CLINICAL STUDY PROTOCOL

NCT Number: NCT02954458

Study Title: A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome Who Completed TED-C14-006

Study Number: SHP633-304

Protocol Version and Date:

Original Protocol:	08 Apr 2016
Amendment 1:	22 Nov 2016
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PROTOCOL: SHP633-304

TITLE:	A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome Who Completed TED-C14-006
DRUG:	Teduglutide
IND:	IND# 058213
EUDRACT NO.:	2016-000849-30
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way, Lexington, MA 02421 USA
PROTOCOL HISTORY:	Original Protocol: 08 April 2016

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 SHP633-304.

Title: A prospective, open label, long-term safety and efficacy study of teduglutide in pediatric patients with short bowel syndrome who completed TED-C14-006

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 Conference on Harmonization (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)	

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 Pharmacovigilance and Risk Management 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 contract research organization Shire Medical Monitor by fax or e-mail using the details below.

[redacted], MD PhD

Email: [redacted]

Fax: [redacted]

For protocol- or safety-related issues <u>during normal business hours (9 am to 5 pm Eastern Standard Time)</u>, the investigator must contact the Shire Medical Monitor:

[redacted], MD PhD, [redacted]

Phone: [redacted]

Mobile: [redacted]

Email: [redacted]

Fax: [redacted]

For protocol- or safety-related issues <u>outside of normal business hours</u>, the investigator must contact Quintiles Medical Support:

[redacted], MD, [redacted]

Phone: [redacted] (medical emergencies – US & Canada)

Phone: [redacted] (medical emergencies – global)

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 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):
[redacted] Shire (USA)

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-HCG	beta-human chorionic gonadotropin
BMI	body mass index
CRA	clinical research associate
CRO	contract research organization
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DILI	drug-induced livery injury
DMC	data monitoring committee
DPP-4	dipeptidyl peptidase 4
EC	ethics committee
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FOBT	fecal occult blood test
FOCBT	female of child-bearing potential
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
GLP-2	glucagon-like peptide 2
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IGF-1	insulin-like growth factor 1
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
IWRS	interactive web-based response system
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NDA	new drug application

NTT	no-teduglutide treatment
PDA	patent ductus arteriosus
PedsQL	Pediatric Quality of Life inventory
PS	parenteral support
PT/INR	prothrombin time/international normalized ratio
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
SOC	standard of care
$t_{1/2}$	elimination half-life
TESAE	treatment-emergent serious adverse event
UK	United Kingdom
ULN	upper limit of normal
US	United States
WHO-DD	World Health Organization – Drug Dictionary

STUDY SYNOPSIS

Protocol number: SHP633-304	**Drug:** Teduglutide
Title of the study: A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome (SBS) Who Completed TED-C14-006	
Number of subjects (total and for each treatment arm): Approximately 34 subjects who completed the TED-C14-006 study, including subjects in the standard of care treatment arm, are expected to enroll in this extension study. This study will enroll up to as many subjects as complete the TED-C14-006 study.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 28 investigational sites in North America and Europe will participate in this extension study	
Study period (planned): October 2016 – September 2019	**Clinical phase:** 3 Extension
Objectives: **Primary:** To evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with SBS. **Secondary:** To evaluate long-term efficacy of teduglutide treatment in pediatric subjects with SBS.	
Rationale: This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects with short bowel syndrome (SBS) who completed the TED-C14-006 study (the core study). In addition to evaluating the long-term safety and durability of efficacy after 24-weeks of treatment, this extension study will evaluate the need for additional teduglutide treatment in these subjects, and will allow the study of first-time treatment of teduglutide-naïve subjects who participated in the standard of care (SOC) treatment arm in TED-C14-006.	
Investigational product, dose, and mode of administration: This study will allow repeat doses of teduglutide 0.05 mg/kg subcutaneous (SC) once daily (QD) injection for eligible pediatric subjects. There is no active comparator or reference product.	
Methodology: This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects who completed the TED-C14-006 study (core study). Once the informed consent (and if applicable, informed assent) have been reviewed and signed, demographics, medical history, and short bowel syndrome history will be obtained. Subjects not receiving teduglutide treatment (ie, in a no-teduglutide treatment [NTT] period), will be seen every 12 weeks for safety, parenteral support (PS) requirements, and quality of life. The first NTT visit will occur approximately 12 weeks after the screening visit. At any point after screening, including during a NTT period, subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed **immediately** to the pre-treatment visit if the investigator, subject, and parent agree to proceed with teduglutide therapy. After the pre-treatment visit, subjects who meet ≥1 of the teduglutide treatment inclusion criteria, and meet none of the teduglutide treatment exclusion criteria, will start a 28- week cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily, followed by a 4- week follow-up period (during which no teduglutide is administered) (Figure 3-1). During the 28-week cycle, clinic visits will occur at weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. Phone visits are required approximately 1 week after adjustments in PS during the TED treatment period, between weeks 1-24, and weekly during the TED follow-up period, between weeks 24 and 28. Safety and PS requirements will be evaluated at every visit, and quality of life assessments will be made approximately every 12 weeks. If a subject has clinical deterioration and meets follow-up period escape criteria after stopping teduglutide,	

the subject may "escape" the follow-up period early and proceed immediately to another pre-treatment visit. Following completion of the 28-week treatment cycle, the subject will proceed to the NTT. The first NTT visit, for a subject that completes a treatment cycle, will occur approximately 12 weeks after the Week 28 (CxW28) visit.

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, all attempts should be made to follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) for decisions regarding PS support reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines, however, is not considered a protocol deviation. (Appendix 1).

Study Design Flow Chart

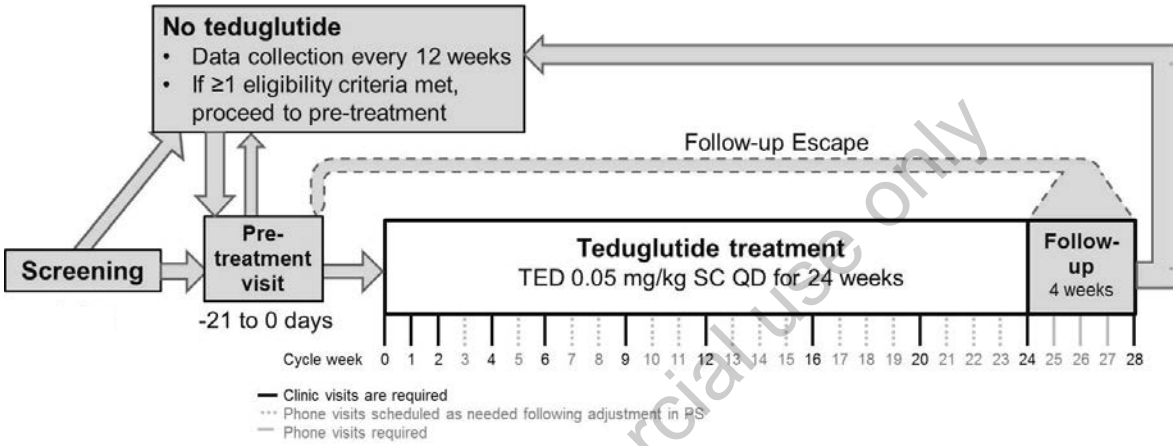

Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured every 12 weeks, but subjects may proceed to the pre-treatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects will enter a 28-week teduglutide cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24 (**solid black lines**). Phone visits are required approximately 1 week after adjustments in PS during the intervening weeks between weeks 2 and 24 (**dashed grey lines**). Subjects discontinue teduglutide at week 24 and enter a 4-week follow-up (no-treatment) period, during which phone visits will be performed weekly (**solid grey lines**). If an escape criterion is met during the follow-up period, subjects may proceed directly to another pre-treatment visit.

Study Inclusion Criteria:

The subject will be considered eligible for the study if they meet **all** of the study inclusion criteria. Teduglutide treatment eligibility does not impact study eligibility.

1. Subject provides written informed consent (subject, parent or legal guardian and, as appropriate, informed assent) to participate in the study before completing any study-related procedures.
2. Subject completed the TED-C14-006 study (including subjects in the standard of care treatment arm).
3. Subject understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Study Exclusion Criteria: There are no exclusion criteria for this study.

Teduglutide Eligibility Criteria: Subjects are eligible for teduglutide treatment if at least one (≥1) of the teduglutide treatment inclusion criteria, and none of the teduglutide treatment exclusion criteria, are met. In addition, the investigator and the subject (and/or parent or legal guardian, as appropriate) must agree to proceed with treatment.

***Teduglutide Treatment Inclusion Criteria*:**

1. Subject is teduglutide-naïve, receiving PS, and unable to significantly reduce PS or advance enteral feeds (eg, 10% or less change in PS or advance in feeds) for at least 3 months prior to and during the

teduglutide pre-treatment visit, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PS returns to within 10% of baseline prior to the event.

2. Subject was previously treated with teduglutide and at least one of the following criteria is satisfied:
    a. Increasing PS requirements following teduglutide discontinuation.
    b. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
    c. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition following teduglutide discontinuation.
    d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
    e. Severe diarrhea related to teduglutide discontinuation.

Teduglutide Treatment Exclusion Criteria:

1. Body weight <10 kg at the pre-treatment visit.
2. Unresected gastrointestinal (GI) polyp, known polyposis condition, pre-malignant change, or malignancy, in the GI tract.
3. History of cancer in the previous 5 years except surgically curative skin cancers.
4. Serial transverse enteroplasty or other major intestinal surgery within 3 months preceding the teduglutide pre-treatment visit. Insertion of a feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, and endoscopic procedures are allowed.
5. Intestinal or other major surgery planned or scheduled to occur during the 28-week cycle.
6. Clinically significant intestinal stricture or obstruction.
7. Clinically significant, active or recurrent pancreatic or biliary disease.
8. Active, severe, or unstable, clinically significant hepatic impairment or injury, including the following laboratory values at the pre-treatment visit:
    a. Total bilirubin ≥2 × upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7 × ULN
    c. Alanine aminotransferase (ALT) ≥7 × ULN
9. Renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2 at the pre-treatment visit.
10. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, or patent ductus arteriosus (PDA) ligation.
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to the pre-treatment visit and for the duration of the 28-week cycle.
12. Treatment with analogs of glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2) (not including teduglutide), insulin-like growth factor-1 (IGF-1), or growth hormone, within 1 month preceding the teduglutide pretreatment visit.
13. Treatment with octreotide or dipeptidyl peptidase 4 (DPP-4) inhibitors within 3 months prior to the pre-treatment visit.
14. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
15. Known history of alcohol or other substance abuse within 1 year prior to the pre-treatment visit.
16. Pregnant or lactating female subjects.

17. Sexually active female subjects of child-bearing potential unwilling to use approved contraception during teduglutide treatment and for 30 days after the treatment period.
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.

Follow-up Period Escape Criteria: At the discretion of the investigator, the follow-up period may be interrupted and the subject may proceed directly to the pre-treatment visit, if 1 of the following criteria is met:

1. Increasing PS requirements following teduglutide discontinuation
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition 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.

Maximum duration of subject involvement in the study:

A subject will be considered enrolled in the study once the subject has provided signed consent, and meets all of the Study Inclusion Criteria. Subjects may participate in multiple NTT periods and/or multiple 28-week treatment cycles. The study will continue for at least 1 year, and until each subject has access (as needed) to teduglutide. The subject's maximum duration of participation is expected to be approximately 3 years. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing End of Study (EOS) visit.

- **Planned duration of no teduglutide treatment periods**: variable, depending on disease course
- **Planned duration of the teduglutide pre-treatment visit:** 1 to 21 days
- **Planned cycle duration**: 28 weeks. Each cycle consists of 24 weeks of teduglutide treatment followed by a 4-week follow-up period (no treatment)

Endpoints and statistical analysis:

- The **safety population** will consist of all enrolled subjects. The safety population will be used for both safety and efficacy analysis.

Efficacy Endpoints

The following efficacy/PD endpoints will be measured. For each endpoint, analyses will be performed using the baseline of this extension study at the following time points: 1) End of each teduglutide treatment period (week 24 or EOT), and 2) each study visit. In addition, the Efficacy/PD endpoints will be analyzed using the baseline of the Core study (TED-C14-006) and the baseline of each treatment cycle. The derivations of the weekly PS volume and 3 baselines will be described in the study Statistical Analysis Plan (SAP) in detail.

- Reduction in PS volume of at least 20%
- Absolute and relative change in PS volume
- Complete weaning off PS
- Change in days per week of PS

Health Economics and Outcomes Research (HEOR) Endpoints

The following HEOR endpoints will be measured. For each endpoint, analyses will be performed using the Baseline of this extension study. In addition, the HEOR endpoints will be analyzed using the Baseline of each treatment cycle at approximately 12 week intervals (weeks 12 and 24 of each teduglutide treatment cycle, and every 12 weeks for subjects not on teduglutide).

- Change in Pediatric Quality of Life Inventory (PedsQL) score
- Change in PedsQL Family Impact Module score
- Change in PedsQL Gastrointestinal Symptoms Module Sub-Scales scores:

- Food and Drink Limits
- Diarrhea

Safety Endpoints

The following safety endpoints will be measured. For each endpoint, analyses will be performed using the Baseline of this extension study. In addition, the safety endpoints will be analyzed using the Baseline of the Core study (TED-C14-006).

- Adverse events, including those pertaining to GI symptoms
- Vital signs, including temperature, heart rate, blood pressure
- Body weight, height (or length), head circumference (up to 36 months of age) trends on growth charts, BMI; z-scores will be calculated for height (or length), weight, head circumference and BMI
- Laboratory safety data (ie, clinical chemistry, hematology, and urinalysis)
- Urine output
- Stool output
- Antibodies to teduglutide
- Gastrointestinal-specific testing (teduglutide treatment eligible subjects only) including colonoscopy or sigmoidoscopy, abdominal ultrasound, and FOBT, upper GI series with small bowel follow through

Statistical Methodology for Efficacy Analysis

No claims of statistical significance will be made; however, 95% confidence intervals will be provided, if applicable. Continuous variables, including those assessed on a discrete scale, 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.

Statistical Methodology for Safety Analysis

Safety data, including laboratory tests and vital signs assessments, will be summarized by visit. AEs will also be collected and summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data.

Sample Size Justification

As this is an extension study, the maximum number of subjects will be determined by enrollment in TED-C14-006.

STUDY SCHEDULE(S)

Table 1-1: Schedule of Events Required for All Subjects

Period	Screening	End of Study or Early Termination
	Scr	EOS/ET
Visit Type	Site	Site
Informed consent/assent[a]	X	
Study eligibility	X	
Demographics, Medical history[b], SBS history[c]	X	
Dispense intake and output diaries	X	
Evaluate teduglutide treatment inclusion criteria[d]	X	
Adverse events	X	X
Concomitant medications and GI procedures[e]	X	X
Physical examination and vital signs, including weight		X
Height and head circumference[f]		X
Review intake and output diaries[g]		X
Record PS and EN prescriptions, and adjust as needed[h]		X
Safety laboratory tests[i]		X
PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales		X
Antibodies to teduglutide[j]		X
Fecal occult blood testing[k]		(X)
Colonoscopy[l]		(X)
Pregnancy testing[m]		(X)

EN=enteral nutrition; EOS =end of study; ET=early termination; GI=gastrointestinal; NTx=no treatment;

PedsQL=Pediatric Quality of Life Inventory; PS=parenteral support; SBS=Short Bowel Syndrome; Scr =Screening.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

[a] Informed Consent (and informed assent, if applicable) must be obtained prior to performing any study-related procedures; consent (and informed assent, if applicable) may be obtained anytime during the Week 28 (or EOS) visit for the TED-C14-006 study. Subject will have up to 7 days after completion of the TED-C14-006 study to sign consent to participate in the SHP633-304 study.

[b] Updates to the medical history will be collected, consisting of adverse events that were ongoing at the time of completion of TED-C14-006, and events that occurred during the period between completion of TED-C14-006 and informed consent to SHP-633-304. New data to be collected as medical history include gestational age at birth and parental heights.

[c] If the subject has any changes to the SBS history that had been collected at the baseline of the TED-C14-006, then the updated SBS history will be collected.

[d] Subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed to the pre-treatment visit if the investigator, subject, and parent or legal guardian agrees to proceed with teduglutide therapy. (Table 1-3).

[e] Concomitant GI procedures include (but are not limited to) endoscopy, radiographic studies, GI and liver biopsies and associated pathology results.

[f] Head circumference will be measured in subjects 36 months of age and younger.

[g] Intake diaries will collect actual PS volume and hours per day, and actual EN volume per day, completed daily for a minimum of 2 weeks prior to each site visit (Section 7.2.11). Urine and stool output should be recorded in the output diary over a 48-hour period of PS and EN stability before every clinic visit (See Section 7.2.12 for more detail).

[h] PS 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 1.

[i] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. For pediatric subjects in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

[j] Required for all teduglutide-exposed subjects

[k] FOBT should be performed on teduglutide-exposed subjects on an annual basis, approximately every 48-60 weeks at a minimum.

[l] The need for colonoscopy in response to a positive FOBT during a no-teduglutide treatment period is at the discretion of the investigator, but all teduglutide-exposed subjects will undergo colonoscopy after they have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure), and subjects who continue to receive teduglutide will undergo colonoscopy at 5 year intervals or more often as needed. See Section 7.2.9 for details.

[m] Pregnancy testing is required for FOCBP at an ET visit if the subject has not had a pregnancy test at least 30 days after study drug discontinuation.

Table 1-2: Schedule of Events for Subjects Not Receiving Teduglutide

Visit Number	**NTx**
Visit Type	**Site**
Visit Frequency	**Every 12 weeks**
Window (days)	**±7**
Dispense intake and output diaries	X
Evaluate teduglutide treatment inclusion criteria[a]	X
Adverse events	X
Concomitant medications and GI procedures[b]	X
Physical examination and vital signs, including weight	X
Height and head circumference[c]	X
Review intake and output diaries[d]	X
Record PS and EN prescriptions, and adjust as needed[e]	X
Safety laboratory tests[f]	X
PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales	X
Antibodies to teduglutide[g]	(X)
Fecal occult blood testing[h]	Annually
Colonoscopy[i]	(X)
Serum sample[j]	Every 24 weeks

EN=enteral nutrition; NTT = no teduglutide treatment; PedsQL = Pediatric Quality of Life Inventory; PS= parenteral support.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

[a] Subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed to the pre-treatment visit if the investigator, subject, and parent or guardian agree to proceed with teduglutide therapy (Table 1-3).

[b] Concomitant GI procedures include (but are not limited to) endoscopy, radiographic studies, GI and liver biopsies and associated pathology results.

[c] Head circumference will be measured in subjects 36 months of age and younger.

[d] Intake diaries will collect actual PS volume and hours per day, and actual EN volume per day, completed daily for a minimum of 2 weeks prior to each study visit (Section 7.2.11). Urine and stool output should be recorded in the output diary over a 48-hour period of PS and EN stability before every clinic visit (See Section 7.2.12 for more detail).

[e] PS 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 1.

[f] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. For pediatric subjects in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

[g] Subjects who have been treated previously and test positive/specific for TED antibodies should have follow-up samples collected every 12 weeks during the study until a negative result is obtained.

[h] FOBT should be performed on teduglutide-exposed subjects on an annual basis, approximately every 48-60 weeks at a minimum.

[i] The need for colonoscopy in response to a positive FOBT during a no-teduglutide treatment period is at the discretion of the investigator, but all teduglutide-exposed subjects will undergo colonoscopy after they have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) and subjects who continue to receive teduglutide will undergo colonoscopy at 5 year intervals or more often as needed. See Section 7.2.9 for details.

[j] Lack of collection of serum samples will not constitute a protocol deviation.

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	Pre-treatment	Teduglutide Treatment															Follow-up	
Visit Number	**Px**	**Cx D1**	**Cx W1**	**Cx W2**		**Cx W4**		**Cx W6**		**Cx W9**		**Cx W12**		**Cx W16**		**Cx W20**		**CxW24 (EOT)**	**CxW25 CxW26 CxW27**	**CxW28 EOS/ET**
Visit Type	**Site**	**Site**	**Site**	**Site**		**Site**		**Site**		**Site**		**Site**		**Site**		**Site**		**Site**	**Phone[a]**	**Site**
Cycle Day	**-21 to 0**	**1**	**8**	**15**		**29**		**43**		**64**		**85**		**113**		**141**		**169**	**176 183 190**	**197**
Window (days)	-21 to 0		**±2**	**±2**		**±2**		**±2**		**±4**		**±4**		**±4**		**±4**		**±4**	**±2**	**±2**
Evaluate teduglutide eligibility (inclusion and exclusion) criteria	X	X[b]			Phone contact is required approximately 1 week after PS adjustment		Phone contact is required approximately 1 week after PS adjustment		Phone contact is required approximately 1 week after PS adjustment		Phone contact is required approximately 1 week after PS adjustment		Phone contact is required approximately 1 week after PS adjustment		Phone contact is required approximately 1 week after PS adjustment		Phone contact is required approximately 1 week after PS adjustment			
Dispense intake and output diaries	X	X	X	X		X		X		X		X		X		X		X		
Adverse events	X	X	X	X		X		X		X		X		X		X		X	X	X
Concomitant medications and GI procedures[c]	X	X	X	X		X		X		X		X		X		X		X	X	X
Physical examination and vital signs, including weight	X	X	X	X		X		X		X		X		X		X		X		X
Height and head circumference[d]	X	X										X						X		
Review intake and output diaries[e]	X	X	X	X		X		X		X		X		X		X		X	X	X
Record PS and EN Rx, and adjust as needed[f]	X	X	X	X		X		X		X		X		X		X		X	X	X
Safety laboratory tests[g]	X[h]	X	X	X		X		X		X		X		X		X		X	(X)	X
PedsQL Generic Core Scale/ Family Impact Module/ GI Symptoms Module Sub-Scales		X										X						X		
Antibodies to teduglutide		X										X						X		X
Fecal occult blood testing[h]	X											X						X		
Colonoscopy[i]	(X)											(X)						(X)		
Pregnancy testing[j]	X	X				X				X		X		X		X		X		X
Serum sample[k]	X																	X		

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	Pre-treatment	Teduglutide Treatment																Follow-up	
Evaluate escape criteria[l]																		X	X
Dispense study drug[m]		X	X	X		X		X		X		X		X		X			

EN=enteral nutrition; EOF = end of follow-up; EOS = end of study; EOT = end of treatment; ET = early termination; FOBT = fecal occult blood test; FU = follow-up; GI = gastrointestinal; PedsQL = Pediatric Quality of Life Inventory; PS= parenteral support; SBS = Short Bowel Syndrome; SC = subcutaneous; Scr = Screening; TED = Teduglutide; Tx = treatment.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

[a] Phone visits are required approximately 1 week after adjustments in PS. The assessments to be performed at phone visits are the same as those described for CxW25-27 (except for evaluation of escape criteria).

[b] Eligibility will need to be re-confirmed prior to the first dose in the cycle. Negative urine pregnancy test is required prior to the first dose of teduglutide, but results of other labs obtained at the CxD1 visit are not required to determine teduglutide treatment eligibility.

[c] Concomitant GI procedures include (but are not limited to) endoscopy, radiographic studies, GI and liver biopsies and associated pathology results.

[d] Head circumference will be measured in subjects 36 months of age and younger.

[e] Intake diaries will collect actual PS volume and hours per day, and actual EN volume per day. Two weeks of intake diary data are required before drug is administered at CxD1.Diaries should be completed daily from CXD1 up to CXW6 visit during Teduglutide treatment. After CXW6 visit, diaries should be completed daily for a minimum of 2 weeks prior to each study visit during Teduglutide treatment (Section 7.2.11). During the 24 week teduglutide treatment period, the intake diary will also be completed for 1 week following PS adjustment, and daily during the 4-week follow-up period. Urine and stool output should be recorded in the output diary over a 48-hour period of PS and EN stability before every clinic visit, and within 1 week of implementing a change in the PS prescription (See Section 7.2.11 for more detail).

[f] PS 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 1.

[g] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Clinical chemistry and urinalysis must also be performed within approximately 5-7 days of any adjustment to the PS prescription. Safety labs performed between clinic visits may be performed locally. Unscheduled lab results will not be captured in the eCRFs. If abnormal results are considered an adverse event, an AE form will be completed. Collect PT/INR at the pre-treatment visit. Additional collection will occur if a potential drug-induced liver injury signal is observed. For pediatric subjects in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

[h] FOBT should be performed on teduglutide-exposed subjects on an annual basis.

[i] The Teduglutide-naïve subjects age 12 and older will undergo colonoscopy at the pre-treatment visit if one has not been performed within 1 year. Subjects of any age with newly positive FOBT results at the pre-treatment visit for which a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy prior to receiving teduglutide. If newly positive FOBT results (for which a readily detectable cause cannot be identified) are obtained at the end of a teduglutide treatment cycle (CxW24/EOT), colonoscopy will be performed. The need for colonoscopy in response to positive FOBTs at CxW12 is at the discretion of the investigator. Teduglutide-exposed subjects who have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) will undergo colonoscopy. See Section 7.2.9 for details.

[j] A serum pregnancy test is performed on all females of child-bearing potential (FOCBP) at the teduglutide pre-treatment visit. Urine pregnancy tests will be administered at all other visits according to the study schedules, or if pregnancy is suspected, or as specified per protocol upon withdrawal of the subject from the study

[k] Lack of collection of serum samples will not constitute a protocol deviation

[l] If escape criteria are met, the subject may proceed directly to another pre-treatment visit at the discretion of the investigator

[m] The first SC injection of teduglutide in treatment-naïve subjects will be administered under the supervision of the investigator/designee after which the subject will be observed

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	Pre-treatment	Teduglutide Treatment	Follow-up

for hypersensitivity reactions for at least 4 hours. The site of administration (arm, thigh, abdomen) of the first teduglutide dose must be specified and recorded in the eCRF

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

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. It is estimated that, at most, there are a few hundred pediatric subjects 1 year and older with (Khan et al. 2015;Wales et al. 2004). 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. Although the small intestine is capable of remarkable adaptation, excessive loss of absorptive surface area or specialized functions can lead to dependence on parenteral nutrition or intravenous (IV) fluids (parenteral support [PS]). Treatment of both pediatric and adult patients is focused on achieving adequate intestinal absorption to allow for minimization or discontinuation of PS. About 30% of infants with SBS become independent of PS requirements by 12 months of age, and an additional 10% wean off PS by 24 months of age. After this time, linear intestinal growth slows. About 60% of pediatric subjects with SBS are able to become independent of PS within 5 years of the initial diagnosis (Khan et al. 2015). Nevertheless, despite optimal medical management, many pediatric subjects remain dependent on PS. Complications of long-term PS include liver disease, catheter-related blood stream infections, central line-associated venous thrombosis and dwindling central venous access. Sepsis is the leading cause of death in these patients and quality of life is poor (Squires et al. 2012). Accelerating the adaptive process and achieving enteral autonomy is an urgent goal for all patients with SBS who are dependent on PS (Khan et al. 2015;Squires et al. 2012).

Intestinal adaptation is driven by hormonal cues in response to nutrient malabsorption (Drucker and Yusta 2014). Chief among these is hormones glucagon-like peptide 2 (GLP-2), which is secreted from L-type enteroendocrine cells that reside in the intestinal epithelium in the ileum and colon. Resection of these regions impairs the adaptive response by limiting endogenous production of GLP-2.

1.2 Product Background

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-IV (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$) in adults of approximately 2 hours 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). The European Commission granted a centralized marketing authorization valid throughout the European Union (EU) for teduglutide (REVESTIVE™) on 30 August 2012 and a New Drug Application (NDA) for teduglutide (GATTEX®) was approved by the United States (US) Food and Drug Administration (FDA) on 21 December 2012 for the treatment of adult patients with SBS who are dependent on PS. Teduglutide is not currently approved for use in pediatric subjects.

1.3 Clinical Studies with Teduglutide in Pediatric subjects

One Phase 3 study, TED-C13-003, was completed in pediatric SBS subjects in the US and United Kingdom (UK). In this study, teduglutide was administered to 3 cohorts of pediatric subjects from ages 1-17. 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 PS volume at Week 12 of 37%, including complete independence from PS 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 PS volume at Week 12 of 39%, including complete independence from PS 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 (TESAEs) related to teduglutide were reported. No discontinuations from study were due to adverse events (AEs).

