, determined by the sponsor or investigator to be related to the investigational product, to the list of events leading to interruption of investigational product administration. This addition is in alignment with the warnings and special precautions listed in the investigator brochure.		Section 8.4
As recommended by the FDA, specified that if the DMC recommends termination of this pediatric study, the recommendations will be communicated to the relevant regulatory agencies within 7 calendar days.		Section 9.4
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout the protocol

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number **3.1**	**Amendment Date** **24 May 2019**	**France-specific**
Description of Change and Rationale		**Section(s) Affected by Change**
Deleted Inclusion Criteria #6, Lack of terminal ileum and ileocecal valve, due to difficulties in enrollment.		Synopsis, Section 4.1
Minor editorial changes and corrections to typographical errors (which do not modify content and/or intent of the original document) were made.		Throughout the protocol

Appendix 2 Guidelines for Nutritional Support Management During the Study

The nutritional support adjustment guidelines are designed to standardize management of parenteral and enteral nutritional support in this study. Adjustments to nutritional support should be considered at every scheduled clinic visit. Adjustments at phone visits may also be performed, but nutritional assessments at phone visits serve primarily to confirm that nutritional adjustments at prior clinic visits were tolerated.

All attempts should be made to follow the guidelines, but departure from the guidelines will not constitute a protocol deviation.

Clinical judgment is required within the algorithm. Each decision point requires integrating multiple sources of information into a yes/no decision. When individual data points are conflicting, the investigator must use their best judgment in the assessment.

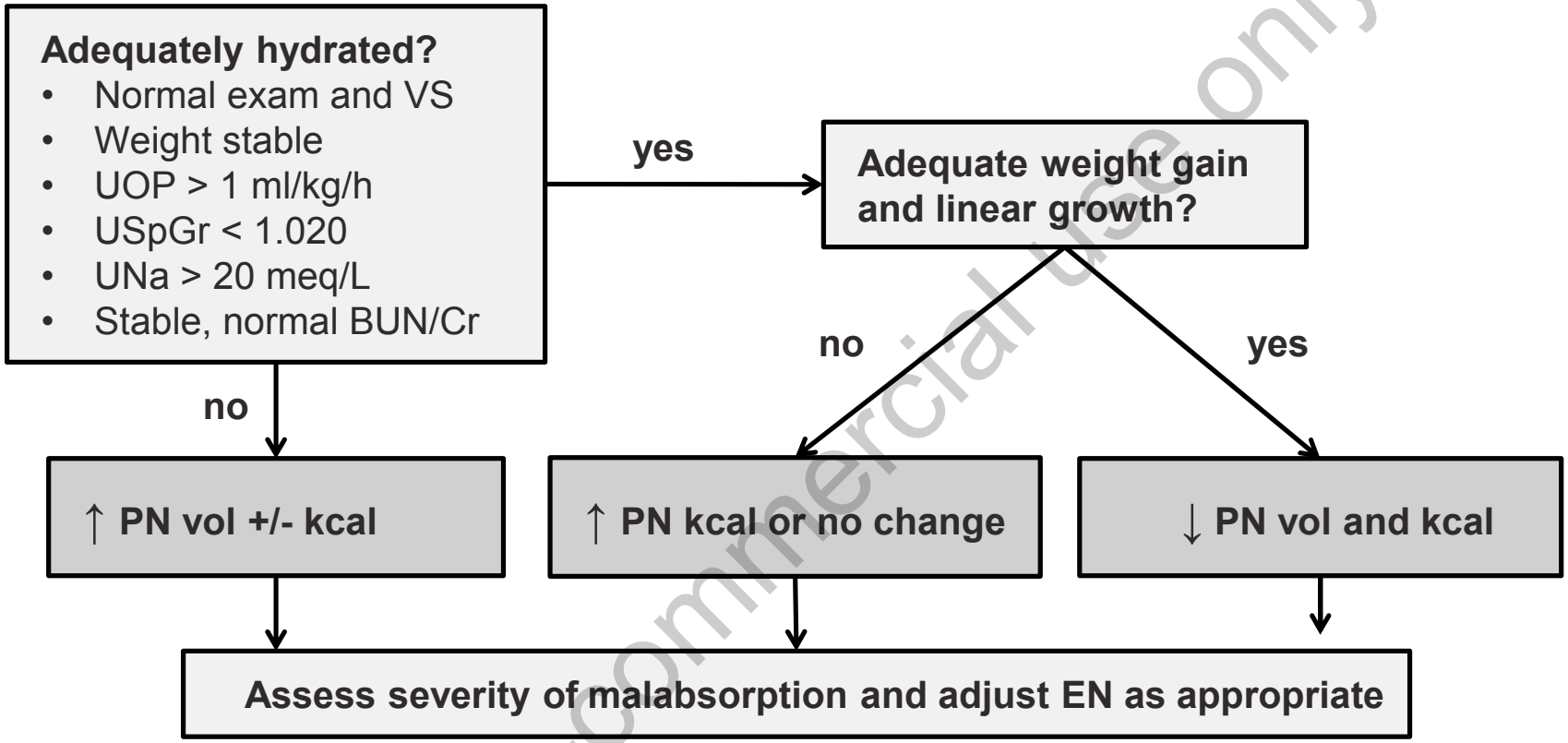
If intestinal adaptation is occurring, reductions in parenteral support volume and calories are expected to be in decrements of 5 to 10% relative to baseline values. Parenteral support components are at the discretion of the investigator, but care should be taken to balance carbohydrate, fat, and protein. Likewise, if intestinal adaptation is occurring, enteral nutrition volume and calories should be increased in increments of approximately 10% relative to baseline values.

Assessment of the severity of malabsorption may require estimation of stool output for children who have mixed stool and urine output.

Adjustments should be based on the actual nutritional support in volume and calories the subject infuses. Subjects should remain compliant with the nutritional support prescription in volume and calories during the study.

During the 48-hour output measurement period prior to the subject's scheduled visit, no further changes to the prescribed nutritional support should be made.

Figure A-1: Parenteral Nutrition/Intravenous Adjustment Algorithm for All Subjects



BUN=blood urea nitrogen; Cr=creatinine; PN=parenteral nutrition; UNa=urine sodium; UOP=urine output; USpGr=Urine specific gravity; VS=vital signs; vol=volume