TED-C14-006 is an ongoing study which includes 2 treatment arms: a teduglutide treatment arm and a standard of care treatment arm. Subjects in both arms participate in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the screening period, subjects will choose into which arm to enroll. During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide treatment arm will receive daily subcutaneous (SC) injections of teduglutide (study drug) in addition to standard medical therapy. The subjects enrolling in the teduglutide treatment arm will be 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.

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 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects with SBS who completed the TED-C14-006 study. In addition to evaluating the long-term safety and durability of efficacy after 24 weeks of treatment, this extension study will evaluate the need for additional teduglutide treatment in these subjects, and will allow for the first-time treatment of teduglutide-naïve subjects who participated in the SOC treatment arm in TED-C14-006.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objective of the study is to evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with SBS who completed TED-C14-006.

2.2.2 Secondary Objectives

The secondary objective of this study is to evaluate the long-term efficacy of teduglutide treatment in pediatric subjects with SBS who completed TED-C14-006.

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects who completed the TED-C14-006 study (core study). At the time of entry into the TED-C14-006 study, subjects were less than 18 years of age, were dependent on parenteral nutrition to provide at least 30% of their caloric or fluid needs, and had not been able to significantly reduce PS for at least 3 months prior to enrollment. During the core study, pediatric subjects in the teduglutide treatment arm were randomized to 0.025 mg/kg or 0.05 mg/kg QD dosing in a double-blinded manner. The TED-C14-006 study will also be referred to as the core study interchangeably throughout this protocol.

Approximately 28 subjects who complete the core study are expected to enroll in this extension study. Subjects who previously received teduglutide during TED-C14-006, as well as subjects who were in the SOC treatment group, may be eligible to receive teduglutide treatment in this extension study. To be eligible, subjects must meet ≥1 of the teduglutide treatment inclusion criteria and none of the teduglutide treatment exclusion criteria.

Re-challenge

Subjects not receiving teduglutide treatment (ie, in a "no teduglutide treatment period"), will be seen every 12 weeks for safety, parenteral support (PS) requirements, and quality of life. At any point during a no teduglutide treatment period, subjects who meet ≥1 *teduglutide treatment inclusion* may proceed directly to the pre-treatment visit if the investigator, subject, and parent agree to proceed with teduglutide therapy.

Rationale: Some pediatric subjects may have a durable beneficial effect after 24 weeks of teduglutide treatment and thus long-term follow-up without additional teduglutide treatment may be appropriate. However, there may be some pediatric subjects who deteriorate or stop improving after discontinuation of teduglutide treatment. In these pediatric subjects, additional teduglutide treatment may be beneficial.

Dose Selection

Analysis suggested that pediatric patients, ages 1 to 17 years old, are likely to require the same dose as used in adults, namely 0.05 mg/kg/day (Mouksassi et al. 2009). In this extension study to TED-C14-006, repeat doses of teduglutide 0.05 mg/kg QD will be administered to eligible pediatric subjects who previously received teduglutide 0.05 or 0.025 mg/kg in Study TED-C14-006.

Rationale: Teduglutide is approved for adult use in the United States and European Union at a dose of 0.05 mg/kg SC once daily. The completed 12-week pediatric 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. In addition, population pharmacokinetic modeling and simulations were conducted to determine the effective 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 the pediatric study (TED- C13- 003) and suggested that the dose in pediatric subjects is likely to be same as the dose in adults (O'Keefe et al. 2006).

Duration of Treatment

The duration of teduglutide treatment in this study mirrors that of the TED-C14-006 study, consisting of 24 weeks of teduglutide treatment, followed by a 4-week follow-up period. The follow-up period is a mechanism to evaluate whether continued teduglutide is needed. If a subject deteriorates during the follow-up period, the subject may be evaluated immediately for additional teduglutide treatment. Subjects who clinically deteriorate or stop improving at any time after the end of the follow-up period will also be assessed for additional treatment.

Rationale: During the teduglutide treatment cycle, visit frequency is similar to frequencies performed in TED-C13-003 and TED-C14-006, to ensure sufficient safety monitoring and weaning of PS. During the No TED treatment, visits occur every 12 weeks, a frequency that is consistent with standard medical practices.

Measures and Parameters

Following the review and signing of the informed consent (and informed assent, if applicable), screening visit procedures will begin including demographics, medical history, and short bowel syndrome history. Subjects who meet ≥1 of the teduglutide treatment inclusion criteria may proceed to the pre-treatment visit.

After the pre-treatment visit, subjects who still meet ≥1 of the teduglutide treatment inclusion criteria, and meet none of the teduglutide treatment exclusion criteria, will start a 28-week cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily, followed by a 4-week follow-up (no treatment) period (Figure 3-1). During the 28-week cycle, clinic visits will occur at weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. Phone visits are required approximately 1 week after adjustments in PS during the TED treatment period, between weeks 1-24, and weekly during the TED follow-up period, between weeks 24 and 28.

Safety and PS requirements will be evaluated on a weekly basis, and quality of life assessments will be made approximately every 12 weeks. 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, all attempts should be made to follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) for decisions regarding PS reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines, however, is not considered a protocol deviation (Appendix 1).

Rationale: Measures of long term safety will include adverse events, growth parameters and anti-drug antibodies. Measure of long term efficacy will include durability of effect as measured by reduction in PS and improvement in pediatric quality of life measures (PedsQL, PedsQL Family Impact Module). A reduction in PS volume of at least 20% at end of treatment (EOT) was used as the primary endpoint in pivotal phase 3 adult clinical trials and the completed phase 3 pediatric study (TED-C13-003), and will be used as an endpoint in this extension study. In previous clinical studies, a reduction of this magnitude was associated with a reduction in the number of days per week of PS, and increases in enteral intake. Reduction in volume and time of PS due to improved enteral absorption may provide a pediatric subject with opportunities for more age-appropriate activities including oral rehabilitation. Quality of life assessments will be performed in this study to quantitate this effect.

Teduglutide has been found to have a targeted intestinotrophic effect. Taking into account the patient population and the pharmacologic effect of teduglutide, GI-specific screening tests, including fecal occult blood testing and colonoscopy, which are commonly part of the routine care of these subjects, will be performed to ensure safety. This study captures long-term safety data on polyps and other colonic mucosal changes in teduglutide-exposed subjects using the surveillance strategy proposed in Section 7.2.9.

Figure 3-1: Study Design Flow Chart

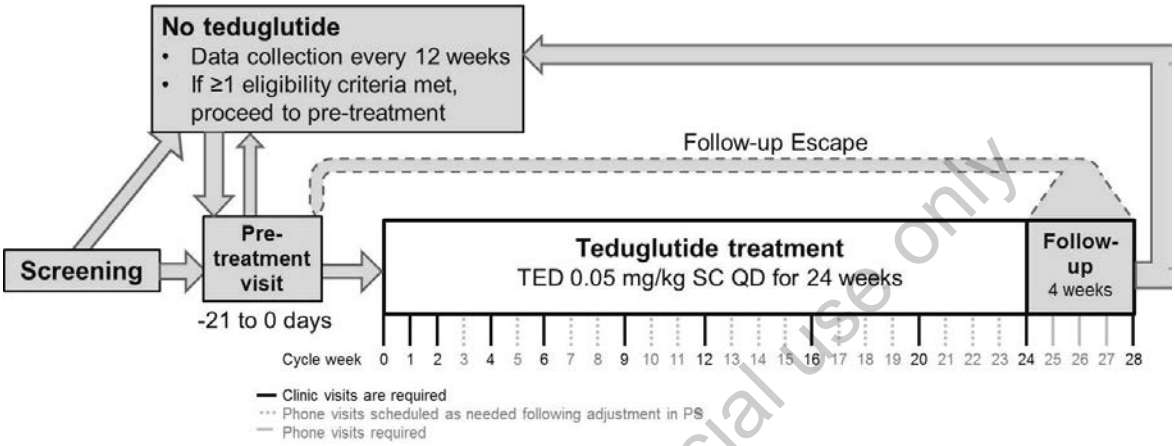

Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured every 12 weeks, but subjects may proceed to the pre-treatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects will enter a 28-week teduglutide cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24 (**solid black lines**). Phone visits are required approximately 1 week after adjustments in PS during the intervening weeks between weeks 2 and 24 (**dashed grey lines**). Subjects discontinue teduglutide at week 24 and enter a 4-week follow-up (no-treatment) period, during which phone visits will be performed weekly (**solid grey lines**). If an escape criterion is met during the follow-up period, subjects may proceed directly to another pre-treatment visit.

3.2 Duration and Study Completion Definition

A subject will be considered enrolled in the study once the subject has provided signed consent, and meets all of the Inclusion Criteria. The study will continue for at least 1 year and until each subject has access, as needed, to teduglutide. The subject's maximum duration of participation is expected to be approximately 3 years. The study will be completed in approximately 40 months. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason, and has completed the End of Study (EOS) visit.

The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact (last safety contact), whichever is later. The study completion date will be used to ascertain timing for study results posting and reporting.

4 STUDY POPULATION

Each subject must review and sign the informed consent (and informed assent, if applicable) before any study-related procedures specified in the protocol are performed. Teduglutide treatment eligibility does not impact study eligibility.

4.1 Study Inclusion Eligibility Criteria

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

1. Subject provides written informed consent (subject, parent or legal guardian and, as appropriate, subject informed assent) to participate in the study before completing any study-related procedures.
2. Subject completed the TED-C14-006 study (including subjects in the standard of care treatment arm).
3. Subject understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.2 Study Exclusion Eligibility Criteria

There are no exclusion criteria for this study.

4.3 Teduglutide Eligibility Criteria

Subjects are eligible for teduglutide treatment if at least 1 (≥1) of the teduglutide treatment inclusion criteria, and none of the teduglutide treatment exclusion criteria can be met. In addition, the investigator and the subject (and/or parent or legal guardian, as appropriate) must agree to proceed with treatment.

4.4 Teduglutide Treatment Inclusion Criteria

1. Subject is teduglutide-naïve, receiving PS, and unable to significantly reduce PS or advance enteral feeds (eg, 10% or less change in PS or advance in feeds) for at least 3 months prior to and during the teduglutide pre-treatment visit, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PS returns to within 10% of baseline prior to the event.
2. Subject was previously treated with teduglutide and at least 1 of the following criteria is satisfied:
    a. Increasing PS requirements following teduglutide discontinuation.
    b. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
    c. Deteriorating nutritional status eg, weight loss or growth failure) despite maximal tolerated enteral nutrition following teduglutide discontinuation.
    d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
    e. Severe diarrhea related to teduglutide discontinuation.

4.5 Teduglutide Treatment Exclusion Criteria

1. Body weight <10 kg at the pre-treatment visit.
2. Unresected GI polyp, known polyposis condition, pre-malignant change, or malignancy, in the GI tract
3. History of cancer in the previous 5 years except surgically curative skin cancers
4. Serial transverse enteroplasty or other major intestinal surgery within 3 months preceding the teduglutide pre-treatment visit. Insertion of a feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, and endoscopic procedures are allowed.
5. Intestinal or other major surgery planned or scheduled to occur during the 28-week cycle
6. Clinically significant intestinal stricture or obstruction
7. Clinically significant, active or recurrent pancreatic or biliary disease
8. Active, severe, or unstable, clinically significant hepatic impairment or injury, including the following laboratory values at the pre-treatment visit:
    a. Total bilirubin ≥2 × upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7 × ULN
    c. Alanine aminotransferase (ALT) ≥7 × ULN
9. Renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2 at the pre-treatment visit
10. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, or patent ductus arteriosus (PDA) ligation
11. Participation in a clinical study using an experimental drug (other than glutamine or Omegaven) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to the pre-treatment visit and for the duration of the 28-week cycle
12. Treatment with analogs of glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2) (not including teduglutide), insulin-like growth factor-1 (IGF-1), or growth hormone, within 1 month preceding the teduglutide pretreatment visit.
13. Treatment with octreotide or dipeptidyl peptidase 4 (DPP-4) inhibitors within 3 months prior to the pre-treatment visit
14. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients
15. Known history of alcohol or other substance abuse within 1 year prior to the pre-treatment visit
16. Pregnant or lactating female subjects
17. Sexually active female subjects of child-bearing potential unwilling to use approved contraception during teduglutide treatment and for 30 days after the treatment period

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.

4.6 Follow-up Period Escape Criteria

At the discretion of the investigator, the follow-up period may be interrupted and the subject may proceed directly to the pre-treatment visit, if 1 of the following criteria is met:

1. Increasing PS requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition 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.

4.7 Reproductive Potential

4.7.1 Female Contraception

To be eligible for treatment with teduglutide, sexually active females of child-bearing potential must use an acceptable form of contraception throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used, they should be administered according to the package insert. Females of child-bearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of investigational product.

To be eligible for treatment with teduglutide, female pediatric subjects and adolescent subjects should be either:

- Pre-menarchal and either Tanner Stage 1 or less than age 9 years, or
- Females of child-bearing potential (FOCBP) with a negative serum beta-human chorionic gonadotropin (β-HCG) pregnancy test at the teduglutide pre-treatment visit**.** Females of child-bearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- Abstinence
- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the pre-treatment visit, plus condoms. Note: if subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.8 Discontinuation of Subjects

4.8.1 Teduglutide Discontinuation

If the investigational product is discontinued prematurely during a teduglutide treatment cycle, regardless of the reason, the evaluations listed for the EOT visit are to be performed as completely as possible. After the appropriate EOT assessments are performed, a subject may remain in the study. A subject who remains in the study would enter a no-teduglutide treatment (NTT) period and could be evaluated for subsequent teduglutide treatment eligibility according to the study schedules. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for permanent treatment discontinuation, dates of investigational product administered (including last date of treatment), and amount of investigational product taken must be recorded in the electronic case report form (eCRF) and source documents, as described in Section 4.8.3. The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor, when possible.

4.8.2 Study Withdrawal

At any time during the study, the investigator or sponsor may withdraw a subject, or a subject may withdraw from the study, for any reason, without prejudice to their future medical care by the physician or at the institution.

If a subject withdraws from the study during a teduglutide cycle, the evaluations listed for the EOT visit are to be performed as completely as possible. Whenever possible, the subject will then be asked to return 4 weeks later for the early termination (ET) visit, and will be contacted weekly by phone during the interim period between EOT and ET for safety follow-up.

If a subject withdraws from the study during a NTT period, the evaluations listed for the ET visit are to be performed as completely as possible.

Subjects who withdraw from the study will not be replaced.

4.8.3 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
- Protocol deviation
- Lack of efficacy
- Physician decision
- Withdrawal by subject
- Lost to follow-up
- Pregnancy (Discontinuation of treatment only)
- Death
- Other

4.8.3.1 Subjects 'Lost to Follow-up' Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact 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 CONCOMITANT TREATMENT

5.1 Concomitant Medications and GI Procedures

Concomitant treatment refers to all treatment taken between the dates of informed consent and EOS, inclusive. Concomitant treatment information must be recorded on the appropriate eCRF page. Concomitant treatments will be assessed at each site visit, and include all non-study treatments (medications, herbal treatments, vitamins, invasive and diagnostic procedures). Concomitant GI procedures include (but are not limited to) endoscopy, radiographic studies, GI and liver biopsies and associated pathology results. Concomitant treatment information must be recorded on the appropriate eCRF page. Details of medication changes and/or dosages will be recorded on the eCRF.

The mechanism of action of teduglutide may increase absorption of drugs (eg, motility medication including narcotics and opioids used for the management of SBS, Coumadin, psychotropics, metronidazole, and digoxin). Accordingly, due consideration should be given to modifying concomitant medication regimens. Down-titration of concomitant medications should be considered when drugs, especially those with a narrow therapeutic range, are prescribed at dosages that are higher than usual.

5.1.1 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.1.2 Prohibited Treatment

The mechanism of action of teduglutide may increase enteral absorption of drugs (eg, motility medication including narcotics and opioids used for the management of SBS, Coumadin, psychotropics, metronidazole, digoxin), so consideration should be given to modifying concomitant enteral medication regimens. Down-titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic range, are given at dosages that are higher than usual.

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the pre-treatment visit:

Table 5-1: Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pre-Treatment Visit
Native/synthetic glucagon-like peptide-2 (not-including teduglutide)	Any
Glucagon-like peptide-1 analog or human growth hormone	1 month
Octreotide or dipeptidyl peptidase 4 inhibitors	3 months
Biological therapy (eg, antitumor necrosis factor)	6 months

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is teduglutide, which 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 SHP633 investigator's brochure.

6.1.1 Blinding the Treatment Assignment

Not applicable for this open-label study.

6.2 Administration of Investigational Product(s)

6.2.1 Interactive Response Technology (IRT) for Investigational Product Management

An interactive web-based response system (IWRS) will be used for screening and enrolling subjects, recording subject visits, investigational product supply dispensation and management, inventory management and supply ordering, investigational product expiration tracking and management, and return of investigational product. Please refer to the Study Manual for additional details regarding the IWRS.

The IWRS will also be used for creating, tracking, and confirming investigational product shipments. A user manual with specific functions and instructions for the IWRS will be provided to the site, and site personnel will receive training.

6.2.2 Allocation of Subjects to Treatment

This is an open-label study. Subjects will retain their assigned subject number from the TED-C14-006 study. Assessment of need for teduglutide treatment should be guided by the teduglutide treatment inclusion criteria. If the investigator, subject, and/or parent/guardian agree to proceed with treatment, a formal evaluation of teduglutide inclusion and exclusion criteria will be performed at the pre-treatment visit (Table 1-3).

6.2.3 Dosing

If teduglutide treatment eligibility is established at the pre-treatment visit and again, confirmed at the Cycle Day 1 visit, the subject will start a teduglutide treatment period, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily. The initial dose will be calculated based on body weight measured at the teduglutide pre-treatment visit, and adjusted as needed, based on body weight measured at Week 12 (CxW12). 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 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 rotated.

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 each 24-week teduglutide 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. At any time during the follow-up period, if escape criteria are met, the subject may proceed directly to another Pre-Treatment visit to assess treatment eligibility for another cycle (Section 4.6). Following the completion of the 4-week follow-up, the subject will continue in the study off teduglutide. Additional 28-week cycles may be repeated if treatment eligibility is established each time.

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification will be applied to the investigational product(s) container.

The study drug will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of study drug will be supplied and these will be labeled in accordance with applicable regulatory requirements. Sterile water for injection syringes will also be provided separately and will be labeled in accordance with the applicable regulatory requirements.

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

6.3.2 Packaging

Investigational product is packaged in the following conditions:

Teduglutide will be provided in a sterile, single-use, glass vial as a lyophilized powder, to be reconstituted with 0.5 mL sterile water for injection provided as the diluent in a prefilled syringe.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

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.

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

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

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. The investigator is to keep a current record of the inventory and dispensation of all clinical supplies. This record will be made available to the sponsor's site monitor for the purpose of accounting for all clinical supplies. Any discrepancy or deficiency will be recorded and will include an explanation. All supplies sent to the investigator must be accounted for and in no case will clinical supplies be used in any unauthorized situation.

The investigator has overall responsibility for administering/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 (as documented by the investigator in the applicable study delegation of authority form) will dispense the investigational product only to subjects eligible for teduglutide treatment following the procedures set out in the study protocol. All dispensed

study medication will be documented in the eCRFs and/or other investigational product record (eg, investigation product accountability form). The investigator is responsible for assuring the retrieval of all study supplies from subjects.

All used and unused study drug vials must be returned by the subjects and/or parent/guardian, and will be retained at the site. All original containers, whether empty or containing study drug will be returned to the pharmacy. Returned study drugs will NOT be relabeled or reassigned for use by other subjects. Contents of the study drug containers will not be combined. All used and unused vials must be returned to the distribution center according to the sponsor's instruction. No vial/kit may be destroyed on site without approval by the sponsor.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

Subjects will be instructed to bring their unused investigational product and empty/used investigational product packaging to every visit. Drug accountability will be assessed 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. The pharmacist/nominated person will record details on the drug accountability form.

Of those subjects eligible for teduglutide treatment, 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 Schedule of Assessments (Table 1-1, Table 1-2, and Table 1-3) and must be referred to in conjunction with the instructions provided in this section.

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 (and assent, as applicable) from the subject. A subject will have up to 7 days, after completion of the TED-C14-006 study, to sign consent to participate in the SHP633-304 study. The first visit after screening (either a no-teduglutide treatment visit or a pre-treatment visit), must occur within 12 weeks of screening.

The screening visit (Scr) assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1-1, and as detailed below:

- Informed consent, and informed assent (if applicable), is obtained
- Study eligibility is determined. A screen failure is a subject who has given informed consent and failed to meet the Study Inclusion Eligibility Criteria. Subjects cannot be rescreened once they have been designated as a screen failure.
- Demographics, medical history, and SBS history
- Intake and output diaries are dispensed
- Evaluate teduglutide treatment inclusion criteria
- Adverse events, concomitant medications and concomitant GI procedures

7.1.2 Visits for Subjects Not Receiving Teduglutide

While outside of the 28-week teduglutide-treatment cycle, subjects will be followed every 12 weeks for safety and efficacy assessments. No-teduglutide treatment visits are numbered sequentially (NT1, NT2, etc.), even if interrupted by the treatment cycles. Assessments will be performed as outlined in Table 1-2 and described below.

- Intake and output diaries are dispensed
- Evaluate teduglutide treatment inclusion criteria
- Adverse events, concomitant medications and concomitant GI procedures
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries
- Record PS and enteral nutrition (EN) prescriptions, and adjust as needed
- Safety Laboratory Tests (ie, clinical chemistry, hematology, and urinalysis)

- PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales
- Antibodies to teduglutide, if and when required
- Fecal occult blood testing, as indicated (see Section 7.2.9.1)
- Colonoscopy, as indicated (see Section 7.2.9.2)
- Serum sample, as indicated

Teduglutide treatment may be considered at any time during the NTT period. If the investigator and the subject (and parent or legal guardian, as appropriate) agrees to proceed with treatment if the subject is eligible, the subject may proceed to the pre-treatment visit to determine eligibility. The pre-treatment visit must occur within 12 weeks of a given NTT visit.

7.1.3 Visits for Subjects Receiving Teduglutide

7.1.3.1 Pre-treatment Visit

Subjects who meet at least 1 of the teduglutide treatment inclusion criteria during the screening visit or during the NTT period may proceed to the pre-treatment visit if the investigator, subject and parent agree to proceed with teduglutide therapy. Similarly, subjects who meet escape criteria during the teduglutide follow-up period may proceed to the pre-treatment visit.

The pre-treatment visit may also be combined with screening visit, and if the pre-treatment visit assessments occur within 7 days of the TED-C14-006 EOS visit (Week 28), both sets of assessments can be combined. A subject must have 2 weeks of intake diary data collected, prior to the first dose administration (CxD1) during any teduglutide treatment cycle. In general, pre-treatment assessments may occur over a period of up to 21 days. The teduglutide pre-treatment visit (Px) assessments and procedures will be performed in Table 1-3 and as described below:

- Evaluate teduglutide eligibility (treatment inclusion/exclusion criteria)
- Dispense intake and output diaries
- Adverse events, concomitant medications and concomitant GI procedures
- Fecal occult blood testing
- Gastrointestinal-specific testing, including colonoscopy or sigmoidoscopy as indicated
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries
- Record PS and EM prescriptions, and adjust as needed.
- Safety Laboratory Tests
  (In addition to clinical chemistry, hematology, and urinalysis, labs at this visit include prothrombin time [PT] international normalized ratio [INR]. Subsequent prothrombin time/international normalized ratio (PT/INR) measurement is only required to evaluate for suspected drug-induced liver injury [DILI]).

- Pregnancy testing (serum)
- Serum sample

7.1.3.2 Teduglutide Treatment Period (CxD1-CxW24)

The open-label teduglutide treatment period will comprise 24 weeks, during which all assessments and procedures listed for Visits CxD1-CxW24 in Table 1-3 shall be completed. Cycles are numbered sequentially, such that the first visit of the first cycle is C1D1, and the first visit of the second cycle is C2D1, etc. Visit windows are calculated based upon the date of first investigational product administration (Visit CxD1).

VISIT CXD1

Assessments and procedures at this visit will be performed as outlined Table 1-3 and as described below.

2 weeks of intake diary data are required before drug is administered at CxD1.

- Confirm teduglutide eligibility
- Dispense intake and output diaries
- Adverse events, concomitant medications and concomitant GI procedures
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries
- Record PS and EN prescriptions, and adjust as needed
- Safety laboratory tests
- Quality of life measurements
- Antibodies to teduglutide
- Pregnancy testing (urine)
- Dispense study drug

7.1.3.3 Site Visits during Teduglutide Treatment Period

Subjects will return for clinic visits on cycle weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24/EOT. Assessments and procedures at these visits will be performed as outlined in Table 1-3 and as described below:

- Dispense/review intake and output diaries
- Physical examination and vital signs, including weight
- Record PS and EN prescriptions, and adjust as needed
- Safety laboratory tests
- Urine pregnancy testing for FOCBP (CxW4, CxW9, CxW12, CxW16, CxW20, CxW24)

- Study drug dispensation (except for CxW24)
- Adverse events, concomitant medications and concomitant GI procedures

In addition, at CxW12 and CxW24 Visits **ONLY**, the following procedures will be performed:

- Height and head circumference
- Antibodies to teduglutide
- Fecal occult blood testing (FOBT)
- GI-specific testing, including colonoscopy or sigmoidoscopy as indicated
- Quality of life measurements

At CxW24 **ONLY**, a serum sample is collected and stored for future analysis. This sample will not be used for genetic testing and lack of collection will not constitute a protocol deviation.

7.1.3.4 Phone Visits

Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period. Phone visit assessments and procedures are outlined in Table 1-3 and described below:

- Review intake and output diaries
- Safety laboratory tests (clinical chemistry and urinalysis)
- Record PS and EN prescriptions, and adjust as needed
- Obtain AEs, concomitant medications, and concomitant GI procedures
- Evaluate escape criteria

7.1.4 Teduglutide Follow-up Period

The safety follow-up period for this protocol is 4 weeks (Weeks 25 – 28 of the cycle). Phone visits will occur on cycle weeks 25, 26, and 27 for all subjects. Phone visit assessments and procedures at weeks 25-27 will be the same as for telephone visits performed during the teduglutide treatment period. In addition, subjects will be evaluated for follow-up period escape criteria. If escape criteria are met at any time during the follow-up period, the subject may proceed directly to another pre-treatment visit at the investigator's discretion.

At cycle week 28 (CxW28), subjects will return to the study site. In addition to the assessments performed at weeks 25-27, the following procedures will be performed at **CxW28 ONLY:**

- Physical examination and vital signs, including weight
- Antibodies to teduglutide
- Pregnancy testing (urine)
- Evaluate escape criteria

7.1.4.1 Study Completion/Early Termination Visit (EOS/ET Visit)

All subjects will return to the study site for the end of study/early termination visit (EOS/ET). Assessments and procedures at this visit will be performed as outlined in Table 1-1 and as

described here. If a subject discontinues the study prematurely, the assessments for the EOS/ET Visit are to be performed as completely as possible.

- Adverse events, concomitant medications and concomitant GI procedures
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries
- Record PS and EN prescriptions, and adjust as needed
- Safety laboratory tests
- Fecal occult blood testing, as indicated
- Gastrointestinal-specific testing, including colonoscopy or sigmoidoscopy as indicated.
- Quality of life measurements
- Antibodies to teduglutide
- Pregnancy testing, as needed

7.2 Study Evaluations and Procedures

7.2.1 Demographics, Medical History, and SBS History

Demographics, medical history, and SBS history will be obtained at screening. Medical history for purposes of this extension study will consist of the following:

- Adverse events that were ongoing at the time of completion of TED-C14-006
- Events that occurred during the period between completion of TED-C14-006 and informed consent to SHP-633-304
- Gestational age at birth and parental heights.

This medical history information will supplement the medical history information collected at the start of the TED-C14-006 core study. If the subject has any changes to the SBS history collected at the baseline visit of the TED-C14-006 study, that information (updated SBS history) will be collected.

7.2.2 Physical Examination

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

7.2.3 Vital Signs, Body Weight, Height, Head Circumference and Body Mass Index (BMI)

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 cuff (using the same method, the same arm, and in the same position throughout the study).

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Height (or length) and head circumference (for subjects ≤36 months of age) will be measured at selected visits. A height z-score, weight z-score, BMI, and BMI z-score will be calculated by the sponsor using the site-provided height and weight data collected at each site visit

New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

7.2.4 Clinical Laboratory Tests

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 1-1, Table 1-2, and Table 1-3) 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 teduglutide treatment period, subjects will also have safety labs within approximately 5-7 days after a PS adjustment. Safety labs performed after PS 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 will not 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 8.1). For pediatric subjects in diapers, urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

New clinically significant labs should be reported as AEs.

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

Table 7-1 List of Laboratory Tests

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

Coagulation:
Prothrombin time/International normalized ratio

Urinalysis:
- Blood
- Glucose
- Leucocytes
- Microscopic analysis
- pH and osmolality
- Protein
- Sodium
- Specific gravity
- **Pregnancy tests** (females of childbearing potential):
  - Serum β-HCG (screening)
  - Urine β-HCG (all other visits)

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
- Uric acid

7.2.5 Serum Sampling

Serum samples will be collected and stored for future analysis at the following times:

- During Teduglutide treatment period: at the pretreatment and CxW24 (EOT) visits.
- During NTT: Approximately every 24 weeks.

The serum sample will not be used for genetic testing. Lack of collection will not constitute a protocol deviation.

The sponsor, sponsor's representatives, biorepositories, and any specialty laboratories will be blinded to the subject's identity. The sample and/or extracted material will otherwise be stored for up to 15 years from the end of the study after which time it will be destroyed. Upon written request, subjects will be permitted to withdraw their sample from the analysis and have their sample and/or extracted material destroyed. Any results already generated from the samples will not be removed from any analyses that have already been performed.

7.2.6 Pregnancy Testing

A serum pregnancy test is performed on all FOCBP at the teduglutide pre-treatment visit. Urine pregnancy tests will be administered at all other visits according to the study schedules, or if pregnancy is suspected, or as specified per protocol upon withdrawal of the subject from the study.

7.2.7 Antibody Testing

Blood samples will be drawn for the analysis of positive/specific antibodies to teduglutide according to the Schedule of Assessments (Table 1-1, Table 1-2, and Table 1-3). Blood samples for antibodies may be drawn from a central line or from peripheral access. The sample drawn on CxD1 must be drawn prior to administration of the first dose of teduglutide. Once the subject has started teduglutide treatment, samples must be drawn at least 14 hours after dosing. Subjects who test positive/specific for antibodies to teduglutide will also be tested for neutralizing antibody. Subjects who have been previously treated with teduglutide, and who test positive/specific for antibodies to teduglutide, will have follow-up blood draws for positive/specific antibodies to teduglutide every 12 weeks while on study until a negative result is obtained.

7.2.8 Volume of Blood

Efforts will be made to minimize the amount of blood drawn from all pediatric subjects enrolled 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 annually are shown in the following table.

Table 7-1: Approximate Volume of Blood to be Drawn from Each Subject Annually

Assessment		Sample Volume (mL)	No. Samples per two 28-week Teduglutide Cycles	Total Volume (mL)
Subjects Receiving Teduglutide Treatment				
Safety	Biochemistry and β-hCG[a]	2.5	24	60
	Hematology	2	24	48
	Coagulation Parameters	1	2	2
	Antibodies	2	8	16
	Serum storage samples	3	4	12
Total mL per 2, 28-week Treatment Cycles (Approximate Annual Volume):				**138**
Subjects Not Receiving Teduglutide Treatment[b]				
Assessment		**Sample Volume (mL)**	**No. Samples per 4 NTT Visits**	**Total Volume (mL)**
Safety	Biochemistry	2.5	4	10
	Hematology	2	4	8
	Serum storage samples	3	2	6
Total mL per 4 "No Teduglutide Treatment" Visits 48-week period:				**24**

Abbreviations: β-hCG=beta-human chorionic gonadotropin

[a] β-hCG testing will only be administered to females who are eligible for teduglutide treatment.

[b] Subjects not receiving TED treatment, but who were exposed to it previously and tested positive for anti-TED antibodies will require blood samples for antibody testing every 12 weeks until they test negative.

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 PS adjustment, and anti-teduglutide antibody testing during no-teduglutide treatment.

7.2.9 Gastrointestinal-specific Testing

7.2.9.1 Fecal Occult Blood Testing

Fecal occult blood testing must be performed on all subjects at the pre-treatment visit, week 12, and week 24 of the teduglutide cycle. During NTT periods, FOBT must be performed on teduglutide-exposed subjects (subjects who have received teduglutide any time in the past and are therefore not teduglutide-naïve) on a roughly annual basis (approximately every 48-60 weeks). Actions to be taken in response to a positive FOBT are described below.

7.2.9.2 Colonoscopy

Teduglutide-naïve subjects age 12 and older will undergo colonoscopy at the pre-treatment visit if one has not been performed within 1 year.

Subjects of any age with newly positive FOBT results at the pre-treatment visit for which a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy prior to receiving teduglutide. If newly positive FOBT results (for which a readily detectable cause cannot be identified) are obtained at the end of a teduglutide treatment cycle (CxW24/EOT), colonoscopy will be performed. The need for colonoscopy in response to positive FOBTs at any other point during the study, or to re-evaluate persistently positive FOBTs is at the discretion of the investigator.

Teduglutide-exposed subjects who have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) will undergo colonoscopy. While receiving additional teduglutide treatment, subjects will undergo colonoscopy at 5 year intervals or more often as needed.

Upper endoscopy may be performed along with any colonoscopy at the investigator's discretion. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. Subjects with unresected GI polyps, polyposis conditions, pre-malignant change or malignancy in the GI tract will be excluded from teduglutide treatment.

7.2.10 Nutritional Support

Nutritional support includes PS, EN, and other food and fluids. Advances in EN and/or reductions to PS will be based on clinical status, including weight, linear growth, hydration status, and safety laboratory results. Intake and output diaries will include data to be considered in the adjustment of each subject's nutritional support. Guidelines for nutritional support management and weaning algorithms are provided in Appendix 1.

7.2.11 Intake Diary

Intake diaries will be used to collect and evaluate each subject's nutritional support. The subject/parent/guardian will complete the appropriate fields of the PS and enteral nutrition (formula) sections of the intake diary 2 weeks prior to ALL scheduled site visits. During the 24-week teduglutide treatment period, the intake diary will also be completed for 1 week following

PS adjustments. The intake diary will also be completed daily during the 4-week follow-up period. The following data will be captured in the intake diaries:

- Parenteral support volume and infusion duration
- Enteral nutrition (formula) volume
- Site personnel will determine the actual PS and EN daily calories based on diary entries.

7.2.12 Output Diary

Urine and stool output should be recorded in the output diary over a 48-hour period of PS and EN stability before every clinic visit; in addition, output should be recorded for subjects that are in a teduglutide treatment cycle within 1 week of implementing a change in the PS prescription, regardless of previous teduglutide exposure.

Urine data:

- Toilet-trained subjects (who do not wear diapers)
- Measure and record all urine output in mL or cc. The subject or parent will perform dipstick specific gravity tests on the first urine produced after the daily infusions of PS.

Nontoilet-trained subjects (who wear diapers)

- 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 may be asked to collect the first void after the daily PS infusion to measure specific gravity.

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

- Toilet-trained subjects WHO DO NOT WEAR DIAPERS
  - Record the occurrence of each bowel movement and score the stool consistency using the Bristol Stool Form Scale (see Output diary)
- Nontoilet-trained subjects WHO WEAR DIAPERS
  - Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency using the Bristol Stool Form Scale (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. Ostomy output will not be scored using the Bristol scale.

All diaries will be reviewed by the investigator or their designee at each clinic and telephone contact to assess clinical status and opportunity for PS reduction and advance in feeds.

7.2.13 Health-related Quality of Life Assessments

Throughout the study, health-related quality of life assessments will be performed using the PedsQL Generic Core Scales. Each PedsQL age-appropriate form takes less than 4 minutes to

complete. The scales include self-reports for pediatric subjects and adolescents aged 5 to 18 years and proxy-reports from parents of pediatric subjects aged 2 to 18 years.

Field trials have shown that the internal consistency reliability of the PedsQL was excellent, with alphas for the generic core scales in both self- and proxy-report greater than the 0.70 standard, and alphas for the full 23-item scale approaching 0.90 for self- and proxy-report. Missing data were minimal. Item response distributions were across the full scale range, with no floor effects, and minimal ceiling effects.

The validity of the PedsQL Generic Core Scales was demonstrated through known group comparisons, and correlations with other measures of disease burden. The PedsQL self- and proxy-report distinguished between pediatric subjects with and without a chronic health condition, and within the group of pediatric subjects with a chronic condition, between those who did or did not have an overnight hospital visit in the last 12 months. Further, both child self-report and parent proxy-report correlated significantly with the number of days the child was too ill to pursue normal activities, needed someone to care for him or her, missed school in the last month, the number of days the parent missed from work in the last month, and parent-report of problems pursuing their normal work routine and concentrating at work. The PedsQL Generic Core Scales are also responsive to clinical change, as demonstrated in field trials.

7.2.13.1 Pediatric Quality of Life Generic Core Scale (PedsQL™), Acute version

The PedsQL Generic Core Scale is designed to measures health-related quality of life (HRQoL) in pediatric subjects and adolescents (2-18 years of age). The developmentally appropriate PedsQL Generic Core Scale will be completed by either the parent or legal guardian and subject as indicated in Table 7-2 at the time points as outlined in Table 1-1, Table 1-2 and Table 1-3.

Table 7-2: Developmentally Appropriate PedsQL™ Generic Core Scales

Report	Completed by
Parent Report for Toddlers (ages 2-4)	Parent or Legal Guardian
Child Self Report and Parent Proxy-Report for Young Pediatric subjects (ages 5-7)	Subject and Parent or Legal Guardian
Child Self Report and Parent Proxy-Report for Pediatric subjects (ages 8-12)	Subject and Parent or Legal Guardian
Child Self Report and Parent Proxy-Report for Teens (ages 13-18)	Subject and Parent or Legal Guardian

Abbreviations: PedsQL=Pediatric Quality of Life Inventory

The Parent Report for Toddlers (ages 2-4) of the PedsQL Generic Core Scale is composed of 21 items comprising 4 dimensions as follows: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), 4) School Functioning (3 items).

The Child and Parent Reports of the PedsQL Generic Core Scale for Young Pediatric subjects (ages 5-7), Pediatric subjects (ages 8-12), and Teens (ages 13-18) are composed of 23 items comprising 4 dimensions as follows: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), 4) School Functioning (5 items).

7.2.13.2 Pediatric Quality of Life Family Impact Module (PedsQL™), Acute version

The PedsQL Family Impact Module is a parent-report multidimensional instrument that will be completed by the parent or legal guardian, as outlined in Table 1-1, Table 1-2, and Table 1-3.

The PedsQL Family Impact Module is a specific module of the PedsQL that is used to measure the impact of pediatric chronic health conditions on parents and the family (Varni et al. 2004). The 36-item PedsQL Family Impact Module consists of 6 scales measuring parent self-reported functioning as follows: 1) Physical Functioning (6 items), 2) Emotional Functioning (5 items), 3) Social Functioning (4 items), 4) Cognitive Functioning (5 items; worries about treatment and disease), 5) Communication (3 items), 6) Worry (5 items). Two additional scales measure parent-reported family functioning as follows: 1) Daily Activities (3 items), and 2) Family Relationships (5 items). The PedsQL Family Impact Module should take the parent or legal guardian approximately 5 to 10 minutes to complete.

7.2.13.3 PedsQL Gastrointestinal Symptoms Module (PedsQL™), Acute version

The PedsQL Gastrointestinal Symptom Module is a disease-specific 58-item module, comprised of 10 different symptom scales that assess gastrointestinal symptom-related quality of life: food and drink limits, trouble swallowing, heartburn and reflux, nausea and vomiting, gas and bloating, constipation, blood in poop, and diarrhea. The PedsQL Gastrointestinal Symptoms Module was designed to allow the selection and scoring of individual scales from the Module. The scales of Food and Drink Limits (6 items) and Diarrhea (7 items) were identified as clinically relevant and appropriate for the symptoms experienced in this pediatric study population, and therefore, are the only scales used in this study. The scales will be completed by either the parent or legal guardian and subject as indicated in Table 7-2 at the time points outlined in Table 1-1, Table 1-2, and Table 1-3.

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 7.1.4. 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.

Note that the severity of AEs that constitute dose interruption criteria will also be evaluated using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading criteria (Table 8-1).

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 study drug that are not resolved at EOT 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 in 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.

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 (eg, 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

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.4.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Global Pharmacovigilance and Risk Management Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the Shire Medical Monitor using the details specified in the emergency contact information section of the protocol. In the event a subject becomes pregnant during the study, teduglutide administration must be discontinued immediately.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by the Protocol. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by the Protocol as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or will determine the pregnancy onset date.

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 Pharmacovigilance and Risk Management 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 Pharmacovigilance and Risk Management 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 Pharmacovigilance and Risk Management 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 7.1.4, and must be reported to the Shire Global Pharmacovigilance and Risk Management 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

Pharmacovigilance and Risk Management 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 and Permanent Discontinuation

The investigator is responsible for contacting the sponsor/designee when the subject's teduglutide dosing regimen is interrupted. Attempts should be made to contact the sponsor/designee prior to dose interruption. Reasons for dosage interruptions may include but are not limited to hospitalization, incidents of certain AEs, SAEs considered to be related to the study drug, a lapse in investigational product delivery, etc.

Study drug must be permanently discontinued if any of the following events occur:

- Pregnancy
- Severe hypersensitivity, such as anaphylaxis determined by the investigator to be related to study drug. This does not include anti-teduglutide antibodies, mild injection site reactions or mild symptoms that according to the investigator do not pose a significant risk to the subject.
- An AE listed in (Table 8-1) that is of NCI CTCAE severity Grade 3 or 4 and considered to be related to study drug administration
- Confirmed drug-induced liver injury (DILI) related to teduglutide (See Section 8.4.2)

8.4.1 Dose Interruption Criteria Based on Known or Possible Risks of Teduglutide

The investigational product may be discontinued if the subject has an AE listed in Table 8-1 that is of severity ≥Grade 3 per the NCI CTCAE. All such AEs should be discussed with Shire's medical monitor as soon as possible. Teduglutide administration must be permanently discontinued if the AE is considered related to the investigational product. The length of the dose interruption, and whether teduglutide administration resumes or is discontinued, depends on the clinical situation.

Investigators and the Data Monitoring Committee (DMC) should be guided by the descriptions of Grade 3 and 4 events, as they relate to known and possible risks associated with the administration of teduglutide.

Table 8-1: CTCAE Criteria for Adverse Events that May Lead to Dose Interruption

Adverse Events	Grade 3 Description	Grade 4 Description
Gastrointestinal Disorders		
Colorectal polyps	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated
Intestinal Obstruction	Hospitalization indicated; elective operative intervention indicated; limiting self-care activities of daily living; disabling	Life-threatening consequences; urgent operative intervention indicated
Gallbladder and Bile Duct Disease		
Cholecystitis	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder perforation	Not Applicable	Life-threatening consequences; urgent intervention indicated
Gallbladder obstruction	Symptomatic and severely altered gastrointestinal function; tube feeding, total parenteral nutrition or hospitalization indicated; nonemergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Adverse Events	**Grade 3 Description**	**Grade 4 Description**
Alkaline Phosphatase increased	>5.0 to 20.0x ULN	>20.0x ULN
Blood bilirubin increased	>3.0 to 10.0x ULN	>10.0x ULN
Bile duct stenosis	Severely altered gastrointestinal function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreatic Disease		
Pancreatitis	Severe pain; vomiting; medical intervention indicated (eg, analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated
Pancreatic duct stenosis	Severely altered gastrointestinal function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreas infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Serum amylase increased[a]	>2.0 to 5.0x ULN	>5.0x ULN

Table 8-1: CTCAE Criteria for Adverse Events that May Lead to Dose Interruption

Lipase increased[a]	>2.0 to 5.0x ULN	>5.0x ULN
Cardiovascular Disease		
Heart failure	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (eg, continuous intravenous therapy or mechanical hemodynamic support)

Source: Common Terminology Criteria for Adverse Events, version 4.03, 14 June 2010

ULN=upper limit of normal

[a] In the setting of clinically acute and symptomatic pancreatitis

8.4.2 Dose Interruption Criteria Based on Drug-Induced Liver Injury

Teduglutide administration for an individual subject may need to be interrupted if the subject has clinical and laboratory evidence of potential DILI, in the absence of an alternative explanation, as identified by the following criteria:

- ALT or AST >8x ULN
- ALT or AST >5x ULN and >2x baseline value for more than 2 weeks
- (ALT or AST >3x ULN and >2x baseline value) and (total bilirubin >2x ULN or INR>1.5)
- ALT or AST >3x ULN and >2x baseline value with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

All laboratory values suggestive of potentially new DILI should be repeated and verified within 3 days. International normalized ratio should be measured with this set of verification laboratory assessments 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 to evaluate the cause of liver injury. This evaluation may include, as clinically indicated, consideration of sepsis, acute viral hepatitis (eg, hepatitis A immunoglobulin [IgM], hepatitis B surface antigen, hepatitis C antibodies, cytomegalovirus IgM, Epstein-Barr virus antibody panel), hepatobiliary obstruction (ultrasound), autoimmune hepatitis (anti-nuclear, anti-smooth muscle, anti-actin, or anti-liver kidney microsomal antibodies), intestinal failure associated liver disease, cardiovascular causes such as ischemic hepatitis, and concomitant hepatotoxic treatments.

Additional evaluations may be performed at the discretion of the investigator in consultation with the Shire medical monitor.

Teduglutide administration must be permanently discontinued if DILI is confirmed and deemed related to study drug.

8.5 Early Termination of the Clinical Study

The DMC may recommend stopping the study if:

- ≥2 subjects being administered investigational product develop the same event listed in Table 8-1 of severity CTCAE Grade 3

  or

- 1 subject develops an event listed in Table 8-1 of severity CTCAE Grade 4 which is attributable to investigational product or is not reasonably related to the underlying disease process.

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol in 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 in 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. Unscheduled safety follow up assessments (conducted after EOS) are not required to be collected.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management process. 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 its agent. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, USA) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the statistical methods and definitions 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.

9.4 Planned Interim Analysis, and Data Monitoring Committee

An interim analysis is planned when 6 months of safety data have been collected.

A DMC will be involved in the management of this study. The DMC members will review the data approximately every 3 months during the study treatment period (date of the first subject's first dose to date of the last subject's last dose). 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.

9.5 Sample Size Calculation and Power Considerations

The number of subjects in this study is not based on statistical power considerations as this is an extension study of the core study, TED-C14-006. The maximum number of subjects will be determined by the enrollment in TED-C14-006.

9.6 Study Population

The safety population includes all enrolled subjects in the study. Safety population will be used for both safety and efficacy analyses.

9.7 Efficacy Analyses

No claims of statistical significance will be made; however, 95% confidence intervals will be provided, if applicable. Continuous variables, including those assessed on a discrete scale, 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.

9.7.1 Efficacy Endpoints

The following efficacy/PD endpoints will be measured. For each endpoint, analyses will be performed using the Baseline of this extension study at the end of each teduglutide treatment period (Week 24 or EOT) and each study visit. In addition, the efficacy/PD endpoints will be analyzed using the Baseline of the Core study (TED-C14-006) and the Baseline of each treatment cycle. The derivations of the weekly PS volume and 3 baselines will be described in the study SAP in detail.

- Reduction in PS volume of at least 20%

  • Absolute and relative change in PS volume
- Complete weaning off PS
- Change in days per week of PS

9.8 Safety Analyses

9.8.1 Safety Endpoints

The following safety endpoints will be measured. For each endpoint, analyses will be performed using the Baseline of this extension study. In addition, the safety endpoints will be analyzed using the Baseline of the Core study (TED-C14-006).

- Adverse events, including those pertaining to GI symptoms
- Vital signs, including temperature, heart rate, blood pressure
- Body weight, height (or length), head circumference (up to 36 months of age) trends on growth charts, BMI; z-scores will be calculated for height (or length), weight, head circumference and BMI
- Laboratory safety data (ie, clinical chemistry, hematology, and urinalysis)
- Urine output
- Stool output
- Antibodies to teduglutide
- Gastrointestinal-specific testing (teduglutide treatment eligible subjects only) including colonoscopy or sigmoidoscopy, abdominal ultrasound, and FOBT, upper GI series with small bowel follow through

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number of events, incidence, and percentage of AEs will be calculated overall, by System Organ Class (SOC) and by preferred term. SAEs will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) with regard to drug class and drug name. The number and percentage of subjects with specific prior medications will be summarized. Medical history (including surgical/procedural history) will be coded using MedDRA. The number and percentage of subjects with specific histories will be summarized by system organ class and preferred term.

For clinical laboratory tests, vital signs, body weight, and fluid balance variables, descriptive statistics (mean, median, standard deviation, minimum and maximum values, the number and percentage of subjects in specified categories) will be calculated to summarize the observed values and change from baseline at each scheduled visit.

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

Additional safety parameters and measures will include change in body weight, height (or length) and head circumference (up to 36 months of age). Derived variables will include height z-score, weight z-score, BMI, and BMI z-score. Descriptive statistics (mean, median, standard deviation, minimum and maximum values, the number and percentage of subjects in specified categories) will be calculated to summarize the absolute values and change from baseline at each scheduled visit.

9.9 Other Analyses

9.9.1 Health-related Quality of Life Analyses

The following HEOR endpoints will be measured. For each endpoint, analyses will be performed using the Baseline of this extension study. In addition, the HEOR endpoints will be analyzed

using the Baseline of each treatment cycle at approximately 12 week intervals (Weeks 12 and 24 of each teduglutide treatment cycle, and every 12 weeks for subjects not on teduglutide).

- Change in Pediatric Quality of Life Inventory (PedsQL) score
- Change in PedsQL Family Impact Module score
- Change in PedsQL Gastrointestinal Symptoms Module Sub-Scales scores:
    - Food and Drink Limits
    - Diarrhea

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 to the CRO 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 (CSR) 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 EOS 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 is appointed to review the final CSR for multicenter studies. Agreement with the final CSR 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 products, 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 international 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 Case Report Forms

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded into eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. 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 into the eCRF.

eCRFs should be approved by the investigator per study specifications and data deliverable requirements.

The clinical research associate (CRA)/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 diary cards, original clinical laboratory reports, and histology and pathology 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 CRA/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 subject 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 Food and Drug Administration (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 and assent, where applicable, from 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 or the subject's legally-authorized representative, as applicable, 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 (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or 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.

Within the source documents, site personnel should document instruction of and understanding by the parent/legally-authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

The principal investigator provides the sponsor with a copy of the consent form, and assent form where applicable, which was reviewed by the IRB/EC and which 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.

For sites within the EU, the applicant for an EC opinion can be the sponsor, the investigator, or for multicenter studies 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 (or 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; for sites within the EU, this can be done by the sponsor, the investigator or for multicenter studies 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 (or 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 review 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 SHP633; national or local regulatory authorities; and the IRBs/ECs 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 2-4 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 current standards. Participation as an investigator does not confer any rights to authorship of publications.

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12 APPENDICES

APPENDIX 1 GUIDELINES FOR NUTRITIONAL SUPPORT MANAGEMENT DURING THE STUDY

Nutritional support adjustment in volume and calories should be considered at all planned visits. Please consider the following clinical parameters identified as markers for adequate management of pediatric SBS. These parameters should also be considered for managing nutritional support (PS and/or oral/enteral feeding) in terms of volume and calories during the treatment period.

- Growth trajectory, including weight, height (or length), and head circumference (for pediatric subjects up to 36 months of age)
- Other clinical evaluations
  - Normal serum electrolytes
  - Stable blood urea nitrogen /creatinine levels
  - Decrease in stool frequency or volume, including mixed output
  - Stool consistency (ie, Bristol Stool Scale)
  - Urine specific gravity
- General consideration to possible clinical deterioration in SBS
  - Inability to maintain weight and growth velocity
  - Diarrhea (≥10 bowel movements per day, ≥80 mL/kg/day from an ostomy, or ≥75 mL/kg/day mixed output)
  - Colic/vomiting frequency increased
  - Electrolyte changes or imbalance
  - Skin breakdown
    - 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.
    - Nutritional support constituents may be adjusted at the discretion of the investigator.
    - During the 48-hour Intake/Output measurement period prior to the subject's scheduled visit, no further changes to the prescribed nutritional support should be made.
    - If there is a change in EN or other food or fluid intake, the investigator should consider this when adjusting the PS/EN support in volume and calories.

Figure A-1 Weaning Algorithm for Subjects Who are NOT Toilet Trained and in Diapers

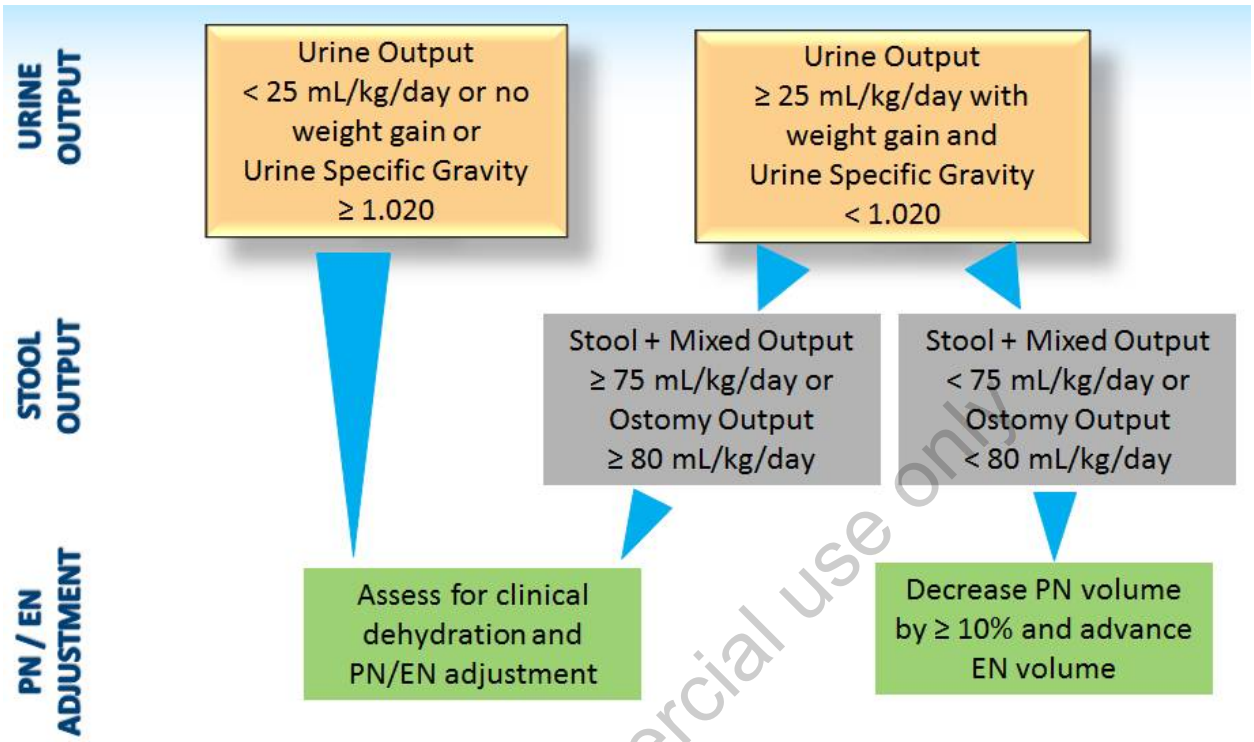


Figure A-2 Weaning Algorithm for Subjects Who are Toilet Trained and NOT in Diapers

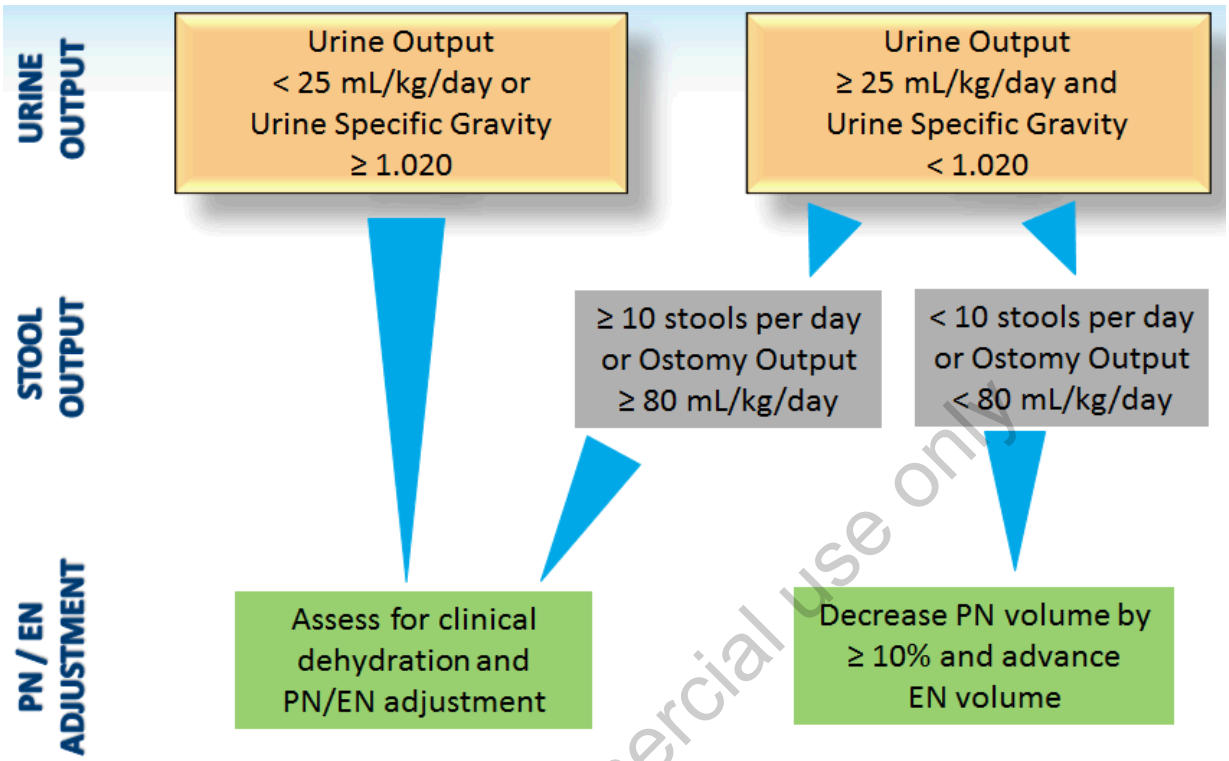
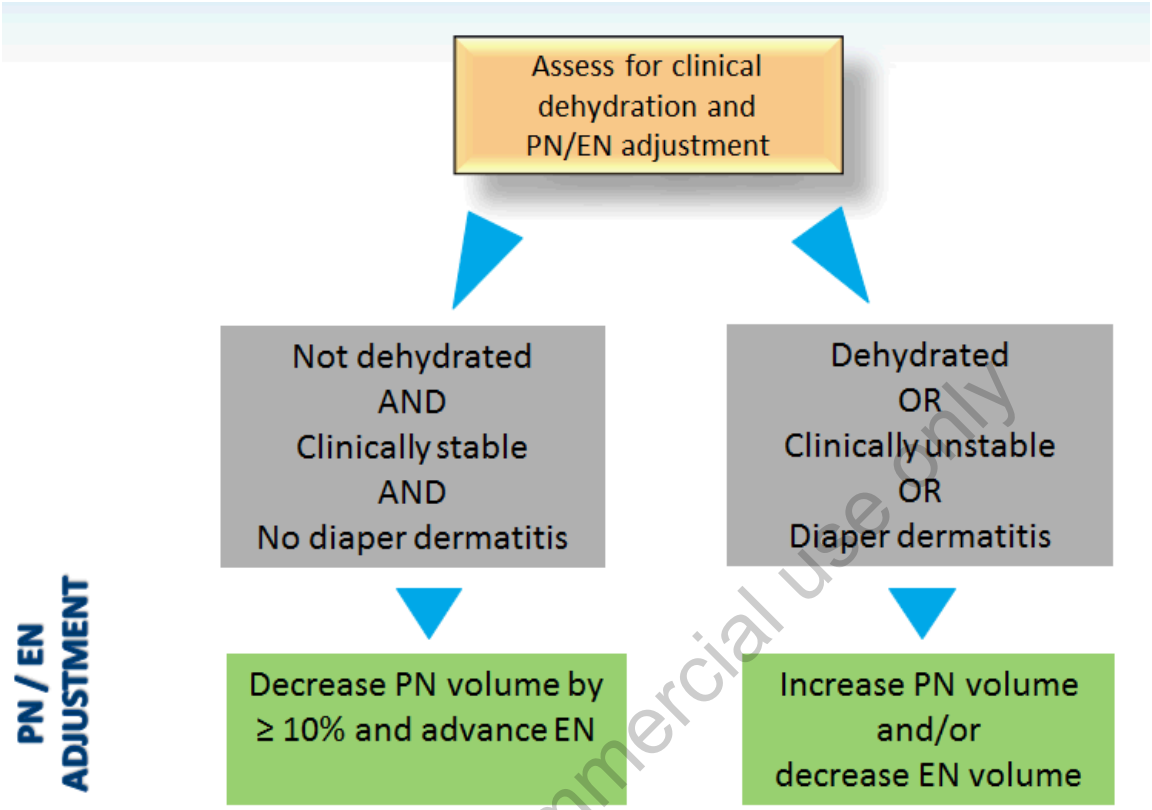


Figure A-3 Clinical Dehydration Assessment and PS/EN Adjustment



PROTOCOL: SHP633-304

TITLE:	A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome Who Completed TED-C14-006
DRUG:	Teduglutide
IND:	IND# 058213
EUDRACT NO.:	2016-000849-30
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way, Lexington, MA 02421 USA
PROTOCOL HISTORY:	Amendment 1: 22 Nov 2016 Original Protocol: 08 April 2016

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 SHP633-304.

Title: A prospective, open label, long-term safety and efficacy study of teduglutide in pediatric patients with short bowel syndrome who completed TED-C14-006

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 Conference on Harmonization (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:**

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **22 Nov 2016**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Title of the Shire medical monitor has been changed to [redacted] for clarity.		Protocol Signature Page Emergency Contact Information
Clarification has been made that during the no-teduglutide treatment period, visits will take place *approximately* every 12 weeks.		Synopsis Sections 3.1, 7.1.2 Figure 3-1
The study design flow chart has been edited for clarity.		Synopsis Figure 3-1
The collection of all actual and prescribed enteral nutrition data has been removed to reduce the burden on the subjects and investigators. Enteral nutrition data are not required as the efficacy endpoints are limited to parenteral support parameters.		Synopsis Table 1-1, Table 1-2, Table 1-3 Sections 7.1.2, 7.1.3.1, 7.1.3.2, 7.1.5, 7.2.11.2, 7.2.11.3
Exclusion criterion 11 has been revised to add Smoflipid as other experimental drugs that are allowed prior and during the study. Like glutamine and Omegaven, Smoflipid is not expected to interfere with the assessments of safety and efficacy of teduglutide and many subjects may already be receiving the treatments off-label as part of standard medical therapy.		Synopsis Section 4.5
Exclusion criterion 12 and prohibited treatment have been refined: exclusion/prohibition of treatment with growth hormone has been extended to 3 months for consistency with other teduglutide studies.		Synopsis Section 4.5 Table 5-1
The language on escape criteria has been corrected for consistency within the protocol.		Synopsis Section 4.6
Language in efficacy and safety endpoints has been clarified.		Synopsis Sections 9.7.1, 9.8.1
Completion and review of intake and output diaries have been clarified.		Table 1-2, Table 1-3 Sections 7.1.3.2, 7.1.5
When the screening and pre-treatment visits are combined, the serum pregnancy test required at the pre-treatment visit should be performed at the local laboratory instead of the central laboratory. This will ensure timely results prior to starting treatment with teduglutide.		Table 1-3 Sections 7.1.3.1, 7.2.6
The requirement for urine specimen collection has been revised so that a lack of urinalysis will not constitute a protocol deviation for any pediatric subjects (not only for subjects wearing diapers).		Table 1-1, Table 1-2, Table 1-3 Section 7.2.4
Clarification has been made that the first no-teduglutide treatment visit after the screening visit will occur within 2 to 12 weeks of the screening (formerly within 12 weeks of screening).		Synopsis Table 1-2 Section 7.1.1
Windows have been clarified for visits during the no-teduglutide and teduglutide treatment periods.		Table 1-2, Table 1-3 Section 7.1.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **22 Nov 2016**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
'Specific' has been deleted from 'positive/specific anti-teduglutide antibodies' to eliminate the redundancy. By definition, positive samples must be specific (as assessed in the confirmatory assay), or otherwise considered negative.		Table 1-2 Sections 7.2.7, 9.8.1
Parental height and gestational age at birth have been removed from medical history.		Table 1-1 (footnote b) Section 7.2.1
For consistency within the protocol, sigmoidoscopy has been added as the alternate to colonoscopy throughout the protocol.		Table 1-1, Table 1-2, Table 1-3 Sections 3.1, 7.1.2, 7.2.9.2
Removal of former footnote i on fecal occult blood test for clarity.		Table 1-3
Clarification has been made on circumstances when the CxW28 visit may be combined with the next pre-treatment or EOS/ET visit.		Table 1-3 Section 7.1.4
The text on PS support requirements over time in pediatric subjects with SBS has been clarified, and text on intestinal adaptation has been refined.		Section 1.1
Status of current teduglutide approvals for use has been updated.		Section 1.2, 3.1
The term 're-challenge' has been replaced with 'additional teduglutide treatment' for clarity and consistency with other studies.		Section 3.1
Number of subjects enrolled has been corrected for consistency with protocol synopsis.		Section 3.1
Definition of a subject's completion of the study has been corrected for consistency within the protocol.		Section 3.2
Evaluations to be performed when a subject discontinues teduglutide or when withdraws from the study have been clarified.		Sections 4.8.1, 4.8.2
Withdrawal by parent/guardian has been added as reason for discontinuation.		Section 4.8.3
COUMADIN has been changed to warfarin for clarity.		Sections 5.1, 5.1.2
Clarification has been made on handling of study drug, which is for single use only and should be used within 3 hours following reconstitution.		Section 6.3.3
The investigator or designee may now dispense the unused study drug vials to the same subject if deemed appropriate to ensure sufficient supplies between visits. Also, documentation of all dispensed study medication has been clarified.		Section 6.4
Clarification has been made that local laboratory results are not required to be entered in the eCRFs.		Section 7.2.4
Collection of urine sodium and urine osmolality has been removed.		Section 7.2.4
Clarification has been made that the serum sample will not be collected at the pre-treatment visit if the subject met a follow-up period escape criterion.		Section 7.2.5
Intake and output diaries (formerly in Sections 7.2.11 and 7.2.12, respectively) have been moved under a new Section 7.2.11 'Diaries' for clarity, and are now Sections 7.2.11.2 and 7.2.11.3, respectively.		Sections 7.2.11, 7.2.11.1, 7.2.11.2, 7.2.11.3

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **22 Nov 2016**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Information on study drug administration diary has been added in Section 7.2.11.1. Clarification has been made that only available diary data will be reviewed at each clinic and telephone visit.		
Performance of dipstick specific gravity tests by the subject at home on the first urine produced after the daily infusions of PS has been removed. It is now at the discretion of the investigator for all subjects, not just those in diapers. This change is to align with standard medical practice.		Section 7.2.11.3
Clarifications have been made to the language on dose interruption.		Sections 8.4, 8.4.1
Unscheduled safety follow up assessments (including visits conducted after EOS) are not to be recorded. However, clarification has been made that they are to be collected where requested.		Section 9.1
The protocol now refers to the data monitoring committee (DMC) Charter for the schedule of DMC reviews.		Section 9.4
Changes have been made to the Health economics and outcomes research endpoints to include the beginning of each treatment cycle (CxD1) as additional baseline. These changes are for clarity and consistency with other teduglutide studies.		Synopsis Section 9.9.1
Minor corrections have been made to the guidelines for nutritional support management during the study.		Appendix 2

See Appendix 1 for protocol history, including all amendments.

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 Pharmacovigilance and Risk Management 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 using the details below.

[redacted], MD PhD

Email: [redacted]

Fax: [redacted]

For protocol- or safety-related issues <u>during normal business hours (9 am to 5 pm Eastern Standard Time)</u>, the investigator must contact the Shire Medical Monitor:

[redacted], MD PhD, [redacted]

Phone: [redacted]

Mobile: [redacted]

Email: [redacted]

Fax: [redacted]

For protocol- or safety-related issues <u>outside of normal business hours</u>, the investigator must contact Quintiles Medical Support:

[redacted], MD, [redacted]

Phone: [redacted] (medical emergencies – US & Canada)

Phone: [redacted] (medical emergencies – global)

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 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):
[redacted] Shire (USA)

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-HCG	beta-human chorionic gonadotropin
BMI	body mass index
CRA	clinical research associate
CRO	contract research organization
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
DILI	drug-induced livery injury
DMC	data monitoring committee
DPP-4	dipeptidyl peptidase 4
EC	ethics committee
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FOBT	fecal occult blood test
FOCBT	female of child-bearing potential
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
GLP-2	glucagon-like peptide 2
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IGF-1	insulin-like growth factor 1
IRB	institutional review board
IV	intravenous

IWRS	interactive web-based response system
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NDA	new drug application
NTT	no-teduglutide treatment
PDA	patent ductus arteriosus
PedsQL	Pediatric Quality of Life inventory
PS	parenteral support
PT/INR	prothrombin time/international normalized ratio
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
SOC	standard of care
$t_{1/2}$	elimination half-life
TESAE	treatment-emergent serious adverse event
UK	United Kingdom
ULN	upper limit of normal
US	United States
WHO-DD	World Health Organization – Drug Dictionary

STUDY SYNOPSIS

Protocol number: SHP633-304	**Drug:** Teduglutide
Title of the study: A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome (SBS) Who Completed TED-C14-006	
Number of subjects (total and for each treatment arm): Approximately 34 subjects who completed the TED-C14-006 study, including subjects in the standard of care treatment arm, are expected to enroll in this extension study. This study will enroll up to as many subjects as complete the TED-C14-006 study.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 28 investigational sites in North America and Europe will participate in this extension study	
Study period (planned): October 2016 – September 2019	**Clinical phase:** 3 Extension
Objectives: **Primary:** To evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with SBS. **Secondary:** To evaluate long-term efficacy of teduglutide treatment in pediatric subjects with SBS.	
Rationale: This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects with short bowel syndrome (SBS) who completed the TED-C14-006 study (the core study). In addition to evaluating the long-term safety and durability of efficacy after 24-weeks of treatment, this extension study will evaluate the need for additional teduglutide treatment in these subjects, and will allow the study of first-time treatment of teduglutide-naïve subjects who participated in the standard of care (SOC) treatment arm in TED-C14-006.	
Investigational product, dose, and mode of administration: This study will allow repeat doses of teduglutide 0.05 mg/kg subcutaneous (SC) once daily (QD) injection for eligible pediatric subjects. There is no active comparator or reference product.	
Methodology: This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects who completed the TED-C14-006 study (core study). Once the informed consent (and if applicable, informed assent) have been reviewed and signed, demographics, and updates to medical history and short bowel syndrome history will be obtained. Subjects not receiving teduglutide treatment (ie, in a no-teduglutide treatment [NTT] period), will be seen approximately every 12 weeks for safety, parenteral support (PS) requirements, and quality of life. The first NTT visit after the screening visit will occur within 2 to 12 weeks of the screening visit. At any point after screening, including during a NTT period, subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed **immediately** to the pre-treatment visit if the investigator, subject, and parent agree to proceed with teduglutide therapy. After the pre-treatment visit, subjects who meet ≥1 of the teduglutide treatment inclusion criteria, and meet none of the teduglutide treatment exclusion criteria, will start a 28-week cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily, followed by a 4-week follow-up period (during which no teduglutide is administered) (Figure 3-1). During the 28-week cycle, clinic visits will occur at weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period (between weeks 1 and 24), and weekly during the teduglutide follow-up period (between weeks 24 and 28). Safety and PS requirements will be evaluated at every visit, and quality of life assessments will be made approximately every 12 weeks. If a subject has clinical deterioration and meets follow-up period escape criteria	

after stopping teduglutide, the subject may "escape" the follow-up period early and proceed immediately to another pre-treatment visit. Following completion of the 28-week treatment cycle, the subject will proceed to an NTT visit within approximately 12 weeks.

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, all attempts should be made to follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) for decisions regarding PS support reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines, however, is not considered a protocol deviation. (Appendix 2).

Study Design Flow Chart

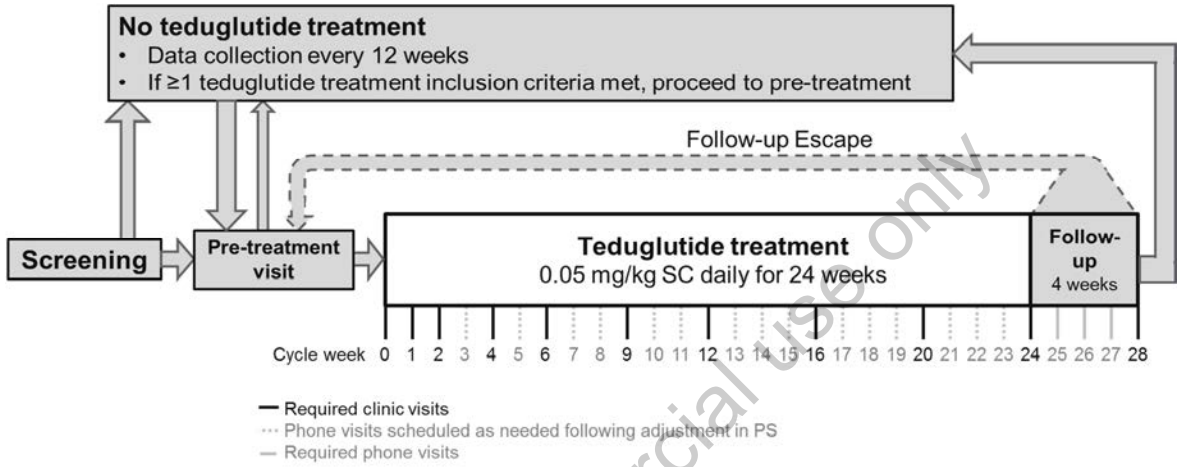

Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pre-treatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects will enter a 28-week teduglutide cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24 (**solid black lines**). Phone visits are required approximately 1 week after adjustments in PS during the intervening weeks between weeks 2 and 24 (**dashed grey lines**). Subjects discontinue teduglutide at week 24 and enter a 4-week follow-up (no-treatment) period, during which phone visits will be performed weekly (**solid grey lines**). If an escape criterion is met during the follow-up period, subjects may proceed directly to another pre-treatment visit.

Study Inclusion Criteria:

The subject will be considered eligible for the study if they meet **all** of the study inclusion criteria. Teduglutide treatment eligibility does not impact study eligibility.

1. Subject provides written informed consent (subject, parent or legal guardian and, as appropriate, informed assent) to participate in the study before completing any study-related procedures.
2. Subject completed the TED-C14-006 study (including subjects in the standard of care treatment arm).
3. Subject understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Study Exclusion Criteria: There are no exclusion criteria for this study.

Teduglutide Eligibility Criteria: Subjects are eligible for teduglutide treatment if at least one (≥1) of the teduglutide treatment inclusion criteria, and none of the teduglutide treatment exclusion criteria, are met. In addition, the investigator and the subject (and/or parent or legal guardian, as appropriate) must agree to proceed with treatment.

***Teduglutide Treatment Inclusion Criteria*:**

1. Subject is teduglutide-naïve, receiving PS, and unable to significantly reduce PS or advance enteral feeds (eg, 10% or less change in PS or advance in feeds) for at least 3 months prior to and during the

teduglutide pre-treatment visit, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PS returns to within 10% of baseline prior to the event.

2. Subject was previously treated with teduglutide and at least one of the following criteria is satisfied:
    a. Increasing PS requirements following teduglutide discontinuation.
    b. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
    c. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition following teduglutide discontinuation.
    d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
    e. Severe diarrhea related to teduglutide discontinuation.

Teduglutide Treatment Exclusion Criteria:

1. Body weight <10 kg at the pre-treatment visit.
2. Unresected gastrointestinal (GI) polyp, known polyposis condition, pre-malignant change, or malignancy, in the GI tract.
3. History of cancer in the previous 5 years except surgically curative skin cancers.
4. Serial transverse enteroplasty or other major intestinal surgery within 3 months preceding the teduglutide pre-treatment visit. Insertion of a feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, and endoscopic procedures are allowed.
5. Intestinal or other major surgery planned or scheduled to occur during the 28-week cycle.
6. Clinically significant intestinal stricture or obstruction.
7. Clinically significant, active or recurrent pancreatic or biliary disease.
8. Active, severe, or unstable, clinically significant hepatic impairment or injury, including the following laboratory values at the pre-treatment visit:
    a. Total bilirubin ≥2 × upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7 × ULN
    c. Alanine aminotransferase (ALT) ≥7 × ULN
9. Renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2 at the pre-treatment visit.
10. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, or patent ductus arteriosus (PDA) ligation.
11. Participation in a clinical study using an experimental drug (other than glutamine, Omegaven, or Smoflipid) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to the pre-treatment visit and for the duration of the 28-week cycle.
12. Treatment with analogs of glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2) (not including teduglutide), insulin-like growth factor-1 (IGF-1), or growth hormone, within 3 months preceding the teduglutide pretreatment visit.
13. Treatment with octreotide or dipeptidyl peptidase 4 (DPP-4) inhibitors within 3 months prior to the pre-treatment visit.
14. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
15. Known history of alcohol or other substance abuse within 1 year prior to the pre-treatment visit.
16. Pregnant or lactating female subjects.

17. Sexually active female subjects of child-bearing potential unwilling to use approved contraception during teduglutide treatment and for 30 days after the treatment period.
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.

Follow-up Period Escape Criteria: At the discretion of the investigator, the follow-up period may be interrupted and the subject may proceed directly to the pre-treatment visit, if ≥1 of the following criteria is met:

1. Increasing PS requirements following teduglutide discontinuation
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition 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.

Maximum duration of subject involvement in the study:

A subject will be considered enrolled in the study once the subject has provided signed consent, and meets all of the Study Inclusion Criteria. Subjects may participate in multiple NTT periods and/or multiple 28-week treatment cycles. The study will continue for at least 1 year, and until each subject has access (as needed) to teduglutide. The subject's maximum duration of participation is expected to be approximately 3 years. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing End of Study (EOS) visit.

- **Planned duration of no-teduglutide treatment periods**: variable, depending on disease course
- **Planned duration of the teduglutide pre-treatment visit:** 1 to 21 days
- **Planned cycle duration**: 28 weeks. Each cycle consists of 24 weeks of teduglutide treatment followed by a 4-week follow-up period (no treatment)

Endpoints and statistical analysis:

- The **safety population** will consist of all enrolled subjects. The safety population will be used for both safety and efficacy analysis.

Efficacy Endpoints

Efficacy endpoints will be analyzed at the end of each teduglutide treatment period (Week 24 or end of treatment [EOT]), and at each study visit, relative to the baseline of the core study (TED-C14-006) and/or first exposure to teduglutide. The following efficacy endpoints will be analyzed:

- Reduction in PS volume of at least 20%
- Absolute and relative change in PS volume
- Complete weaning off PS
- Change in days per week of PS

Health Economics and Outcomes Research Endpoints

Health economics and outcomes research endpoints will be analyzed at approximately 12-week intervals (Weeks 12 and 24 of each teduglutide treatment cycle, and every 12 weeks for subjects not on teduglutide), relative to the study baseline. The beginning of each treatment cycle (CxD1) will be an additional baseline.

- Change in Pediatric Quality of Life Inventory (PedsQL) score
- Change in PedsQL Family Impact Module score
- Change in PedsQL Gastrointestinal Symptoms Module Sub-Scales scores:
  - Food and Drink Limits
  - Diarrhea

Safety Endpoints

The following safety endpoints will be analyzed:

- Adverse events
- Vital signs, including temperature, heart rate, blood pressure
- Laboratory safety data (ie, clinical chemistry, hematology, and urinalysis)
- Urine output
- Stool output
- Antibodies to teduglutide
- Gastrointestinal-specific testing, including fecal occult blood testing and colonoscopy or sigmoidoscopy
- Z-scores for weight, height (or length), head circumference (up to 36 months of age), and body mass index

Statistical Methodology for Efficacy Analysis

No claims of statistical significance will be made; however, 95% confidence intervals will be provided, if applicable. Continuous variables, including those assessed on a discrete scale, 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.

Statistical Methodology for Safety Analysis

Safety data, including laboratory tests and vital signs assessments, will be summarized by visit. AEs will also be collected and summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data.

Sample Size Justification

As this is an extension study, the maximum number of subjects was determined by enrollment in TED-C14-006.

STUDY SCHEDULE(S)

Table 1-1: Schedule of Events Required for All Subjects

Period	Screening	End of Study or Early Termination
	Scr	EOS/ET
Visit Type	Site	Site
Informed consent/assent[a]	X	
Study eligibility	X	
Demographics, Medical history[b], SBS history[c]	X	
Dispense intake and output diaries	X	
Evaluate teduglutide treatment inclusion criteria[d]	X	
Adverse events	X	X
Concomitant medications and GI procedures[e]	X	X
Physical examination and vital signs, including weight		X
Height and head circumference[f]		X
Review intake and output diaries[g]		X
Record PS prescription and adjust as needed[h]		X
Safety laboratory tests[i]		X
PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales		X
Antibodies to teduglutide[j]		X
Fecal occult blood testing[k]		(X)
Colonoscopy or sigmoidoscopy[l]		(X)
Pregnancy testing[m]		(X)

FOBT = fecal occult blood testing; FOCBP = female of child-bearing potential; EOS =end of study; ET=early termination; GI=gastrointestinal; NTx=no treatment;

PedsQL=Pediatric Quality of Life Inventory; PS=parenteral support; SBS=Short Bowel Syndrome; Scr =Screening.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

[a] Informed Consent (and informed assent, if applicable) must be obtained prior to performing any study-related procedures; consent (and informed assent, if applicable) may be obtained anytime during the Week 28 (or EOS) visit for the TED-C14-006 study. Subject will have up to 7 days after completion of the TED-C14-006 study to sign consent to participate in the SHP633-304 study.

[b] Updates to the medical history will be collected, consisting of adverse events that were ongoing at the time of completion of TED-C14-006, and events that occurred during the period between completion of TED-C14-006 and informed consent to SHP-633-304.

[c] If the subject has any changes to the SBS history that had been collected at the baseline of the TED-C14-006, then the updated SBS history will be collected.

[d] Subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed to the pre-treatment visit if the investigator, subject, and parent or legal guardian agrees to proceed with teduglutide therapy (Table 1-3).

[e] Concomitant GI procedures include (but are not limited to) endoscopy, radiographic studies, GI and liver biopsies and associated pathology results.

[f] Head circumference will be measured in subjects 36 months of age and younger.

[g] The intake diary should be completed daily for a minimum of 2 weeks prior to the EOS/ET visit. The output diary should be completed daily over a 48-hour period of nutritional stability before the EOS/ET visit.

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

[i] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

[j] Required for all teduglutide-exposed subjects

[k] FOBT should be performed on teduglutide-exposed subjects on an annual basis, approximately every 48-60 weeks at a minimum.

[l] The need for colonoscopy/sigmoidoscopy in response to a positive FOBT during a no-teduglutide treatment period is at the discretion of the investigator, but all teduglutide-exposed subjects will undergo colonoscopy/sigmoidoscopy after they have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure), and subjects who continue to receive teduglutide will undergo colonoscopy/sigmoidoscopy at 5 year intervals or more often as needed. See Section 7.2.9 for details.

[m] Pregnancy testing is required for FOCBP at an ET visit if the subject has not had a pregnancy test at least 30 days after study drug discontinuation.

Table 1-2: Schedule of Events for Subjects Not Receiving Teduglutide

Visit Number	**NTx**
Visit Type	**Site**
Visit Frequency[a]	**Every 12 weeks**
Window (days)[b]	**±7**
Dispense intake and output diaries	X
Evaluate teduglutide treatment inclusion criteria[c]	X
Adverse events	X
Concomitant medications and GI procedures[d]	X
Physical examination and vital signs, including weight	X
Height and head circumference[e]	X
Review intake and output diaries[f]	X
Record PS prescription and adjust as needed[g]	X
Safety laboratory tests[h]	X
PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales	X
Antibodies to teduglutide[i]	(X)
Fecal occult blood testing[j]	Annually
Colonoscopy or sigmoidoscopy[k]	(X)
Serum sample[l]	Every 24 weeks

FOBT = fecal occult blood testing; NTT = no-teduglutide treatment; PedsQL = Pediatric Quality of Life Inventory; PS= parenteral support; TED = teduglutide.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

[a] The first NTx visit following the screening visit must occur within 2 to 12 weeks of screening.

[b] Window is relative to the first NTx visit in the current no-teduglutide treatment period.

[c] Subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed to the pre-treatment visit if the investigator, subject, and parent or guardian agree to proceed with teduglutide therapy (Table 1-3).

[d] Concomitant GI procedures include (but are not limited to) endoscopy, radiographic studies, GI and liver biopsies and associated pathology results.

[e] Head circumference will be measured in subjects 36 months of age and younger.

[f] Intake diaries will collect actual PS volume and hours per day, completed daily for a minimum of 2 weeks prior to each study visit (see Section 7.2.11.2). Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit (see Section 7.2.11.3 for more detail).

[g] PS 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.

[h] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

[i] Subjects who have been treated previously and test positive for teduglutide antibodies should have follow-up samples collected every 12 weeks during the study until a negative result is obtained.

[j] FOBT should be performed on teduglutide-exposed subjects on an annual basis, approximately every 48-60 weeks at a minimum.

[k] The need for colonoscopy/sigmoidoscopy in response to a positive FOBT during a no-teduglutide treatment period is at the discretion of the investigator, but all teduglutide-exposed subjects will undergo colonoscopy/sigmoidoscopy after they have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) and subjects who continue to receive teduglutide will undergo colonoscopy/sigmoidoscopy at 5 year intervals or more often as needed. See Section 7.2.9 for details.

[l] Lack of collection of serum samples will not constitute a protocol deviation.

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	Pre-treatment	Teduglutide Treatment															Follow-up	
Visit Number	**Px**	**Cx D1**	**Cx W1**	**Cx W2**		**Cx W4**		**Cx W6**		**Cx W9**		**Cx W12**		**Cx W16**		**Cx W20**		**CxW24 (EOT)**	**CxW25 CxW26 CxW27**	**CxW28[b]**
Visit Type	**Site**	**Site**	**Site**	**Site**		**Site**		**Site**		**Site**		**Site**		**Site**		**Site**		**Site**	**Phone[a]**	**Site**
Cycle Day	**-21 to 0**	**1**	**8**	**15**		**29**		**43**		**64**		**85**		**113**		**141**		**169**	**176 183 190**	**197**
Window (days)[c]	-21 to 0		**±2**	**±2**		**±2**		**±2**		**±4**		**±4**		**±4**		**±4**		**±4**	**±2**	**±2**
Evaluate teduglutide eligibility (inclusion and exclusion) criteria	X	X[d]																		
Dispense intake and output diaries	X	X	X	X		X		X		X		X		X		X		X		X
Adverse events	X	X	X	X		X		X		X		X		X		X		X	X	X
Concomitant medications and GI procedures[e]	X	X	X	X		X		X		X		X		X		X		X	X	X
Physical examination and vital signs, including weight	X	X	X	X		X		X		X		X		X		X		X		X
Height and head circumference[f]	X	X										X						X		
Review intake and output diaries[g]	X	X	X	X		X		X		X		X		X		X		X	X	X
Record PS Rx and adjust as needed[h]	X	X	X	X		X		X		X		X		X		X		X	X	X
Safety laboratory tests[i]	X[i]	X	X	X		X		X		X		X		X		X		X	(X)	X
PedsQL Generic Core Scale/ Family Impact Module/ GI Symptoms Module Sub-Scales		X										X						X		
Antibodies to teduglutide[j]		X										X						X		X
Fecal occult blood testing	X											X						X		
Colonoscopy/ sigmoidoscopy[k]	(X)											(X)						(X)		
Pregnancy testing[l]	X	X				X				X		X		X		X		X		X

Phone contact is required approximately 1 week after PS adjustment

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	Pre-treatment	Teduglutide Treatment																Follow-up	
Serum sample[m]	X																X		
Evaluate escape criteria[n]																		X	X
Dispense study drug[o]		X	X	X		X		X		X		X		X		X			

EOS = end of study; EOT = end of treatment; ET = early termination; FOBT = fecal occult blood test; FOCBP = female of child-bearing potential; FU = follow-up; GI = gastrointestinal; PedsQL = Pediatric Quality of Life Inventory; PS= parenteral support; SBS = Short Bowel Syndrome; SC = subcutaneous; Scr = Screening; TED = teduglutide; Tx = treatment.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

[a] Phone visits are required approximately 1 week after adjustments in PS. The assessments to be performed at phone visits are the same as those described for CxW25-27 (except for evaluation of escape criteria).

[b] The investigator may combine the CxW28 visit with the next pre-treatment visit if at least one escape criterion is met at the CxW28 visit, and the pre-treatment assessments occur within 7 days of the CxW28 visit. If a subject is completing the study at the CxW28 visit, the EOS/ET visit (Table 1-1) will take place in lieu of the CxW28 visit.

[c] Visit windows are relative to the CxD1 visit.

[d] Eligibility will need to be re-confirmed prior to the first dose in the cycle. Negative urine pregnancy test is required prior to the first dose of teduglutide, but results of other labs obtained at the CxD1 visit are not required to determine teduglutide treatment eligibility.

[e] Concomitant GI procedures include (but are not limited to) endoscopy, radiographic studies, GI and liver biopsies and associated pathology results.

[f] Head circumference will be measured in subjects 36 months of age and younger.

[g] Intake diaries will collect actual PS volume and hours per day. Intake diaries should be completed daily for a minimum of 2 weeks immediately prior to each clinic visit (except at pre-treatment visit), for 1 week following PS adjustment, and daily during the 4-week follow-up period. 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 PS prescription. See Section 7.2.11 for more detail.

[h] PS 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] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Clinical chemistry and urinalysis must also be performed within approximately 5-7 days of any adjustment to the PS prescription. Safety labs performed between clinic visits may be performed locally. Unscheduled lab results will not be captured in the eCRFs. If abnormal results are considered an adverse event, an AE form will be completed. Collect PT/INR at the pre-treatment visit. Additional collection will occur if a potential drug-induced liver injury signal is observed. Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

[j] Samples collected on CxD1 must be drawn prior to first administration of teduglutide. Samples collected while subjects are receiving teduglutide (CxW12 and CxW24) must be drawn at least 14 hours after dosing.

[k] The teduglutide-naïve subjects age 12 and older will undergo colonoscopy/sigmoidoscopy at the pre-treatment visit if one has not been performed within 1 year. Subjects of any age with newly positive FOBT results at the pre-treatment visit for which a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy/sigmoidoscopy prior to receiving teduglutide. If newly positive FOBT results (for which a readily detectable cause cannot be identified) are obtained at the end of a teduglutide treatment cycle (CxW24/EOT), colonoscopy/sigmoidoscopy will be performed. The need for colonoscopy/sigmoidoscopy in response to positive FOBTs at CxW12 is at the discretion of the investigator. Teduglutide-exposed subjects who have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) will undergo colonoscopy/sigmoidoscopy. See Section 7.2.9 for details.

[l] A serum pregnancy test is performed on all FOCBP at the teduglutide pre-treatment visit (when the pre-treatment and screening visits are combined, the serum pregnancy test

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	Pre-treatment	Teduglutide Treatment	Follow-up

should be performed at the local laboratory). Urine pregnancy tests will be administered at all other visits according to the study schedules, or if pregnancy is suspected, or as specified per protocol upon withdrawal of the subject from the study.

[m] Lack of collection of serum samples will not constitute a protocol deviation.

[n] If escape criteria are met, the subject may proceed directly to another pre-treatment visit at the discretion of the investigator.

[o] The first SC injection of teduglutide in treatment-naïve subjects will be administered under the supervision of the investigator/designee after which the subject will be observed for hypersensitivity reactions for at least 4 hours. The site of administration (arm, thigh, abdomen) of the first teduglutide dose must be specified and recorded in the eCRF. See Section 6.2.3 for dose adjustment.

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

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. It is estimated that, at most, there are a few hundred pediatric subjects 1 year and older with SBS (Khan et al. 2015; Wales et al. 2004). 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. Although the small intestine is capable of remarkable adaptation, excessive loss of absorptive surface area or specialized functions can lead to dependence on parenteral nutrition or intravenous (IV) fluids (parenteral support [PS]). Treatment of both pediatric and adult patients is focused on achieving adequate intestinal absorption to allow for minimization or discontinuation of PS. About 30% of infants with SBS become independent of PS requirements within 12 months of the initial insult, and an additional 10% wean off PS within 24 months. After this time, linear intestinal growth slows. About 60% of pediatric subjects with SBS are able to become independent of PS within 5 years of the initial diagnosis (Khan et al. 2015). Nevertheless, despite optimal medical management, many pediatric subjects remain dependent on PS. Complications of long-term PS include liver disease, catheter-related blood stream infections, central line-associated venous thrombosis and dwindling central venous access. Sepsis is the leading cause of death in these patients and quality of life is poor (Squires et al. 2012). Accelerating the adaptive process and achieving enteral autonomy is an urgent goal for all patients with SBS who are dependent on PS (Khan et al. 2015; Squires et al. 2012).

Intestinal adaptation is driven by hormonal cues in response to nutrient malabsorption (Drucker and Yusta 2014). Chief among these is hormones glucagon-like peptide 2 (GLP-2), which is secreted from L-type enteroendocrine cells that reside in the intestinal epithelium in the ileum and colon. Resection of these regions may impair the adaptive response by limiting endogenous production of GLP-2.

1.2 Product Background

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-IV (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$) in adults of approximately 2 hours 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). The European Commission granted a centralized marketing authorization valid throughout the European Union (EU) for teduglutide (Revestive™) on 30 August 2012 and a New Drug Application (NDA) for teduglutide (Gattex®) was approved by the United States (US) Food and Drug Administration (FDA) on 21 December 2012 for the treatment of adult patients with SBS who are dependent on PS. Teduglutide has also been approved for use in adult patients with SBS in Canada and Switzerland. On 29 Jun 2016, the

European Commission granted an extension of the Market Authorization for teduglutide (REVESTIVE™) for the treatment of patients aged 1 year and above with SBS; patients should be stable following a period of intestinal adaptation.

1.3 Clinical Studies with Teduglutide in Pediatric subjects

One Phase 3 study, TED-C13-003, was completed in pediatric SBS subjects in the US and United Kingdom (UK). In this study, teduglutide was administered to 3 cohorts of pediatric subjects from ages 1-17. 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 PS volume at Week 12 of 37%, including complete independence from PS 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 PS volume at Week 12 of 39%, including complete independence from PS 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 (TESAEs) related to teduglutide were reported. No discontinuations from study were due to adverse events (AEs).

TED-C14-006 is an ongoing study which includes 2 treatment arms: a teduglutide treatment arm and a standard of care treatment arm. Subjects in both arms participate in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the screening period, subjects will choose into which arm to enroll. During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide treatment arm will receive daily subcutaneous (SC) injections of teduglutide (study drug) in addition to standard medical therapy. The subjects enrolling in the teduglutide treatment arm will be 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.

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 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects with SBS who completed the TED-C14-006 study. In addition to evaluating the long-term safety and durability of efficacy after 24 weeks of treatment, this extension study will evaluate the need for additional teduglutide treatment in these subjects, and will allow for the first-time treatment of teduglutide-naïve subjects who participated in the SOC treatment arm in TED-C14-006.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objective of the study is to evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with SBS who completed TED-C14-006.

2.2.2 Secondary Objectives

The secondary objective of this study is to evaluate the long-term efficacy of teduglutide treatment in pediatric subjects with SBS who completed TED-C14-006.

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects who completed the TED-C14-006 study (core study). At the time of entry into the TED-C14-006 study, subjects were less than 18 years of age, were dependent on parenteral nutrition to provide at least 30% of their caloric or fluid needs, and had not been able to significantly reduce PS for at least 3 months prior to enrollment. During the core study, pediatric subjects in the teduglutide treatment arm were randomized to 0.025 mg/kg or 0.05 mg/kg once daily (QD) dosing in a double-blinded manner. The TED-C14-006 study will also be referred to as the core study interchangeably throughout this protocol.

Approximately 34 subjects who complete the core study are expected to enroll in this extension study. Subjects who previously received teduglutide during TED-C14-006, as well as subjects who were in the SOC treatment group, may be eligible to receive teduglutide treatment in this extension study. To be eligible, subjects must meet ≥1 of the teduglutide treatment inclusion criteria and none of the teduglutide treatment exclusion criteria.

Additional Teduglutide Treatment

Subjects not receiving teduglutide treatment (ie, in a "no-teduglutide treatment period"), will be seen approximately every 12 weeks for safety, parenteral support (PS) requirements, and quality of life. At any point during a no-teduglutide treatment period, subjects who meet ≥1 *teduglutide treatment inclusion* may proceed directly to the pre-treatment visit if the investigator, subject, and parent agree to proceed with teduglutide therapy.

Rationale: Some pediatric subjects may have a durable beneficial effect after 24 weeks of teduglutide treatment and thus long-term follow-up without additional teduglutide treatment may be appropriate. However, there may be some pediatric subjects who deteriorate or stop improving after discontinuation of teduglutide treatment. In these pediatric subjects, additional teduglutide treatment may be beneficial.

Dose Selection

Analysis suggested that pediatric patients, ages 1 to 17 years old, are likely to require the same dose as used in adults, namely 0.05 mg/kg/day (Mouksassi et al. 2009). In this extension study to TED-C14-006, repeat doses of teduglutide 0.05 mg/kg QD will be administered to eligible pediatric subjects who previously received teduglutide 0.05 or 0.025 mg/kg in Study TED-C14-006.

Rationale: Teduglutide is approved for adult use in the US and EU, and for pediatric use in the EU, at a dose of 0.05 mg/kg SC once daily. The completed 12-week pediatric 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. In addition, population pharmacokinetic modeling and simulations were conducted to determine the effective 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 the

pediatric study (TED- C13- 003) and suggested that the dose in pediatric subjects is likely to be same as the dose in adults (O'Keefe et al. 2006).

Duration of Treatment

The duration of teduglutide treatment in this study mirrors that of the TED-C14-006 study, consisting of 24 weeks of teduglutide treatment, followed by a 4-week follow-up period. The follow-up period is a mechanism to evaluate whether continued teduglutide is needed. If a subject deteriorates during the follow-up period, the subject may be evaluated immediately for additional teduglutide treatment. Subjects who clinically deteriorate or stop improving at any time after the end of the follow-up period will also be assessed for additional treatment.

Rationale: During the teduglutide treatment cycle, visit frequency is similar to frequencies performed in TED-C13-003 and TED-C14-006, to ensure sufficient safety monitoring and weaning of PS. During the no-teduglutide treatment, visits occur every 12 weeks, a frequency that is consistent with standard medical practices.

Measures and Parameters

Following the review and signing of the informed consent (and informed assent, if applicable), screening visit procedures will begin including demographics, and updates to medical history and SBS history. Subjects who meet ≥1 of the teduglutide treatment inclusion criteria may proceed to the pre-treatment visit.

After the pre-treatment visit, subjects who still meet ≥1 of the teduglutide treatment inclusion criteria, and meet none of the teduglutide treatment exclusion criteria, will start a 28-week cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily, followed by a 4-week follow-up (no treatment) period (Figure 3-1). During the 28-week cycle, clinic visits will occur at weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period (between weeks 1-24), and weekly during the teduglutide follow-up period (between weeks 24 and 28).

Safety and PS requirements will be evaluated on a weekly basis, and quality of life assessments will be made approximately every 12 weeks. 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, all attempts should be made to follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) for decisions regarding PS reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines, however, is not considered a protocol deviation (Appendix 2).

Rationale: Measures of long term safety will include adverse events, growth parameters and anti-drug antibodies. Measure of long term efficacy will include durability of effect as measured by reduction in PS and improvement in pediatric quality of life measures (PedsQL, PedsQL Family Impact Module). A reduction in PS volume of at least 20% at end of treatment (EOT) was used as the primary endpoint in pivotal phase 3 adult clinical trials and the completed phase 3 pediatric study (TED-C13-003), and will be used as an endpoint in this extension study. In previous clinical studies, a reduction of this magnitude was associated with a reduction in the

number of days per week of PS, and increases in enteral intake. Reduction in volume and time of PS due to improved enteral absorption may provide a pediatric subject with opportunities for more age-appropriate activities including oral rehabilitation. Quality of life assessments will be performed in this study to quantitate this effect.

Teduglutide has been found to have a targeted intestinotrophic effect. Taking into account the patient population and the pharmacologic effect of teduglutide, GI-specific screening tests, including fecal occult blood testing and colonoscopy/sigmoidoscopy, which are commonly part of the routine care of these subjects, will be performed to ensure safety. This study captures long-term safety data on polyps and other colonic mucosal changes in teduglutide-exposed subjects using the surveillance strategy proposed in Section 7.2.9.

Figure 3-1: Study Design Flow Chart

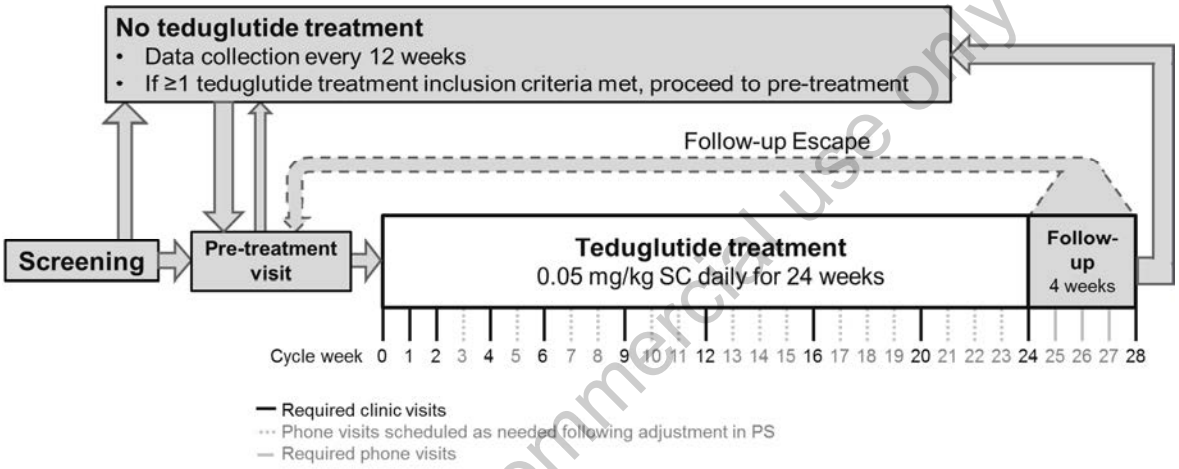

Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pre-treatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects will enter a 28-week teduglutide cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24 (**solid black lines**). Phone visits are required approximately 1 week after adjustments in PS during the intervening weeks between weeks 2 and 24 (**dashed grey lines**). Subjects discontinue teduglutide at week 24 and enter a 4-week follow-up (no-treatment) period, during which phone visits will be performed weekly (**solid grey lines**). If an escape criterion is met during the follow-up period, subjects may proceed directly to another pre-treatment visit.

3.2 Duration and Study Completion Definition

A subject will be considered enrolled in the study once the subject has provided signed consent, and meets all of the Inclusion Criteria. The study will continue for at least 1 year and until each subject has access, as needed, to teduglutide. The subject's maximum duration of participation is expected to be approximately 3 years. The study will be completed in approximately 40 months. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing the End of Study (EOS) visit.

The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact (last safety contact), whichever is later. The study completion date will be used to ascertain timing for study results posting and reporting.

4 STUDY POPULATION

Each subject must review and sign the informed consent (and informed assent, if applicable) before any study-related procedures specified in the protocol are performed. Teduglutide treatment eligibility does not impact study eligibility.

4.1 Study Inclusion Eligibility Criteria

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

1. Subject provides written informed consent (subject, parent or legal guardian and, as appropriate, subject informed assent) to participate in the study before completing any study-related procedures.
2. Subject completed the TED-C14-006 study (including subjects in the standard of care treatment arm).
3. Subject understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.2 Study Exclusion Eligibility Criteria

There are no exclusion criteria for this study.

4.3 Teduglutide Eligibility Criteria

Subjects are eligible for teduglutide treatment if at least 1 (≥1) of the teduglutide treatment inclusion criteria, and none of the teduglutide treatment exclusion criteria are met. In addition, the investigator and the subject (and/or parent or legal guardian, as appropriate) must agree to proceed with treatment.

4.4 Teduglutide Treatment Inclusion Criteria

1. Subject is teduglutide-naïve, receiving PS, and unable to significantly reduce PS or advance enteral feeds (eg, 10% or less change in PS or advance in feeds) for at least 3 months prior to and during the teduglutide pre-treatment visit, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PS returns to within 10% of baseline prior to the event.
2. Subject was previously treated with teduglutide and at least 1 of the following criteria is satisfied:
    a. Increasing PS requirements following teduglutide discontinuation.
    b. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
    c. Deteriorating nutritional status eg, weight loss or growth failure) despite maximal tolerated enteral nutrition following teduglutide discontinuation.
    d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.

e. Severe diarrhea related to teduglutide discontinuation.

4.5 Teduglutide Treatment Exclusion Criteria

1. Body weight <10 kg at the pre-treatment visit.
2. Unresected GI polyp, known polyposis condition, pre-malignant change, or malignancy, in the GI tract
3. History of cancer in the previous 5 years except surgically curative skin cancers
4. Serial transverse enteroplasty or other major intestinal surgery within 3 months preceding the teduglutide pre-treatment visit. Insertion of a feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, and endoscopic procedures are allowed.
5. Intestinal or other major surgery planned or scheduled to occur during the 28-week cycle
6. Clinically significant intestinal stricture or obstruction
7. Clinically significant, active or recurrent pancreatic or biliary disease
8. Active, severe, or unstable, clinically significant hepatic impairment or injury, including the following laboratory values at the pre-treatment visit:
    a. Total bilirubin ≥2 × upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7 × ULN
    c. Alanine aminotransferase (ALT) ≥7 × ULN
9. Renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2 at the pre-treatment visit
10. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, or patent ductus arteriosus (PDA) ligation
11. Participation in a clinical study using an experimental drug (other than glutamine, Omegaven, or Smoflipid) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to the pre-treatment visit and for the duration of the 28-week cycle
12. Treatment with analogs of glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2) (not including teduglutide), insulin-like growth factor-1 (IGF-1), or growth hormone, within 3 months preceding the teduglutide pretreatment visit.
13. Treatment with octreotide or dipeptidyl peptidase 4 (DPP-4) inhibitors within 3 months prior to the pre-treatment visit
14. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients
15. Known history of alcohol or other substance abuse within 1 year prior to the pre-treatment visit
16. Pregnant or lactating female subjects
17. Sexually active female subjects of child-bearing potential unwilling to use approved contraception during teduglutide treatment and for 30 days after the treatment period

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.

4.6 Follow-up Period Escape Criteria

At the discretion of the investigator, the follow-up period may be interrupted and the subject may proceed directly to the pre-treatment visit, if ≥1 of the following criteria is met:

1. Increasing PS requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition 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.

4.7 Reproductive Potential

4.7.1 Female Contraception

To be eligible for treatment with teduglutide, sexually active females of child-bearing potential must use an acceptable form of contraception throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used, they should be administered according to the package insert. Females of child-bearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of investigational product.

To be eligible for treatment with teduglutide, female pediatric subjects and adolescent subjects should be either:

- Pre-menarchal and either Tanner Stage 1 or less than age 9 years, or
- Females of child-bearing potential (FOCBP) with a negative serum beta-human chorionic gonadotropin (β-HCG) pregnancy test at the teduglutide pre-treatment visit. Females of child-bearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- Abstinence
- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the pre-treatment visit, plus condoms. Note: if subject becomes

sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.8 Discontinuation of Subjects

4.8.1 Teduglutide Discontinuation

If the investigational product is discontinued prematurely during a teduglutide treatment cycle and the subject wishes to remain in the study, the evaluations listed for the EOT visit are to be performed. A 4-week follow-up period will ensue, consisting of weekly telephone visits (CxW25-27) and the week 28 clinic visit (CxW28). The subject would then enter a no-teduglutide treatment (NTT) period and could be evaluated for subsequent teduglutide treatment eligibility according to the study schedules. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for permanent treatment discontinuation, dates of investigational product administered (including last date of treatment), and amount of investigational product taken must be recorded in the electronic case report form (eCRF) and source documents, as described in Section 4.8.3. The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor, when possible.

4.8.2 Study Withdrawal

At any time during the study, the investigator or sponsor may withdraw a subject, or a subject may withdraw from the study, for any reason, without prejudice to their future medical care by the physician or at the institution.

If a subject withdraws from the study during a teduglutide cycle, the evaluations listed for the EOT visit are to be performed as completely as possible. Whenever possible, the subject will then be asked to return 4 weeks later for the early termination (ET) visit, and will be contacted weekly by phone during the interim period between EOT and ET for safety follow-up.

If a subject withdraws from the study during a NTT period, the evaluations listed for the ET visit are to be performed as soon and completely as possible.

Subjects who withdraw from the study will not be replaced.

4.8.3 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

Protocol deviation

Lack of efficacy

Physician decision

Withdrawal by subject

Withdrawal by parent/guardian

Lost to follow-up

Pregnancy (Discontinuation of treatment only)

Death

Other

4.8.3.1 Subjects 'Lost to Follow-up' Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact 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 CONCOMITANT TREATMENT

5.1 Concomitant Medications and GI Procedures

Concomitant treatment refers to all treatment taken between the dates of informed consent and EOS, inclusive. Concomitant treatment information must be recorded on the appropriate eCRF page. Concomitant treatments will be assessed at each site visit, and include all non-study treatments (medications, herbal treatments, vitamins, invasive and diagnostic procedures). Concomitant GI procedures include (but are not limited to) endoscopy, radiographic studies, GI and liver biopsies and associated pathology results. Concomitant treatment information must be recorded on the appropriate eCRF page. Details of medication changes and/or dosages will be recorded on the eCRF.

The mechanism of action of teduglutide may increase absorption of drugs (eg, motility medication including narcotics and opioids used for the management of SBS, warfarin, psychotropics, metronidazole, and digoxin). Accordingly, due consideration should be given to modifying concomitant medication regimens. Down-titration of concomitant medications should be considered when drugs, especially those with a narrow therapeutic range, are prescribed at dosages that are higher than usual.

5.1.1 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.1.2 Prohibited Treatment

The mechanism of action of teduglutide may increase enteral absorption of drugs (eg, motility medication including narcotics and opioids used for the management of SBS, warfarin, psychotropics, metronidazole, digoxin), so consideration should be given to modifying concomitant enteral medication regimens. Down-titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic range, are given at dosages that are higher than usual.

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the pre-treatment visit:

Table 5-1: Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pre-Treatment Visit
Native/synthetic glucagon-like peptide-2 (not-including teduglutide)	Any
Glucagon-like peptide-1 analog or human growth hormone	3 months
Octreotide or dipeptidyl peptidase 4 inhibitors	3 months
Biological therapy (eg, antitumor necrosis factor)	6 months

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is teduglutide, which 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 SHP633 investigator's brochure.

6.1.1 Blinding the Treatment Assignment

Not applicable for this open-label study.

6.2 Administration of Investigational Product(s)

6.2.1 Interactive Response Technology for Investigational Product Management

An interactive web-based response system (IWRS) will be used for screening and enrolling subjects, recording subject visits, investigational product supply dispensation and management, inventory management and supply ordering, investigational product expiration tracking and management, and return of investigational product. Please refer to the Study Manual for additional details regarding the IWRS.

The IWRS will also be used for creating, tracking, and confirming investigational product shipments. A user manual with specific functions and instructions for the IWRS will be provided to the site, and site personnel will receive training.

6.2.2 Allocation of Subjects to Treatment

This is an open-label study. Subjects will retain their assigned subject number from the TED-C14-006 study. Assessment of need for teduglutide treatment should be guided by the teduglutide treatment inclusion criteria. If the investigator, subject, and/or parent/guardian agree to proceed with treatment, a formal evaluation of teduglutide inclusion and exclusion criteria will be performed at the pre-treatment visit (Table 1-3).

6.2.3 Dosing

If teduglutide treatment eligibility is established at the pre-treatment visit and again, confirmed at the CxD1 visit, the subject will start a teduglutide treatment period, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily. The initial dose will be calculated based on body weight measured at the teduglutide pre-treatment visit, and adjusted as needed, based on body weight measured at Week 12 (CxW12). 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 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 rotated.

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 each 24-week teduglutide 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. At any time during the follow-up period, if escape criteria are met, the subject may proceed directly to another Pre-Treatment visit to assess treatment eligibility for another cycle (Section 4.6). Following the completion of the 4-week follow-up, the subject will continue in the study off teduglutide. Additional 28-week cycles may be repeated if treatment eligibility is established each time.

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification will be applied to the investigational product(s) container.

The study drug will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of study drug will be supplied and these will be labeled in accordance with applicable regulatory requirements. Sterile water for injection syringes will be provided separately and will be labeled in accordance with the applicable regulatory requirements.

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

6.3.2 Packaging

Investigational product is packaged in the following conditions:

Teduglutide will be provided in a sterile, single-use, glass vial as a lyophilized powder, to be reconstituted with 0.5 mL sterile water for injection provided as the diluent in a prefilled syringe.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 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.

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

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. The investigator is to keep a current record of the inventory and dispensation of all clinical supplies. This record will be made available to the sponsor's site monitor for the purpose of accounting for

all clinical supplies. Any discrepancy or deficiency will be recorded and will include an explanation. All supplies sent to the investigator must be accounted for and in no case will clinical supplies be used in any unauthorized situation.

The investigator has overall responsibility for administering/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 (as documented by the investigator in the applicable study delegation of authority form) will dispense the investigational product only to subjects eligible for teduglutide treatment following the procedures set out in the study protocol. All dispensed study medication will be documented in the interactive response technology system and/or other investigational product record (eg, investigation product accountability form). The investigator is responsible for assuring the retrieval of all study supplies from subjects.

All used and unused study drug vials must be returned by the subjects and/or parent/guardian, and will be retained at the site. If deemed appropriate, the investigator or his/her designee may dispense the unused study drug vials to the same subject. All original containers, whether empty or containing study drug will be returned to the pharmacy. Returned study drugs will NOT be relabeled or reassigned for use by other subjects. Contents of the study drug containers will not be combined. All used and unused vials must be returned to the distribution center according to the sponsor's instruction. No vial/kit may be destroyed on site without approval by the sponsor.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

Subjects will be instructed to bring their unused investigational product and empty/used investigational product packaging to every visit. Drug accountability will be assessed 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. The pharmacist/nominated person will record details on the drug accountability form.

Of those subjects eligible for teduglutide treatment, 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 Schedule of Assessments (Table 1-1, Table 1-2, and Table 1-3) and must be referred to in conjunction with the instructions provided in this section.

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 (and assent, as applicable) from the subject. A subject will have up to 7 days, after completion of the TED-C14-006 study, to sign consent to participate in the SHP633-304 study. The first visit after screening must occur within 12 weeks of screening for a pre-treatment visit, and within 2 to 12 weeks of screening for an NTx visit.

The screening visit (Scr) assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1-1, and as detailed below:

Informed consent, and informed assent (if applicable), is obtained

Study eligibility is determined. A screen failure is a subject who has given informed consent and failed to meet the Study Inclusion Eligibility Criteria. Subjects cannot be rescreened once they have been designated as a screen failure.

Demographics, updates to medical history and SBS history

Intake and output diaries are dispensed

Evaluate teduglutide treatment inclusion criteria

Adverse events, concomitant medications and concomitant GI procedures

7.1.2 Visits for Subjects Not Receiving Teduglutide

While outside of the 28-week teduglutide-treatment cycle, subjects will be followed approximately every 12 weeks for safety and efficacy assessments. No-teduglutide treatment visits are numbered sequentially (NT1, NT2, etc.), even if interrupted by the treatment cycles. The visit window (±7 days) is relative to the first NTx visit in the current NTT period. Assessments will be performed as outlined in Table 1-2 and described below.

Intake and output diaries are dispensed

Evaluate teduglutide treatment inclusion criteria

Adverse events, concomitant medications and concomitant GI procedures

Physical examination and vital signs, including weight

Height and head circumference

Review intake and output diaries

Record PS prescription and adjust as needed

Safety Laboratory Tests (ie, clinical chemistry, hematology, and urinalysis)

PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales

Antibodies to teduglutide, if and when required

Fecal occult blood testing, as indicated (Section 7.2.9.1)

Colonoscopy/sigmoidoscopy, as indicated (see Section 7.2.9.2)

Serum sample, as indicated

Teduglutide treatment may be considered at any time during the NTT period. If the investigator and the subject (and parent or legal guardian, as appropriate) agrees to proceed with treatment if the subject is eligible, the subject may proceed to the pre-treatment visit immediately to determine eligibility.

7.1.3 Visits for Subjects Receiving Teduglutide

7.1.3.1 Pre-treatment Visit

Subjects who meet at least 1 of the teduglutide treatment inclusion criteria during the screening visit or during the NTT period may proceed to the pre-treatment visit immediately if the investigator, subject and parent agree to proceed with teduglutide therapy. Similarly, subjects who meet escape criteria during the teduglutide follow-up period may proceed to the pre-treatment visit immediately.

The pre-treatment visit may also be combined with screening visit, and if the pre-treatment visit assessments occur within 7 days of the TED-C14-006 EOS visit (Week 28), both sets of assessments can be combined. A subject must have 2 weeks of intake diary data collected, prior to the first dose administration (CxD1) during any teduglutide treatment cycle. In general, pre-treatment assessments may occur over a period of up to 21 days. The teduglutide pre-treatment visit (Px) assessments and procedures will be performed as in Table 1-3 and as described below:

Evaluate teduglutide eligibility (treatment inclusion/exclusion criteria)

Dispense intake and output diaries

Adverse events, concomitant medications and concomitant GI procedures

Fecal occult blood testing

Gastrointestinal-specific testing, including colonoscopy or sigmoidoscopy as indicated

Physical examination and vital signs, including weight

Height and head circumference

Review intake and output diaries

Record PS prescription and adjust as needed.

Safety Laboratory Tests
(In addition to clinical chemistry, hematology, and urinalysis, labs at this visit include prothrombin time [PT] international normalized ratio [INR]. Subsequent prothrombin time/international normalized ratio (PT/INR) measurement is only required to evaluate for suspected drug-induced liver injury [DILI]).

Serum pregnancy testing (when the pre-treatment and screening visits are combined, the serum pregnancy test should be performed at the local laboratory)

Serum sample

7.1.3.2 Teduglutide Treatment Period (CxD1-CxW24)

The open-label teduglutide treatment period will comprise 24 weeks, during which all assessments and procedures listed for Visits CxD1-CxW24 in Table 1-3 shall be completed. Cycles are numbered sequentially, such that the first visit of the first cycle is C1D1, and the first visit of the second cycle is C2D1, etc. Visit windows are calculated based upon the date of first investigational product administration (Visit CxD1).

VISIT CXD1
Assessments and procedures at this visit will be performed as outlined Table 1-3 and as described below.

Two weeks of intake diary data are required before drug is administered at CxD1.

Confirm teduglutide treatment eligibility

Dispense intake and output diaries

Adverse events, concomitant medications and concomitant GI procedures

Physical examination and vital signs, including weight

Height and head circumference

Review intake and output diaries

Record PS prescription and adjust as needed

Safety laboratory tests

Quality of life measurements

Antibodies to teduglutide

Pregnancy testing (urine)

Dispense study drug

SITE VISITS DURING TEDUGLUTIDE TREATMENT PERIOD

Subjects will return for clinic visits on cycle weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24/EOT. Assessments and procedures at these visits will be performed as outlined in Table 1-3 and as described below:

Dispense/review intake and output diaries (every effort should be made to complete 2 weeks of intake diary entries prior to each clinic visit and to complete 48 hours of output diary entries during a period of nutritional stability prior to each clinic visit)

Physical examination and vital signs, including weight

Record PS prescription and adjust as needed

Safety laboratory tests

Urine pregnancy testing for FOCBP (CxW4, CxW9, CxW12, CxW16, CxW20, CxW24)

Study drug dispensation (except for CxW24)

Adverse events, concomitant medications and concomitant GI procedures

In addition, at CxW12 and CxW24 Visits **ONLY**, the following procedures will be performed:

Height and head circumference

Antibodies to teduglutide

Fecal occult blood testing (FOBT)

GI-specific testing, including colonoscopy or sigmoidoscopy as indicated

Quality of life measurements

At CxW24 **ONLY**, a serum sample is collected and stored for future analysis. This sample will not be used for genetic testing and lack of collection will not constitute a protocol deviation.

PHONE VISITS

Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period. Phone visit assessments and procedures are outlined in Table 1-3 and described below:

Review intake and output diaries

Safety laboratory tests (clinical chemistry and urinalysis)

Record PS prescription and adjust as needed

Obtain AEs, concomitant medications, and concomitant GI procedures

Evaluate escape criteria

7.1.4 Teduglutide Follow-up Period

The safety follow-up period for this protocol is 4 weeks (Weeks 25 – 28 of the cycle). Phone visits will occur on cycle weeks 25, 26, and 27 for all subjects. Phone visit assessments and procedures at weeks 25-27 will be the same as for telephone visits performed during the teduglutide treatment period. In addition, subjects will be evaluated for follow-up period escape criteria. If escape criteria are met at any time during the follow-up period, the subject may proceed directly to another pre-treatment visit at the investigator's discretion. The investigator may combine the CxW28 visit with the next pre-treatment visit if at least one escape criterion is met at the CxW28 visit, and the pre-treatment assessments occur within 7 days of the CxW28 visit. If a subject is completing the study at the CxW28 visit, the EOS/ET visit (Section 7.1.5) will take place in lieu of the CxW28 visit. Otherwise, following completion of the 28-week treatment cycle, the subject will proceed to an NTT visit within approximately 12 weeks.

At cycle week 28 (CxW28), subjects will return to the study site. In addition to the assessments performed at weeks 25-27, the following procedures will be performed at **CxW28 ONLY:**

Dispense intake and output diaries

Physical examination and vital signs, including weight

Antibodies to teduglutide

Pregnancy testing (urine)

Evaluate escape criteria

7.1.5 Study Completion/Early Termination Visit (EOS/ET Visit)

All subjects will return to the study site for the end of study/early termination visit (EOS/ET). Assessments and procedures at this visit will be performed as outlined in Table 1-1 and as described here. If a subject discontinues the study prematurely, the assessments for the EOS/ET Visit are to be performed as completely as possible (see Section 4.8.2).

Adverse events, concomitant medications and concomitant GI procedures

Physical examination and vital signs, including weight

Height and head circumference

Review intake and output diaries (the intake diary should be completed daily for a minimum of 2 weeks prior to the EOS/ET visit. The output diary should be completed daily over a 48-hour period of nutritional stability before the EOS/ET visit)

Record PS prescription and adjust as needed

Safety laboratory tests

Fecal occult blood testing, as indicated

Gastrointestinal-specific testing, including colonoscopy or sigmoidoscopy as indicated.

Quality of life measurements

Antibodies to teduglutide

Pregnancy testing, as needed

7.2 Study Evaluations and Procedures

7.2.1 Demographics, Medical History, and SBS History

Demographics, medical history, and SBS history will be obtained at screening. Medical history for purposes of this extension study will consist of the following:

Adverse events that were ongoing at the time of completion of TED-C14-006

Events that occurred during the period between completion of TED-C14-006 and informed consent to SHP-633-304

This medical history information will supplement the medical history information collected at the start of the TED-C14-006 core study. If the subject has any changes to the SBS history collected at the baseline visit of the TED-C14-006 study, that information (updated SBS history) will be collected.

7.2.2 Physical Examination

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

7.2.3 Vital Signs, Body Weight, Height, Head Circumference and Body Mass Index (BMI)

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 cuff (using the same method, the same arm, and in the same position throughout the study).

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Height (or length) and head circumference (for subjects ≤36 months of age) will be measured at selected visits. A height z-score, weight z-score, BMI, and BMI z-score will be calculated by the sponsor using the site-provided height and weight data collected at each site visit

New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

7.2.4 Clinical Laboratory Tests

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 1-1, Table 1-2, and Table 1-3) 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 teduglutide treatment period, subjects will also have safety labs within approximately 5-7 days after a PS adjustment. Safety labs performed after PS 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 8.1). Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

New clinically significant labs should be reported as AEs.

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

Table 7-1 List of Laboratory Tests

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

Coagulation:
Prothrombin time/International normalized ratio

Urinalysis:
- Blood
- Glucose
- Leukocytes
- Microscopic analysis
- pH
- Protein
- Specific gravity

Pregnancy tests (females of childbearing potential):
- Serum β-HCG (screening)
- Urine β-HCG (all other visits)

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
- Uric acid

7.2.5 Serum Sampling

Serum samples will be collected and stored for future analysis at the following times:

At the pre-treatment visit. If the subject met a follow-up period escape criterion, the serum sample will not be collected at the pre-treatment visit

At the CxW24 (EOT) visit

During NTT: Approximately every 24 weeks

The serum sample will not be used for genetic testing. Lack of collection will not constitute a protocol deviation.

The sponsor, sponsor's representatives, biorepositories, and any specialty laboratories will be blinded to the subject's identity. The sample and/or extracted material will otherwise be stored for up to 15 years from the end of the study after which time it will be destroyed. Upon written request, subjects will be permitted to withdraw their sample from the analysis and have their

sample and/or extracted material destroyed. Any results already generated from the samples will not be removed from any analyses that have already been performed.

7.2.6 Pregnancy Testing

A serum pregnancy test is performed on all FOCBP at the teduglutide pre-treatment visit (when the pre-treatment and screening visits are combined, the serum pregnancy test should be performed at the local laboratory). Urine pregnancy tests will be administered at all other visits according to the study schedules, or if pregnancy is suspected, or as specified per protocol upon withdrawal of the subject from the study.

7.2.7 Antibody Testing

Blood samples will be drawn for the analysis of antibodies to teduglutide according to the Schedule of Assessments (Table 1-1, Table 1-2, and Table 1-3). Blood samples for antibodies may be drawn from a central line or from peripheral access. The sample drawn on CxD1 must be drawn prior to administration of the first dose of teduglutide. Once the subject has started teduglutide treatment, samples must be drawn at least 14 hours after dosing. Subjects who test positive for antibodies to teduglutide will also be tested for neutralizing antibody. Subjects who have been previously treated with teduglutide, and who test positive for antibodies to teduglutide, will have follow-up blood draws for antibodies to teduglutide every 12 weeks while on study until a negative result is obtained.

7.2.8 Volume of Blood

Efforts will be made to minimize the amount of blood drawn from all pediatric subjects enrolled 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 annually are shown in Table 7-1.

Table 7-1: Approximate Volume of Blood to be Drawn from Each Subject Annually

Assessment		Sample Volume (mL)	No. Samples per two 28-week Teduglutide Cycles	Total Volume (mL)
Subjects Receiving Teduglutide Treatment				
Safety	Biochemistry and β-hCG[a]	2.5	24	60
	Hematology	2	24	48
	Coagulation Parameters	1	2	2
	Antibodies	2	8	16
	Serum storage samples	3	4	12
Total mL per 2, 28-week Treatment Cycles (Approximate Annual Volume):				**138**
Subjects Not Receiving Teduglutide Treatment[b]				
Assessment		**Sample Volume (mL)**	**No. Samples per 4 NTT Visits**	**Total Volume (mL)**
Safety	Biochemistry	2.5	4	10
	Hematology	2	4	8
	Serum storage samples	3	2	6
Total mL per 4 "No-Teduglutide Treatment" Visits 48-week period:				**24**

Table 7-1: Approximate Volume of Blood to be Drawn from Each Subject Annually

Assessment	Sample Volume (mL)	No. Samples per two 28-week Teduglutide Cycles	Total Volume (mL)

Abbreviations: β-hCG=beta-human chorionic gonadotropin; NTT=no-teduglutide treatment

[a] β-hCG testing will only be administered to females who are eligible for teduglutide treatment.

[b] Subjects not receiving teduglutide treatment, but who were exposed to it previously and tested positive for anti-teduglutide antibodies will require blood samples for antibody testing every 12 weeks until they test negative.

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 PS adjustment, and anti-teduglutide antibody testing during no-teduglutide treatment.

7.2.9 Gastrointestinal-specific Testing

7.2.9.1 Fecal Occult Blood Testing

Fecal occult blood testing must be performed on all subjects at the pre-treatment visit, week 12, and week 24 of the teduglutide cycle. During NTT periods, FOBT must be performed on teduglutide-exposed subjects (subjects who have received teduglutide any time in the past and are therefore not teduglutide-naïve) on a roughly annual basis (approximately every 48-60 weeks). Actions to be taken in response to a positive FOBT are described below.

7.2.9.2 Colonoscopy or Sigmoidoscopy

Teduglutide-naïve subjects age 12 and older will undergo colonoscopy or sigmoidoscopy at the pre-treatment visit if one has not been performed within 1 year.

Subjects of any age with newly positive FOBT results at the pre-treatment visit for which a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy or sigmoidoscopy prior to receiving teduglutide. If newly positive FOBT results (for which a readily detectable cause cannot be identified) are obtained at the end of a teduglutide treatment cycle (CxW24/EOT), colonoscopy or sigmoidoscopy will be performed. The need for colonoscopy or sigmoidoscopy in response to positive FOBTs at any other point during the study, or to re-evaluate persistently positive FOBTs is at the discretion of the investigator.

Teduglutide-exposed subjects who have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) will undergo colonoscopy or sigmoidoscopy. While receiving additional teduglutide treatment, subjects will undergo colonoscopy or sigmoidoscopy at 5 year intervals or more often as needed.

Upper endoscopy may be performed along with any colonoscopy or sigmoidoscopy at the investigator's discretion. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. Subjects with unresected GI polyps, polyposis conditions, pre-malignant change or malignancy in the GI tract will be excluded from teduglutide treatment.

7.2.10 Nutritional Support

Nutritional support includes PS, enteral nutrition, and other food and fluids. Advances in enteral nutrition and/or reductions to PS will be based on clinical status, including weight, linear growth, hydration status, and safety laboratory results. Intake and output diaries will include data to be considered in the adjustment of each subject's nutritional support. Guidelines for nutritional support management and weaning algorithms are provided in Appendix 2.

7.2.11 Diaries

7.2.11.1 Study Drug Administration Diary

A study drug administration diary will record administration of teduglutide. This diary should be completed by the subject (or parent/legal guardian, as applicable) daily during the teduglutide treatment period (between visits CxD1 and CxW24).

7.2.11.2 Intake Diary

Intake diaries will be used to collect and evaluate each subject's nutritional support. The subject/parent/guardian will complete the appropriate fields of the PS section of the intake diary 2 weeks prior to ALL scheduled site visits (except at pre-treatment visit). During the 24-week teduglutide treatment period, the intake diary will also be completed for 1 week following PS adjustments. The intake diary will also be completed daily during the 4-week follow-up period. The following data will be captured in the intake diaries:

Parenteral support volume and infusion duration

Site personnel will determine the actual PS daily calories based on diary entries.

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 PS reduction and advance in feeds.

7.2.11.3 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 that are in a teduglutide treatment cycle within 1 week of implementing a change in the PS prescription, regardless of previous teduglutide exposure.

Urine data:

Toilet-trained subjects (who do not wear diapers)
Measure and record all urine output in mL or cc

Nontoilet-trained subjects (who wear diapers)
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 may be asked to collect the first void after the daily PS infusion to measure specific gravity

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

> Toilet-trained subjects (who do not wear diapers)
> Record the occurrence of each bowel movement and score the stool consistency using the Bristol Stool Form Scale (see Output diary)
>
> Nontoilet-trained subjects (who wear diapers)
> Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency using the Bristol Stool Form Scale (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. Ostomy output will not be scored using the Bristol scale.

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 PS reduction and advance in feeds.

7.2.12 Health-related Quality of Life Assessments

Throughout the study, health-related quality of life assessments will be performed using the PedsQL Generic Core Scales. Each PedsQL age-appropriate form takes less than 4 minutes to complete. The scales include self-reports for pediatric subjects and adolescents aged 5 to 18 years and proxy-reports from parents of pediatric subjects aged 2 to 18 years.

Field trials have shown that the internal consistency reliability of the PedsQL was excellent, with alphas for the generic core scales in both self- and proxy-report greater than the 0.70 standard, and alphas for the full 23-item scale approaching 0.90 for self- and proxy-report. Missing data were minimal. Item response distributions were across the full scale range, with no floor effects, and minimal ceiling effects.

The validity of the PedsQL Generic Core Scales was demonstrated through known group comparisons, and correlations with other measures of disease burden. The PedsQL self- and proxy-report distinguished between pediatric subjects with and without a chronic health condition, and within the group of pediatric subjects with a chronic condition, between those who did or did not have an overnight hospital visit in the last 12 months. Further, both child self-report and parent proxy-report correlated significantly with the number of days the child was too ill to pursue normal activities, needed someone to care for him or her, missed school in the last month, the number of days the parent missed from work in the last month, and parent-report of problems pursuing their normal work routine and concentrating at work. The PedsQL Generic Core Scales are also responsive to clinical change, as demonstrated in field trials.

7.2.12.1 Pediatric Quality of Life Generic Core Scale (PedsQL™), Acute version

The PedsQL Generic Core Scale is designed to measures health-related quality of life (HRQoL) in pediatric subjects and adolescents (2-18 years of age). The developmentally appropriate PedsQL Generic Core Scale will be completed by either the parent or legal guardian and subject as indicated in Table 7-2 at the time points as outlined in Table 1-1, Table 1-2, and Table 1-3.

Table 7-2: Developmentally Appropriate PedsQL™ Generic Core Scales

Report	Completed by
Parent Report for Toddlers (ages 2-4)	Parent or Legal Guardian
Child Self Report and Parent Proxy-Report for Young Pediatric subjects (ages 5-7)	Subject and Parent or Legal Guardian
Child Self Report and Parent Proxy-Report for Pediatric subjects (ages 8-12)	Subject and Parent or Legal Guardian
Child Self Report and Parent Proxy-Report for Teens (ages 13-18)	Subject and Parent or Legal Guardian

Abbreviations: PedsQL=Pediatric Quality of Life Inventory

The Parent Report for Toddlers (ages 2-4) of the PedsQL Generic Core Scale is composed of 21 items comprising 4 dimensions as follows: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), 4) School Functioning (3 items).

The Child and Parent Reports of the PedsQL Generic Core Scale for Young Pediatric subjects (ages 5-7), Pediatric subjects (ages 8-12), and Teens (ages 13-18) are composed of 23 items comprising 4 dimensions as follows: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), 4) School Functioning (5 items).

7.2.12.2 Pediatric Quality of Life Family Impact Module (PedsQL™), Acute version

The PedsQL Family Impact Module is a parent-report multidimensional instrument that will be completed by the parent or legal guardian, as outlined in Table 1-1, Table 1-2, and Table 1-3.

The PedsQL Family Impact Module is a specific module of the PedsQL that is used to measure the impact of pediatric chronic health conditions on parents and the family (Varni et al. 2004). The 36-item PedsQL Family Impact Module consists of 6 scales measuring parent self-reported functioning as follows: 1) Physical Functioning (6 items), 2) Emotional Functioning (5 items), 3) Social Functioning (4 items), 4) Cognitive Functioning (5 items; worries about treatment and disease), 5) Communication (3 items), 6) Worry (5 items). Two additional scales measure parent-reported family functioning as follows: 1) Daily Activities (3 items), and 2) Family Relationships (5 items). The PedsQL Family Impact Module should take the parent or legal guardian approximately 5 to 10 minutes to complete.

7.2.12.3 PedsQL Gastrointestinal Symptoms Module (PedsQL™), Acute version

The PedsQL Gastrointestinal Symptom Module is a disease-specific 58-item module, comprised of 10 different symptom scales that assess gastrointestinal symptom-related quality of life: food and drink limits, trouble swallowing, heartburn and reflux, nausea and vomiting, gas and bloating, constipation, blood in poop, and diarrhea. The PedsQL Gastrointestinal Symptoms Module was designed to allow the selection and scoring of individual scales from the Module. The scales of Food and Drink Limits (6 items) and Diarrhea (7 items) were identified as clinically relevant and appropriate for the symptoms experienced in this pediatric study population, and therefore, are the only scales used in this study. The scales will be completed by either the parent or legal guardian and subject as indicated in Table 7-2 at the time points outlined in Table 1-1, Table 1-2, and Table 1-3.

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 7.1.4. 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.

Note that the severity of AEs that constitute dose interruption criteria will also be evaluated using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading criteria (Table 8-1).

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 study drug that are not resolved at EOT 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 in 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.

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 (eg, 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

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.4.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Global Pharmacovigilance and Risk Management Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the Shire Medical Monitor using the details specified in the emergency contact information section of the protocol. In the event a subject becomes pregnant during the study, teduglutide administration must be discontinued immediately.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Adverse Event Form

for Serious Adverse Events (SAEs) and Non-serious AEs as Required by the Protocol. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by the Protocol as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or will determine the pregnancy onset date.

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 Pharmacovigilance and Risk Management 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 Pharmacovigilance and Risk Management 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 Pharmacovigilance and Risk Management 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 7.1.4, and must be reported to the Shire Global Pharmacovigilance and Risk Management 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 Pharmacovigilance and Risk Management 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 of Individual Subjects

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

Study drug must be discontinued if any of the following events occur:

- Pregnancy
- Severe hypersensitivity, such as anaphylaxis determined by the investigator to be related to study drug. This does not include the presence of anti-teduglutide antibodies, mild injection site reactions or mild symptoms that according to the investigator do not pose a significant risk to the subject.

- An AE listed in (Table 8-1) that is of NCI CTCAE severity Grade 3 or 4 and considered to be related to study drug administration

- Confirmed drug-induced liver injury (DILI) related to teduglutide (see Section 8.4.2)

8.4.1 Dose Interruption Criteria Based on Known or Possible Risks of Teduglutide

The investigational product may be discontinued if the subject has an AE listed in Table 8-1 that is of severity ≥Grade 3 per the NCI CTCAE. All such AEs should be discussed with Shire's medical monitor or designee as soon as possible. Teduglutide administration must be discontinued if the AE is considered related to the investigational product. The length of the dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

Investigators and the Data Monitoring Committee (DMC) should be guided by the descriptions of Grade 3 and 4 events, as they relate to known and possible risks associated with the administration of teduglutide.

Table 8-1: CTCAE Criteria for Adverse Events that May Lead to Dose Interruption

Adverse Events	Grade 3 Description	Grade 4 Description
Gastrointestinal Disorders		
Colorectal polyps	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care activities of daily living	Life-threatening consequences; urgent intervention indicated
Intestinal Obstruction	Hospitalization indicated; elective operative intervention indicated; limiting self-care activities of daily living; disabling	Life-threatening consequences; urgent operative intervention indicated
Gallbladder and Bile Duct Disease		
Cholecystitis	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder perforation	Not Applicable	Life-threatening consequences; urgent intervention indicated
Gallbladder obstruction	Symptomatic and severely altered gastrointestinal function; tube feeding, total parenteral nutrition or hospitalization indicated; nonemergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Gallbladder infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated

Table 8-1: CTCAE Criteria for Adverse Events that May Lead to Dose Interruption

Adverse Events	Grade 3 Description	Grade 4 Description
Alkaline Phosphatase increased	>5.0 to 20.0x ULN	>20.0x ULN
Blood bilirubin increased	>3.0 to 10.0x ULN	>10.0x ULN
Bile duct stenosis	Severely altered gastrointestinal function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreatic Disease		
Pancreatitis	Severe pain; vomiting; medical intervention indicated (eg, analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated
Pancreatic duct stenosis	Severely altered gastrointestinal function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated
Pancreas infection	Intravenous antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Serum amylase increased[a]	>2.0 to 5.0x ULN	>5.0x ULN
Lipase increased[a]	>2.0 to 5.0x ULN	>5.0x ULN
Cardiovascular Disease		
Heart failure	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (eg, continuous intravenous therapy or mechanical hemodynamic support)

Source: Common Terminology Criteria for Adverse Events, version 4.03, 14 June 2010

ULN=upper limit of normal

[a] In the setting of clinically acute and symptomatic pancreatitis

8.4.2 Dose Interruption Criteria Based on Drug-Induced Liver Injury

Teduglutide administration for an individual subject may need to be interrupted if the subject has clinical and laboratory evidence of potential DILI, in the absence of an alternative explanation, as identified by the following criteria:

- ALT or AST >8x ULN
- ALT or AST >5x ULN and >2x baseline value for more than 2 weeks
- (ALT or AST >3x ULN and >2x baseline value) and (total bilirubin >2x ULN or INR>1.5)
- ALT or AST >3x ULN and >2x baseline value with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

All laboratory values suggestive of potentially new DILI should be repeated and verified within 3 days. International normalized ratio should be measured with this set of verification laboratory assessments 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 to evaluate the cause of liver injury. This evaluation may include, as clinically indicated, consideration of sepsis, acute viral hepatitis (eg, hepatitis A immunoglobulin [IgM], hepatitis B surface antigen, hepatitis C antibodies, cytomegalovirus IgM, Epstein-Barr virus antibody panel), hepatobiliary obstruction (ultrasound), autoimmune hepatitis (anti-nuclear, anti-smooth muscle, anti-actin, or anti-liver kidney microsomal antibodies), intestinal failure associated liver disease, cardiovascular causes such as ischemic hepatitis, and concomitant hepatotoxic treatments.

Additional evaluations may be performed at the discretion of the investigator in consultation with the Shire medical monitor.

Teduglutide administration must be permanently discontinued if DILI is confirmed and deemed related to study drug.

8.5 Early Termination of the Clinical Study

The DMC may recommend stopping the study if:

- ≥2 subjects being administered investigational product develop the same event listed in Table 8-1 of severity CTCAE Grade 3

  or

- 1 subject develops an event listed in Table 8-1 of severity CTCAE Grade 4 which is attributable to investigational product or is not reasonably related to the underlying disease process.

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol in 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 in 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. Unscheduled safety follow up assessments (including visits conducted after EOS) are not to be collected unless requested.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management process. 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 its agent. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, USA) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the statistical methods and definitions 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.

9.4 Planned Interim Analysis, and Data Monitoring Committee

An interim analysis is planned when 6 months of safety data have been collected.

A 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.

9.5 Sample Size Calculation and Power Considerations

The number of subjects in this study is not based on statistical power considerations as this is an extension study of the core study, TED-C14-006. The maximum number of subjects was determined by the enrollment in TED-C14-006.

9.6 Study Population

The safety population includes all enrolled subjects in the study. Safety population will be used for both safety and efficacy analyses.

9.7 Efficacy Analyses

No claims of statistical significance will be made; however, 95% confidence intervals will be provided, if applicable. Continuous variables, including those assessed on a discrete scale, 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.

9.7.1 Efficacy Endpoints

Efficacy endpoints will be analyzed at the end of each teduglutide treatment period (Week 24 or EOT), and at each study visit, relative to the baseline of the core study (TED-C14-006) and/or first exposure to teduglutide. The following efficacy endpoints will be analyzed:

- Reduction in PS volume of at least 20%
- Absolute and relative change in PS volume
- Complete weaning off PS
- Change in days per week of PS

9.8 Safety Analyses

9.8.1 Safety Endpoints

The following safety endpoints will be analyzed:

- Adverse events
- Vital signs, including temperature, heart rate, and blood pressure
- Laboratory safety data (ie, clinical chemistry, hematology, and urinalysis)
- Urine output
- Stool output
- Antibodies to teduglutide
- Gastrointestinal-specific testing , including fecal occult blood testing and colonoscopy or sigmoidoscopy
- Z-scores for weight, height (or length), head circumference (up to 36 months of age), and body mass index

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number of events, incidence, and percentage of AEs will be calculated overall, by System Organ Class (SOC) and by preferred term. SAEs will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) with regard to drug class and drug name. The number and percentage of subjects with specific prior medications will be summarized. Medical history (including surgical/procedural history) will be coded using MedDRA. The number and percentage of subjects with specific histories will be summarized by system organ class and preferred term.

For clinical laboratory tests, vital signs, body weight, and fluid balance variables, descriptive statistics (mean, median, standard deviation, minimum and maximum values, the number and percentage of subjects in specified categories) will be calculated to summarize the observed values and change from baseline at each scheduled visit.

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

Additional safety parameters and measures will include change in body weight, height (or length) and head circumference (up to 36 months of age). Derived variables will include height z-score, weight z-score, BMI, and BMI z-score. Descriptive statistics (mean, median, standard deviation, minimum and maximum values, the number and percentage of subjects in specified categories) will be calculated to summarize the absolute values and change from baseline at each scheduled visit.

9.9 Other Analyses

9.9.1 Health-related Quality of Life Analyses

Health economics and outcomes research endpoints will be analyzed at approximately 12-week intervals (Weeks 12 and 24 of each teduglutide treatment cycle, and every 12 weeks for subjects not on teduglutide), relative to the study baseline. The beginning of each treatment cycle (CxD1) will be an additional baseline.

- Change in Pediatric Quality of Life Inventory (PedsQL) score
- Change in PedsQL Family Impact Module score
- Change in PedsQL Gastrointestinal Symptoms Module Sub-Scales scores:
    - Food and Drink Limits
    - Diarrhea

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 to the CRO 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 (CSR) 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 EOS 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 is appointed to review the final CSR for multicenter studies. Agreement with the final CSR 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 products, 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 international 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 Case Report Forms

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded into eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. 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 into the eCRF.

eCRFs should be approved by the investigator per study specifications and data deliverable requirements.

The clinical research associate (CRA)/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 diary cards, original clinical laboratory reports, and histology and pathology 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 CRA/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 subject 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 Food and Drug Administration (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 and assent, where applicable, from 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 or the subject's legally-authorized representative, as applicable, 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 (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or 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.

Within the source documents, site personnel should document instruction of and understanding by the parent/legally-authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

The principal investigator provides the sponsor with a copy of the consent form, and assent form where applicable, which was reviewed by the IRB/EC and which 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.

For sites within the EU, the applicant for an EC opinion can be the sponsor, the investigator, or for multicenter studies 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 (or 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; for sites within the EU, this can be done by the sponsor, the investigator or for multicenter studies 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 (or 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 review 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 SHP633; national or local regulatory authorities; and the IRBs/ECs 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 2-4 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 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	08 April 2016	Global
Amendment 1	22 Nov 2016	Global

APPENDIX 2 GUIDELINES FOR NUTRITIONAL SUPPORT MANAGEMENT DURING THE STUDY

Nutritional support adjustment in volume and calories should be considered at all planned visits. Please consider the following clinical parameters identified as markers for adequate management of pediatric SBS. These parameters should also be considered for managing nutritional support (PS and/or oral/enteral feeding) in terms of volume and calories during the treatment period.

- Growth trajectory, including weight, height (or length), and head circumference (for pediatric subjects up to 36 months of age)
- Other clinical evaluations
  - Serum electrolytes
  - Blood urea nitrogen /creatinine levels
  - Changes in stool frequency or volume, including mixed output
  - Stool consistency (ie, Bristol Stool Scale)
  - Urine specific gravity
- General consideration to possible clinical deterioration in SBS
  - Inability to maintain weight and growth velocity
  - Diarrhea (≥10 bowel movements per day, ≥80 mL/kg/day from an ostomy, or ≥75 mL/kg/day mixed output)
  - Colic/vomiting frequency increased
  - Electrolyte changes or imbalance
  - Skin breakdown
- 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.
- Nutritional support constituents may be adjusted at the discretion of the investigator.
- 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.
- If there is a change in enteral nutrition (EN) or other food or fluid intake, the investigator should consider this when adjusting the PS/EN support in volume and calories.

Figure A-1 Weaning Algorithm for Subjects Who are NOT Toilet Trained and in Diapers

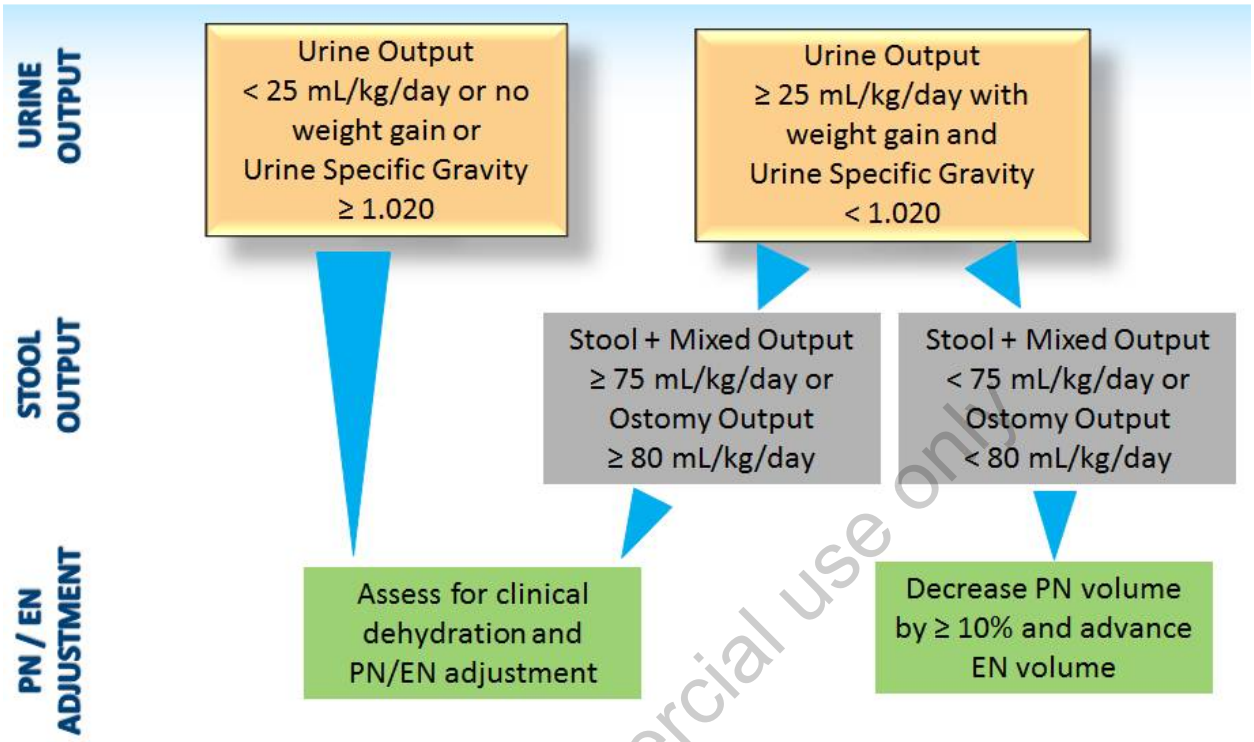


Figure A-2 Weaning Algorithm for Subjects Who are Toilet Trained and NOT in Diapers

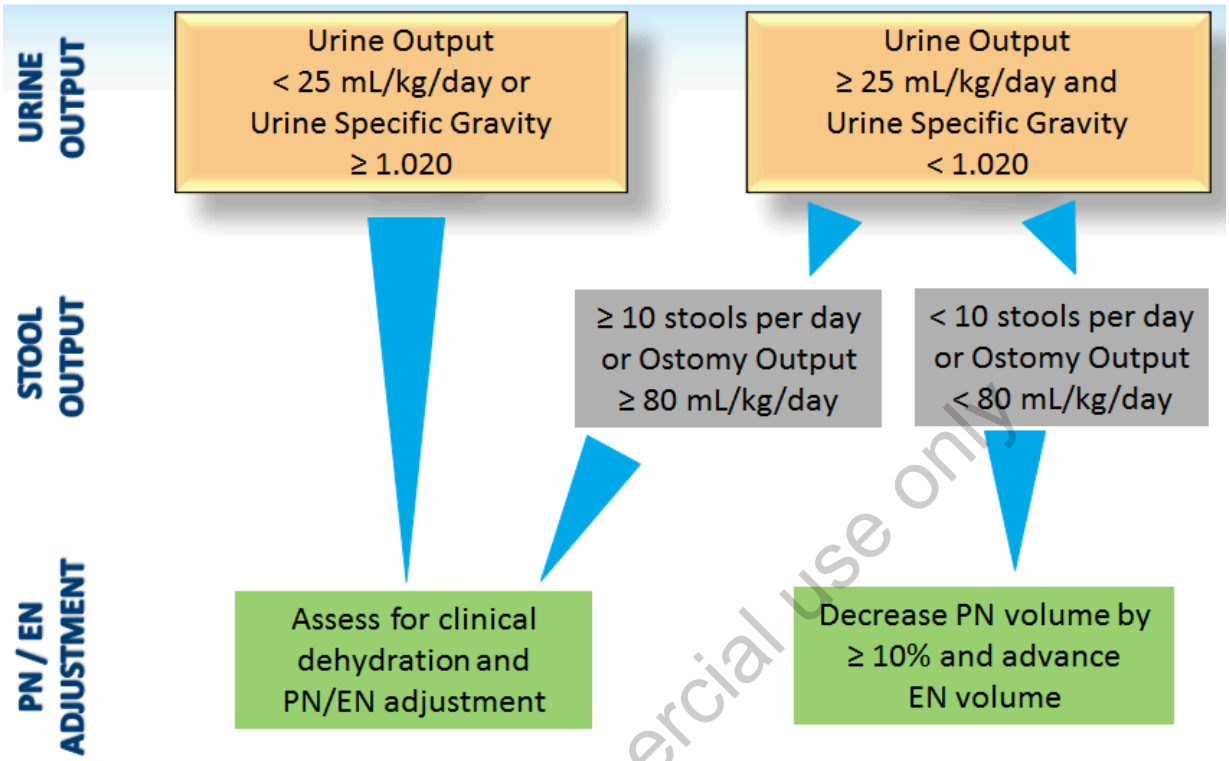
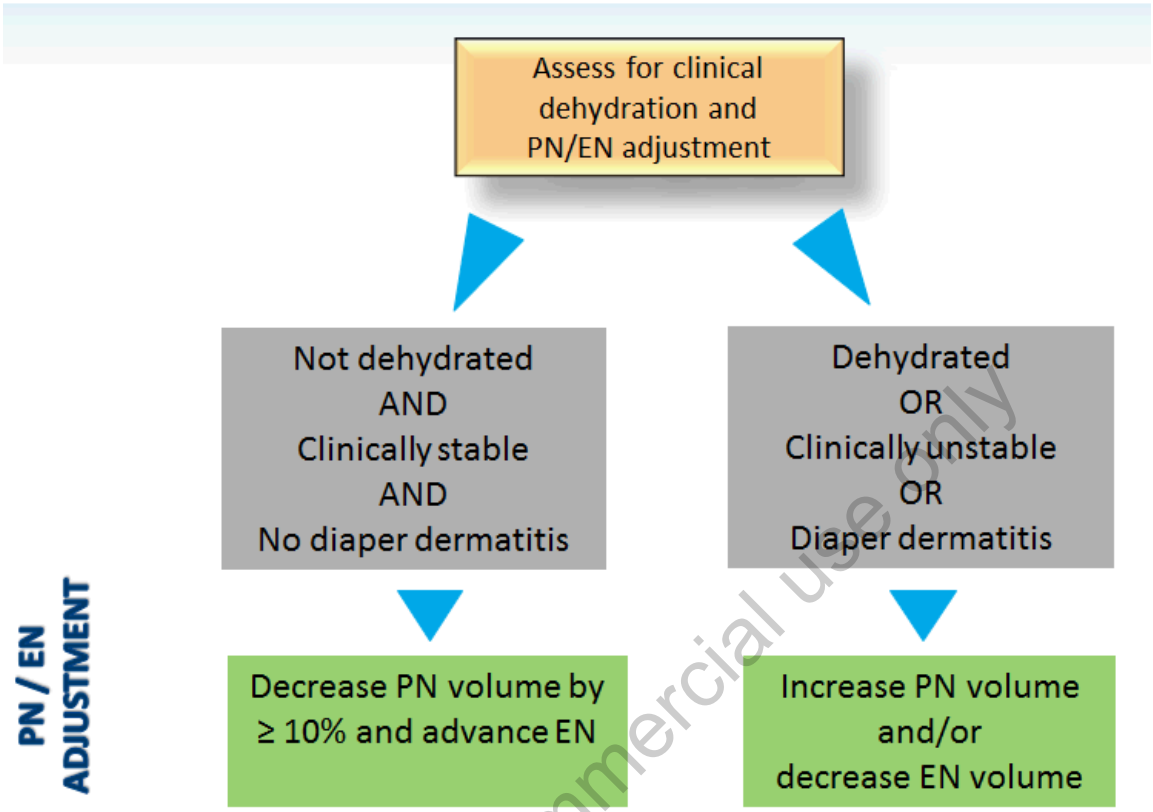


Figure A-3 Clinical Dehydration Assessment and PS/EN Adjustment



PROTOCOL: SHP633-304

TITLE:	A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome Who Completed TED-C14-006
DRUG:	Teduglutide
IND:	IND# 058213
EUDRACT NO.:	2016-000849-30
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way, Lexington, MA 02421 USA
PROTOCOL HISTORY:	Amendment 2: 23 Mar 2017 Amendment 1: 22 Nov 2016 Original Protocol: 08 April 2016

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

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

[redacted], MD PhD

Global Clinical Development

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-304.

Title: A prospective, open label, long-term safety and efficacy study of teduglutide in pediatric patients with short bowel syndrome who completed TED-C14-006

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 Conference on Harmonization (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)	

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	**Amendment Date** **23 Mar 2017**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Updated emergency contact information		Emergency Contact Information; Section 8.1.6; Section 8.2.2; Section 8.2.4
To allow for approximately 7 days for subjects to transfer from Study TED-C14-006 to Study SHP633-304 (instead of up to 7 days).		Table 1-1; Section 7.1.1
A footnote was added at the pre-treatment visit in the Schedule of Events for Subjects While Receiving Teduglutide to underscore that, when the first pre-treatment visit (P1) follows the screening visit, it must occur within 12 weeks of screening.		Table 1-3
Revised the language on abstinence as a contraceptive method for consistency with the Medicines and Healthcare Products Regulatory Agency (MHRA) Clinical Trial Facilitation Group's "Recommendations related to contraception and pregnancy testing in clinical trials."		Section 4.7.1
Clarification that ancillary components, in addition to sterile water for injection syringes, will also be provided and labeled in accordance with the applicable regulatory requirements.		Section 6.3.1
A footnote was added in Table 7-2 to clarify that subjects older than 18 years of age will continue to use the Child Self Report and Parent Proxy-Report for Teens (ages 13-18) when completing the Pediatric Quality of Life Generic Core Scale (PEDSQL™).		Section 7.2.12.1 (Table 7-3)
Revised the text on severity categorization to specify that a severe treatment-emergent adverse event (TEAE) that might lead to dose interruption (Section 8.4.1) or early termination of the study (Section 8.5) will also be graded according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) severity grading criteria, in addition to the standard severity categorization. These events are no longer limited to only the events described in Table 8-1, entitled "CTCAE Criteria for Adverse Events that May Lead to Dose Interruption (Prospective Period of Observation Only)." Therefore, Table 8-1 has been deleted.		Section 8.1.1; Section 8.4; Section 8.4.1 Table 8-1 (deleted)
Revised the criteria for early termination of the study: stopping criteria were extended to all NCI CTCAE Grade 3 and 4 severity events reported as related to the investigational product, and no longer limited to the events described in Table 8-1, entitled "CTCAE Criteria for Adverse Events that May Lead to Dose Interruption (Prospective Period of Observation Only)."		Section 8.5

See Appendix 1 for protocol history, including all amendments.

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 using the details below.

[redacted], MD PhD

Email: [redacted]

Fax: [redacted]

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

Primary contact for North America (NA) and backup contact for European Union (EU)

[redacted], MD, [redacted]

Mobile: [redacted]

US Toll Free number: [redacted]

Phone: [redacted] (medical emergencies – NA)

Email: [redacted]

Primary contact for EU and backup contact for NA

[redacted], MD, [redacted]

Mobile: [redacted]

Phone: [redacted]

Phone: [redacted] (medical emergencies – EU)

Email: [redacted]

In addition, the investigator may also contact the Shire Medical Monitor:

[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 (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 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):
[redacted] Shire (USA)

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-HCG	beta-human chorionic gonadotropin
BMI	body mass index
CRA	clinical research associate
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced livery injury
DMC	data monitoring committee
DPP-4	dipeptidyl peptidase 4
EC	ethics committee
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FOBT	fecal occult blood test
FOCBP	female of child-bearing potential
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
GLP-2	glucagon-like peptide 2
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IGF-1	insulin-like growth factor 1
IRB	institutional review board
IV	intravenous

IWRS	interactive web-based response system
MedDRA	Medical Dictionary for Regulatory Activities
NA	North America
NCI	National Cancer Institute
NDA	new drug application
NTT	no-teduglutide treatment
PDA	patent ductus arteriosus
PedsQL	Pediatric Quality of Life inventory
PS	parenteral support
PT/INR	prothrombin time/international normalized ratio
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
SOC	standard of care
$t_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
UK	United Kingdom
ULN	upper limit of normal
US	United States
WHO-DD	World Health Organization – Drug Dictionary

STUDY SYNOPSIS

Protocol number: SHP633-304	**Drug:** Teduglutide
Title of the study: A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome (SBS) Who Completed TED-C14-006	
Number of subjects (total and for each treatment arm): Approximately 34 subjects who completed the TED-C14-006 study, including subjects in the standard of care treatment arm, are expected to enroll in this extension study. This study will enroll up to as many subjects as complete the TED-C14-006 study.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 28 investigational sites in North America and Europe will participate in this extension study	
Study period (planned): October 2016 – September 2019	**Clinical phase:** 3 Extension
Objectives: **Primary:** To evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with SBS. **Secondary:** To evaluate long-term efficacy of teduglutide treatment in pediatric subjects with SBS.	
Rationale: This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects with short bowel syndrome (SBS) who completed the TED-C14-006 study (the core study). In addition to evaluating the long-term safety and durability of efficacy after 24-weeks of treatment, this extension study will evaluate the need for additional teduglutide treatment in these subjects, and will allow the study of first-time treatment of teduglutide-naïve subjects who participated in the standard of care (SOC) treatment arm in TED-C14-006.	
Investigational product, dose, and mode of administration: This study will allow repeat doses of teduglutide 0.05 mg/kg subcutaneous (SC) once daily (QD) injection for eligible pediatric subjects. There is no active comparator or reference product.	
Methodology: This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects who completed the TED-C14-006 study (core study). Once the informed consent (and if applicable, informed assent) have been reviewed and signed, demographics, and updates to medical history and short bowel syndrome history will be obtained. Subjects not receiving teduglutide treatment (ie, in a no-teduglutide treatment [NTT] period), will be seen approximately every 12 weeks for safety, parenteral support (PS) requirements, and quality of life. The first NTT visit after the screening visit will occur within 2 to 12 weeks of the screening visit. At any point after screening, including during a NTT period, subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed **immediately** to the pre-treatment visit if the investigator, subject, and parent agree to proceed with teduglutide therapy. After the pre-treatment visit, subjects who meet ≥1 of the teduglutide treatment inclusion criteria, and meet none of the teduglutide treatment exclusion criteria, will start a 28-week cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily, followed by a 4-week follow-up period (during which no teduglutide is administered) (Figure 3-1). During the 28-week cycle, clinic visits will occur at weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period (between weeks 1 and 24), and weekly during the teduglutide follow-up period (between weeks 24 and 28). Safety and PS requirements will be evaluated at every visit, and quality of life assessments will be made	

approximately every 12 weeks. If a subject has clinical deterioration and meets follow-up period escape criteria after stopping teduglutide, the subject may "escape" the follow-up period early and proceed immediately to another pre-treatment visit. Following completion of the 28-week treatment cycle, the subject will proceed to an NTT visit within approximately 12 weeks.

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, all attempts should be made to follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) for decisions regarding PS support reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines, however, is not considered a protocol deviation. (Appendix 2).

Study Design Flow Chart

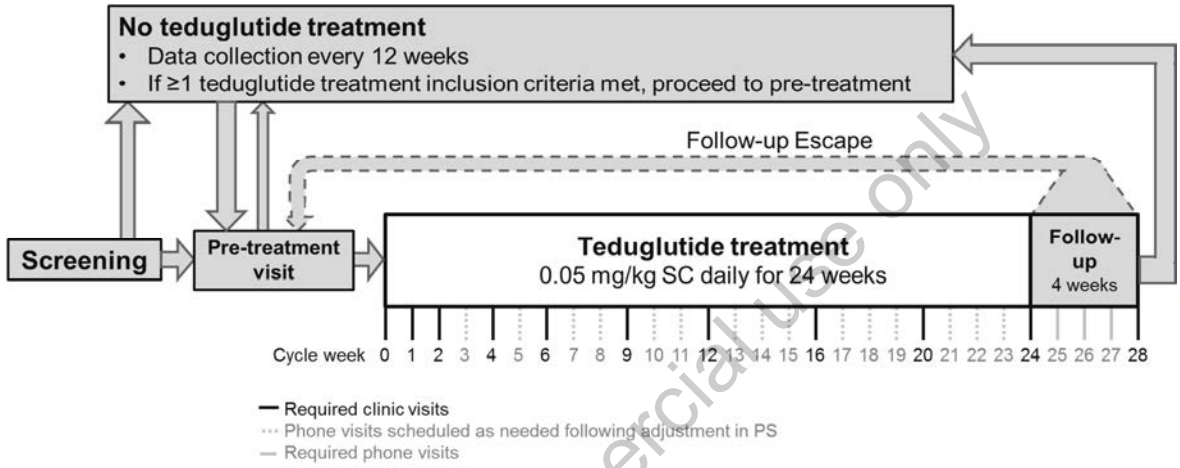

Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pre-treatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects will enter a 28-week teduglutide cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24 (**solid black lines**). Phone visits are required approximately 1 week after adjustments in PS during the intervening weeks between weeks 2 and 24 (**dashed grey lines**). Subjects discontinue teduglutide at week 24 and enter a 4-week follow-up (no-treatment) period, during which phone visits will be performed weekly (**solid grey lines**). If an escape criterion is met during the follow-up period, subjects may proceed directly to another pre-treatment visit.

Study Inclusion Criteria:

The subject will be considered eligible for the study if they meet **all** of the study inclusion criteria. Teduglutide treatment eligibility does not impact study eligibility.

1. Subject provides written informed consent (subject, parent or legal guardian and, as appropriate, informed assent) to participate in the study before completing any study-related procedures.
2. Subject completed the TED-C14-006 study (including subjects in the standard of care treatment arm).
3. Subject understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Study Exclusion Criteria: There are no exclusion criteria for this study.

Teduglutide Eligibility Criteria: Subjects are eligible for teduglutide treatment if at least one (≥1) of the teduglutide treatment inclusion criteria, and none of the teduglutide treatment exclusion criteria, are met. In addition, the investigator and the subject (and/or parent or legal guardian, as appropriate) must agree to proceed with treatment.

***Teduglutide Treatment Inclusion Criteria*:**

1. Subject is teduglutide-naïve, receiving PS, and unable to significantly reduce PS or advance enteral feeds

(eg, 10% or less change in PS or advance in feeds) for at least 3 months prior to and during the teduglutide pre-treatment visit, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PS returns to within 10% of baseline prior to the event.

2. Subject was previously treated with teduglutide and at least one of the following criteria is satisfied:
    a. Increasing PS requirements following teduglutide discontinuation.
    b. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
    c. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition following teduglutide discontinuation.
    d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
    e. Severe diarrhea related to teduglutide discontinuation.

Teduglutide Treatment Exclusion Criteria:

1. Body weight <10 kg at the pre-treatment visit.
2. Unresected gastrointestinal (GI) polyp, known polyposis condition, pre-malignant change, or malignancy, in the GI tract.
3. History of cancer in the previous 5 years except surgically curative skin cancers.
4. Serial transverse enteroplasty or other major intestinal surgery within 3 months preceding the teduglutide pre-treatment visit. Insertion of a feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, and endoscopic procedures are allowed.
5. Intestinal or other major surgery planned or scheduled to occur during the 28-week cycle.
6. Clinically significant intestinal stricture or obstruction.
7. Clinically significant, active or recurrent pancreatic or biliary disease.
8. Active, severe, or unstable, clinically significant hepatic impairment or injury, including the following laboratory values at the pre-treatment visit:
    a. Total bilirubin ≥2 × upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7 × ULN
    c. Alanine aminotransferase (ALT) ≥7 × ULN
9. Renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2 at the pre-treatment visit.
10. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, or patent ductus arteriosus (PDA) ligation.
11. Participation in a clinical study using an experimental drug (other than glutamine, Omegaven, or Smoflipid) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to the pre-treatment visit and for the duration of the 28-week cycle.
12. Treatment with analogs of glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2) (not including teduglutide), insulin-like growth factor-1 (IGF-1), or growth hormone, within 3 months preceding the teduglutide pretreatment visit.
13. Treatment with octreotide or dipeptidyl peptidase 4 (DPP-4) inhibitors within 3 months prior to the pre-treatment visit.
14. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
15. Known history of alcohol or other substance abuse within 1 year prior to the pre-treatment visit.

16. Pregnant or lactating female subjects.
17. Sexually active female subjects of child-bearing potential unwilling to use approved contraception during teduglutide treatment and for 30 days after the treatment period.
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.

Follow-up Period Escape Criteria: At the discretion of the investigator, the follow-up period may be interrupted and the subject may proceed directly to the pre-treatment visit, if ≥1 of the following criteria is met:

1. Increasing PS requirements following teduglutide discontinuation
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition 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.

Maximum duration of subject involvement in the study:

A subject will be considered enrolled in the study once the subject has provided signed consent, and meets all of the Study Inclusion Criteria. Subjects may participate in multiple NTT periods and/or multiple 28-week treatment cycles. The study will continue for at least 1 year, and until each subject has access (as needed) to teduglutide. The subject's maximum duration of participation is expected to be approximately 3 years. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing End of Study (EOS) visit.

- **Planned duration of no-teduglutide treatment periods**: variable, depending on disease course
- **Planned duration of the teduglutide pre-treatment visit:** 1 to 21 days
- **Planned cycle duration**: 28 weeks. Each cycle consists of 24 weeks of teduglutide treatment followed by a 4-week follow-up period (no treatment)

Endpoints and statistical analysis:

- The **safety population** will consist of all enrolled subjects. The safety population will be used for both safety and efficacy analysis.

Efficacy Endpoints

Efficacy endpoints will be analyzed at the end of each teduglutide treatment period (Week 24 or end of treatment [EOT]), and at each study visit, relative to the baseline of the core study (TED-C14-006) and/or first exposure to teduglutide. The following efficacy endpoints will be analyzed:

- Reduction in PS volume of at least 20%
- Absolute and relative change in PS volume
- Complete weaning off PS
- Change in days per week of PS

Health Economics and Outcomes Research Endpoints

Health economics and outcomes research endpoints will be analyzed at approximately 12-week intervals (Weeks 12 and 24 of each teduglutide treatment cycle, and every 12 weeks for subjects not on teduglutide), relative to the study baseline. The beginning of each treatment cycle (CxD1) will be an additional baseline.

- Change in Pediatric Quality of Life Inventory (PedsQL) score
- Change in PedsQL Family Impact Module score
- Change in PedsQL Gastrointestinal Symptoms Module Sub-Scales scores:
  - Food and Drink Limits
  - Diarrhea

Safety Endpoints

The following safety endpoints will be analyzed:

- Adverse events
- Vital signs, including temperature, heart rate, blood pressure
- Laboratory safety data (ie, clinical chemistry, hematology, and urinalysis)
- Urine output
- Stool output
- Antibodies to teduglutide
- Gastrointestinal-specific testing, including fecal occult blood testing and colonoscopy or sigmoidoscopy
- Z-scores for weight, height (or length), head circumference (up to 36 months of age), and body mass index

Statistical Methodology for Efficacy Analysis

No claims of statistical significance will be made; however, 95% confidence intervals will be provided, if applicable. Continuous variables, including those assessed on a discrete scale, 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.

Statistical Methodology for Safety Analysis

Safety data, including laboratory tests and vital signs assessments, will be summarized by visit. AEs will also be collected and summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data.

Sample Size Justification

As this is an extension study, the maximum number of subjects was determined by enrollment in TED-C14-006.

STUDY SCHEDULE(S)

Table 1-1: Schedule of Events Required for All Subjects

Period	Screening	End of Study or Early Termination
	Scr	EOS/ET
Visit Type	**Site**	**Site**
Informed consent/assent[a]	X	
Study eligibility	X	
Demographics, medical history[b], SBS history[c]	X	
Dispense intake and output diaries	X	
Evaluate teduglutide treatment inclusion criteria[d]	X	
Adverse events	X	X
Concomitant medications and GI procedures[e]	X	X
Physical examination and vital signs, including weight		X
Height and head circumference[f]		X
Review intake and output diaries[g]		X
Record PS prescription and adjust as needed[h]		X
Safety laboratory tests[i]		X
PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales		X
Antibodies to teduglutide[j]		X
Fecal occult blood testing[k]		(X)
Colonoscopy or sigmoidoscopy[l]		(X)
Pregnancy testing[m]		(X)

FOBT = fecal occult blood testing; FOCBP = female of child-bearing potential; EOS =end of study; ET=early termination; GI=gastrointestinal; NTx=no treatment;

PedsQL=Pediatric Quality of Life Inventory; PS=parenteral support; SBS=Short Bowel Syndrome; Scr =Screening.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

[a] Informed Consent (and informed assent, if applicable) must be obtained prior to performing any study-related procedures; consent (and informed assent, if applicable) may be obtained anytime during the Week 28 (or EOS) visit for the TED-C14-006 study. Subject will have approximately 7 days after completion of the TED-C14-006 study to sign consent to participate in the SHP633-304 study.

[b] Updates to the medical history will be collected, consisting of adverse events that were ongoing at the time of completion of TED-C14-006, and events that occurred during the period between completion of TED-C14-006 and informed consent to SHP-633-304.

[c] If the subject has any changes to the SBS history that had been collected at the baseline of the TED-C14-006, then the updated SBS history will be collected.

[d] Subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed to the pre-treatment visit if the investigator, subject, and parent or legal guardian agrees to proceed with teduglutide therapy (Table 1-3).

[e] Concomitant GI procedures include (but are not limited to) endoscopy, radiographic studies, GI and liver biopsies and associated pathology results.

[f] Head circumference will be measured in subjects 36 months of age and younger.

[g] The intake diary should be completed daily for a minimum of 2 weeks prior to the EOS/ET visit. The output diary should be completed daily over a 48-hour period of nutritional stability before the EOS/ET visit.

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

[i] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

[j] Required for all teduglutide-exposed subjects

[k] FOBT should be performed on teduglutide-exposed subjects on an annual basis, approximately every 48-60 weeks at a minimum.

[l] The need for colonoscopy/sigmoidoscopy in response to a positive FOBT during a no-teduglutide treatment period is at the discretion of the investigator, but all teduglutide-exposed subjects will undergo colonoscopy/sigmoidoscopy after they have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure), and subjects who continue to receive teduglutide will undergo colonoscopy/sigmoidoscopy at 5 year intervals or more often as needed. See Section 7.2.9 for details.

[m] Pregnancy testing is required for FOCBP at an ET visit if the subject has not had a pregnancy test at least 30 days after study drug discontinuation.

Table 1-2: Schedule of Events for Subjects Not Receiving Teduglutide

Visit Number	**NTx**
Visit Type	**Site**
Visit Frequency[a]	**Every 12 weeks**
Window (days)[b]	**±7**
Dispense intake and output diaries	X
Evaluate teduglutide treatment inclusion criteria[c]	X
Adverse events	X
Concomitant medications and GI procedures[d]	X
Physical examination and vital signs, including weight	X
Height and head circumference[e]	X
Review intake and output diaries[f]	X
Record PS prescription and adjust as needed[g]	X
Safety laboratory tests[h]	X
PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales	X
Antibodies to teduglutide[i]	(X)
Fecal occult blood testing[j]	Annually
Colonoscopy or sigmoidoscopy[k]	(X)
Serum sample[l]	Every 24 weeks

FOBT = fecal occult blood testing; NTT = no-teduglutide treatment; PedsQL = Pediatric Quality of Life Inventory; PS= parenteral support; TED = teduglutide.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

[a] The first NTx visit following the screening visit must occur within 2 to 12 weeks of screening.

[b] Window is relative to the first NTx visit in the current no-teduglutide treatment period.

[c] Subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed to the pre-treatment visit if the investigator, subject, and parent or guardian agree to proceed with teduglutide therapy (Table 1-3).

[d] Concomitant GI procedures include (but are not limited to) endoscopy, radiographic studies, GI and liver biopsies and associated pathology results.

[e] Head circumference will be measured in subjects 36 months of age and younger.

[f] Intake diaries will collect actual PS volume and hours per day, completed daily for a minimum of 2 weeks prior to each study visit (see Section 7.2.11.2). Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit (see Section 7.2.11.3 for more detail).

[g] PS 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.

[h] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

[i] Subjects who have been treated previously and test positive for teduglutide antibodies should have follow-up samples collected every 12 weeks during the study until a negative result is obtained.

[j] FOBT should be performed on teduglutide-exposed subjects on an annual basis, approximately every 48-60 weeks at a minimum.

[k] The need for colonoscopy/sigmoidoscopy in response to a positive FOBT during a no-teduglutide treatment period is at the discretion of the investigator, but all teduglutide-exposed subjects will undergo colonoscopy/sigmoidoscopy after they have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) and subjects who continue to receive teduglutide will undergo colonoscopy/sigmoidoscopy at 5 year intervals or more often as needed. See Section 7.2.9 for details.

[l] Lack of collection of serum samples will not constitute a protocol deviation.

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	Pre-treatment	Teduglutide Treatment															Follow-up	
Visit Number	**Px[a]**	**Cx D1**	**Cx W1**	**Cx W2**	Phone contact is required approximately 1 week after PS adjustment	**Cx W4**	Phone contact is required approximately 1 week after PS adjustment	**Cx W6**	Phone contact is required approximately 1 week after PS adjustment	**Cx W9**	Phone contact is required approximately 1 week after PS adjustment	**Cx W12**	Phone contact is required approximately 1 week after PS adjustment	**Cx W16**	Phone contact is required approximately 1 week after PS adjustment	**Cx W20**	Phone contact is required approximately 1 week after PS adjustment	**CxW24 (EOT)**	**CxW25 CxW26 CxW27**	**CxW28[c]**
Visit Type	**Site**	**Site**	**Site**	**Site**		**Site**		**Site**		**Site**		**Site**		**Site**		**Site**		**Site**	**Phone[b]**	**Site**
Cycle Day	**-21 to 0**	**1**	**8**	**15**		**29**		**43**		**64**		**85**		**113**		**141**		**169**	**176 183 190**	**197**
Window (days)[d]	-21 to 0		**±2**	**±2**		**±2**		**±2**		**±4**		**±4**		**±4**		**±4**		**±4**	**±2**	**±2**
Evaluate teduglutide eligibility (inclusion and exclusion) criteria	X	X[e]																		
Dispense intake and output diaries	X	X	X	X		X		X		X		X		X		X		X		X
Adverse events	X	X	X	X		X		X		X		X		X		X		X	X	X
Concomitant medications and GI procedures[f]	X	X	X	X		X		X		X		X		X		X		X	X	X
Physical examination and vital signs, including weight	X	X	X	X		X		X		X		X		X		X		X		X
Height and head circumference[g]	X	X										X						X		
Review intake and output diaries[h]	X	X	X	X		X		X		X		X		X		X		X	X	X
Record PS Rx and adjust as needed[i]	X	X	X	X		X		X		X		X		X		X		X	X	X
Safety laboratory tests[j]	X[j]	X	X	X		X		X		X		X		X		X		X	(X)	X
PedsQL Generic Core Scale/ Family Impact Module/ GI Symptoms Module Sub-Scales		X										X						X		
Antibodies to teduglutide[k]		X										X						X		X
Fecal occult blood testing	X											X						X		
Colonoscopy/ sigmoidoscopy[l]	(X)											(X)						(X)		
Pregnancy testing[m]	X	X				X				X		X		X		X		X		X

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	Pre-treatment	Teduglutide Treatment																Follow-up	
Serum sample[n]	X																X		
Evaluate escape criteria[o]																		X	X
Dispense study drug[p]		X	X	X		X		X		X		X		X		X			

EOS = end of study; EOT = end of treatment; ET = early termination; FOBT = fecal occult blood test; FOCBP = female of child-bearing potential; FU = follow-up; GI = gastrointestinal; PedsQL = Pediatric Quality of Life Inventory; PS= parenteral support; SBS = Short Bowel Syndrome; SC = subcutaneous; Scr = Screening; TED = teduglutide; Tx = treatment.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

[a] If the first pre-treatment visit (P1) follows the screening visit, it must occur within 12 weeks of screening.

[b] Phone visits are required approximately 1 week after adjustments in PS. The assessments to be performed at phone visits are the same as those described for CxW25-27 (except for evaluation of escape criteria).

[c] The investigator may combine the CxW28 visit with the next pre-treatment visit if at least one escape criterion is met at the CxW28 visit, and the pre-treatment assessments occur within 7 days of the CxW28 visit. If a subject is completing the study at the CxW28 visit, the EOS/ET visit (Table 1-1) will take place in lieu of the CxW28 visit.

[d] Visit windows are relative to the CxD1 visit.

[e] Eligibility will need to be re-confirmed prior to the first dose in the cycle. Negative urine pregnancy test is required prior to the first dose of teduglutide, but results of other labs obtained at the CxD1 visit are not required to determine teduglutide treatment eligibility.

[f] Concomitant GI procedures include (but are not limited to) endoscopy, radiographic studies, GI and liver biopsies and associated pathology results.

[g] Head circumference will be measured in subjects 36 months of age and younger.

[h] Intake diaries will collect actual PS volume and hours per day. Intake diaries should be completed daily for a minimum of 2 weeks immediately prior to each clinic visit (except at pre-treatment visit), for 1 week following PS adjustment, and daily during the 4-week follow-up period. 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 PS prescription. See Section 7.2.11 for more detail.

[i] PS 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.

[j] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Clinical chemistry and urinalysis must also be performed within approximately 5-7 days of any adjustment to the PS prescription. Safety labs performed between clinic visits may be performed locally. Unscheduled lab results will not be captured in the eCRFs. If abnormal results are considered an adverse event, an AE form will be completed. Collect PT/INR at the pre-treatment visit. Additional collection will occur if a potential drug-induced liver injury signal is observed. Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

[k] Samples collected on CxD1 must be drawn prior to first administration of teduglutide. Samples collected while subjects are receiving teduglutide (CxW12 and CxW24) must be drawn at least 14 hours after dosing.

[l] The teduglutide-naïve subjects age 12 and older will undergo colonoscopy/sigmoidoscopy at the pre-treatment visit if one has not been performed within 1 year. Subjects of any age with newly positive FOBT results at the pre-treatment visit for which a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy/sigmoidoscopy prior to receiving teduglutide. If newly positive FOBT results (for which a readily detectable cause cannot be identified) are obtained at the end of a teduglutide treatment cycle (CxW24/EOT), colonoscopy/sigmoidoscopy will be performed. The need for colonoscopy/sigmoidoscopy in response to positive FOBTs at CxW12 is at the discretion of the investigator. Teduglutide-exposed subjects who have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) will undergo

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	Pre-treatment	Teduglutide Treatment	Follow-up

colonoscopy/sigmoidoscopy. See Section 7.2.9 for details.

[m] A serum pregnancy test is performed on all FOCBP at the teduglutide pre-treatment visit (when the pre-treatment and screening visits are combined, the serum pregnancy test should be performed at the local laboratory). Urine pregnancy tests will be administered at all other visits according to the study schedules, or if pregnancy is suspected, or as specified per protocol upon withdrawal of the subject from the study.

[n] Lack of collection of serum samples will not constitute a protocol deviation.

[o] If escape criteria are met, the subject may proceed directly to another pre-treatment visit at the discretion of the investigator.

[p] The first SC injection of teduglutide in treatment-naïve subjects will be administered under the supervision of the investigator/designee after which the subject will be observed for hypersensitivity reactions for at least 4 hours. The site of administration (arm, thigh, abdomen) of the first teduglutide dose must be specified and recorded in the eCRF. See Section 6.2.3 for dose adjustment.

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

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. It is estimated that, at most, there are a few hundred pediatric subjects 1 year and older with SBS (Khan et al., 2015; Wales et al., 2004). 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. Although the small intestine is capable of remarkable adaptation, excessive loss of absorptive surface area or specialized functions can lead to dependence on parenteral nutrition or intravenous (IV) fluids (parenteral support [PS]). Treatment of both pediatric and adult patients is focused on achieving adequate intestinal absorption to allow for minimization or discontinuation of PS. About 30% of infants with SBS become independent of PS requirements within 12 months of the initial insult, and an additional 10% wean off PS within 24 months. After this time, linear intestinal growth slows. About 60% of pediatric subjects with SBS are able to become independent of PS within 5 years of the initial diagnosis (Khan et al., 2015). Nevertheless, despite optimal medical management, many pediatric subjects remain dependent on PS. Complications of long-term PS include liver disease, catheter-related blood stream infections, central line-associated venous thrombosis and dwindling central venous access. Sepsis is the leading cause of death in these patients and quality of life is poor (Squires et al., 2012). Accelerating the adaptive process and achieving enteral autonomy is an urgent goal for all patients with SBS who are dependent on PS (Khan et al., 2015; Squires et al., 2012).

Intestinal adaptation is driven by hormonal cues in response to nutrient malabsorption (Drucker and Yusta, 2014). Chief among these is hormones glucagon-like peptide 2 (GLP-2), which is secreted from L-type enteroendocrine cells that reside in the intestinal epithelium in the ileum and colon. Resection of these regions may impair the adaptive response by limiting endogenous production of GLP-2.

1.2 Product Background

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-IV (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$) in adults of approximately 2 hours 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). The European Commission granted a centralized marketing authorization valid throughout the European Union (EU) for teduglutide (Revestive™) on 30 August 2012 and a New Drug Application (NDA) for teduglutide (Gattex®) was approved by the United States (US) Food and Drug Administration (FDA) on 21 December 2012 for the treatment of adult patients with SBS who are dependent on PS. Teduglutide has also been approved for use in adult patients with SBS in Canada and Switzerland. On 29 Jun 2016, the

European Commission granted an extension of the Market Authorization for teduglutide (REVESTIVE™) for the treatment of patients aged 1 year and above with SBS; patients should be stable following a period of intestinal adaptation.

1.3 Clinical Studies with Teduglutide in Pediatric Subjects

One Phase 3 study, TED-C13-003, was completed in pediatric SBS subjects in the US and United Kingdom (UK). In this study, teduglutide was administered to 3 cohorts of pediatric subjects from ages 1-17. 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 PS volume at Week 12 of 37%, including complete independence from PS 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 PS volume at Week 12 of 39%, including complete independence from PS 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 (TESAEs) related to teduglutide were reported. No discontinuations from study were due to adverse events (AEs).

TED-C14-006 is an ongoing study which includes 2 treatment arms: a teduglutide treatment arm and a standard of care treatment arm. Subjects in both arms participate in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the screening period, subjects will choose into which arm to enroll. During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide treatment arm will receive daily subcutaneous (SC) injections of teduglutide (study drug) in addition to standard medical therapy. The subjects enrolling in the teduglutide treatment arm will be 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.

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 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects with SBS who completed the TED-C14-006 study. In addition to evaluating the long-term safety and durability of efficacy after 24 weeks of treatment, this extension study will evaluate the need for additional teduglutide treatment in these subjects, and will allow for the first-time treatment of teduglutide-naïve subjects who participated in the SOC treatment arm in TED-C14-006.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objective of the study is to evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with SBS who completed TED-C14-006.

2.2.2 Secondary Objectives

The secondary objective of this study is to evaluate the long-term efficacy of teduglutide treatment in pediatric subjects with SBS who completed TED-C14-006.

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects who completed the TED-C14-006 study (core study). At the time of entry into the TED-C14-006 study, subjects were less than 18 years of age, were dependent on parenteral nutrition to provide at least 30% of their caloric or fluid needs, and had not been able to significantly reduce PS for at least 3 months prior to enrollment. During the core study, pediatric subjects in the teduglutide treatment arm were randomized to 0.025 mg/kg or 0.05 mg/kg once daily (QD) dosing in a double-blinded manner. The TED-C14-006 study will also be referred to as the core study interchangeably throughout this protocol.

Approximately 34 subjects who complete the core study are expected to enroll in this extension study. Subjects who previously received teduglutide during TED-C14-006, as well as subjects who were in the SOC treatment group, may be eligible to receive teduglutide treatment in this extension study. To be eligible, subjects must meet ≥1 of the teduglutide treatment inclusion criteria and none of the teduglutide treatment exclusion criteria.

Additional Teduglutide Treatment

Subjects not receiving teduglutide treatment (ie, in a "no-teduglutide treatment period"), will be seen approximately every 12 weeks for safety, parenteral support (PS) requirements, and quality of life. At any point during a no-teduglutide treatment period, subjects who meet ≥1 *teduglutide treatment inclusion* may proceed directly to the pre-treatment visit if the investigator, subject, and parent agree to proceed with teduglutide therapy.

Rationale: Some pediatric subjects may have a durable beneficial effect after 24 weeks of teduglutide treatment and thus long-term follow-up without additional teduglutide treatment may be appropriate. However, there may be some pediatric subjects who deteriorate or stop improving after discontinuation of teduglutide treatment. In these pediatric subjects, additional teduglutide treatment may be beneficial.

Dose Selection

Analysis suggested that pediatric patients, ages 1 to 17 years old, are likely to require the same dose as used in adults, namely 0.05 mg/kg/day (Mouksassi et al., 2009). In this extension study to TED-C14-006, repeat doses of teduglutide 0.05 mg/kg QD will be administered to eligible pediatric subjects who previously received teduglutide 0.05 or 0.025 mg/kg in Study TED-C14-006.

Rationale: Teduglutide is approved for adult use in the US and EU, and for pediatric use in the EU, at a dose of 0.05 mg/kg SC once daily. The completed 12-week pediatric 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. In addition, population pharmacokinetic modeling and simulations were conducted to determine the effective 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 the pediatric study (TED- C13- 003) and suggested that the dose in pediatric subjects is likely to be same as the dose in adults (O'Keefe et al., 2006).

Duration of Treatment

The duration of teduglutide treatment in this study mirrors that of the TED-C14-006 study, consisting of 24 weeks of teduglutide treatment, followed by a 4-week follow-up period. The follow-up period is a mechanism to evaluate whether continued teduglutide is needed. If a subject deteriorates during the follow-up period, the subject may be evaluated immediately for additional teduglutide treatment. Subjects who clinically deteriorate or stop improving at any time after the end of the follow-up period will also be assessed for additional treatment.

Rationale: During the teduglutide treatment cycle, visit frequency is similar to frequencies performed in TED-C13-003 and TED-C14-006, to ensure sufficient safety monitoring and weaning of PS. During the no-teduglutide treatment, visits occur every 12 weeks, a frequency that is consistent with standard medical practices.

Measures and Parameters

Following the review and signing of the informed consent (and informed assent, if applicable), screening visit procedures will begin including demographics, and updates to medical history and SBS history. Subjects who meet ≥1 of the teduglutide treatment inclusion criteria may proceed to the pre-treatment visit.

After the pre-treatment visit, subjects who still meet ≥1 of the teduglutide treatment inclusion criteria, and meet none of the teduglutide treatment exclusion criteria, will start a 28-week cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily, followed by a 4-week follow-up (no treatment) period (Figure 3-1). During the 28-week cycle, clinic visits will occur at weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period (between weeks 1-24), and weekly during the teduglutide follow-up period (between weeks 24 and 28).

Safety and PS requirements will be evaluated on a weekly basis, and quality of life assessments will be made approximately every 12 weeks. 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, all attempts should be made to follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) for decisions regarding PS reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines, however, is not considered a protocol deviation (Appendix 2).

Rationale: Measures of long term safety will include adverse events, growth parameters and anti-drug antibodies. Measure of long term efficacy will include durability of effect as measured by reduction in PS and improvement in pediatric quality of life measures (PedsQL, PedsQL Family Impact Module). A reduction in PS volume of at least 20% at end of treatment (EOT) was used as the primary endpoint in pivotal phase 3 adult clinical trials and the completed phase 3 pediatric study (TED-C13-003), and will be used as an endpoint in this extension study. In previous clinical studies, a reduction of this magnitude was associated with a reduction in the number of days per week of PS, and increases in enteral intake. Reduction in volume and time of PS due to improved enteral absorption may provide a pediatric subject with opportunities for more age-appropriate activities including oral rehabilitation. Quality of life assessments will be performed in this study to quantitate this effect.

Teduglutide has been found to have a targeted intestinotrophic effect. Taking into account the patient population and the pharmacologic effect of teduglutide, GI-specific screening tests, including fecal occult blood testing and colonoscopy/sigmoidoscopy, which are commonly part of the routine care of these subjects, will be performed to ensure safety. This study captures long-term safety data on polyps and other colonic mucosal changes in teduglutide-exposed subjects using the surveillance strategy proposed in Section 7.2.9.

Figure 3-1: Study Design Flow Chart

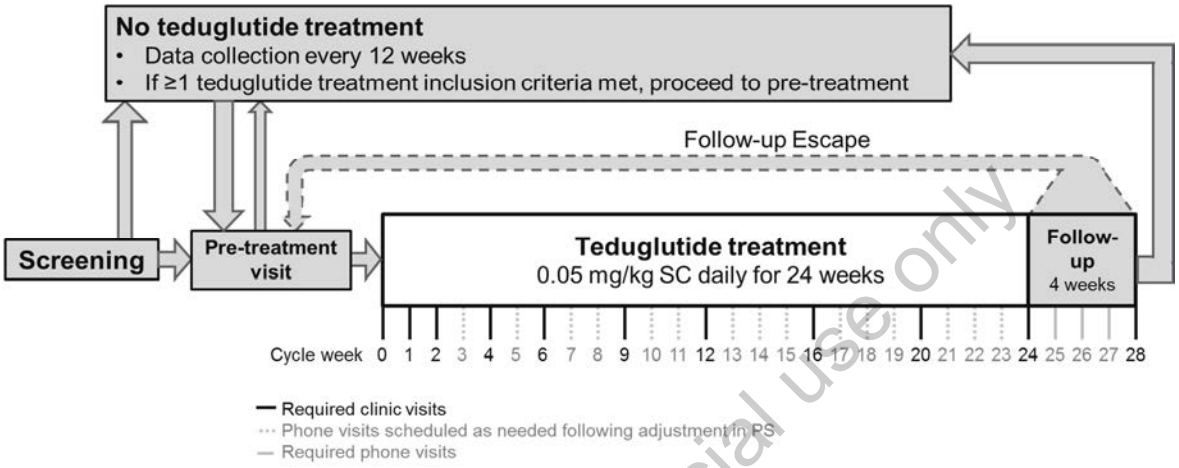

Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pre-treatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects will enter a 28-week teduglutide cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24 (**solid black lines**). Phone visits are required approximately 1 week after adjustments in PS during the intervening weeks between weeks 2 and 24 (**dashed grey lines**). Subjects discontinue teduglutide at week 24 and enter a 4-week follow-up (no-treatment) period, during which phone visits will be performed weekly (**solid grey lines**). If an escape criterion is met during the follow-up period, subjects may proceed directly to another pre-treatment visit.

3.2 Duration and Study Completion Definition

A subject will be considered enrolled in the study once the subject has provided signed consent, and meets all of the Inclusion Criteria. The study will continue for at least 1 year and until each subject has access, as needed, to teduglutide. The subject's maximum duration of participation is expected to be approximately 3 years. The study will be completed in approximately 40 months. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing the End of Study (EOS) visit.

The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact (last safety contact), whichever is later. The study completion date will be used to ascertain timing for study results posting and reporting.

4 STUDY POPULATION

Each subject must review and sign the informed consent (and informed assent, if applicable) before any study-related procedures specified in the protocol are performed. Teduglutide treatment eligibility does not impact study eligibility.

4.1 Study Inclusion Eligibility Criteria

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

1. Subject provides written informed consent (subject, parent or legal guardian and, as appropriate, subject informed assent) to participate in the study before completing any study-related procedures.
2. Subject completed the TED-C14-006 study (including subjects in the standard of care treatment arm).
3. Subject understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.2 Study Exclusion Eligibility Criteria

There are no exclusion criteria for this study.

4.3 Teduglutide Eligibility Criteria

Subjects are eligible for teduglutide treatment if at least 1 (≥1) of the teduglutide treatment inclusion criteria, and none of the teduglutide treatment exclusion criteria are met. In addition, the investigator and the subject (and/or parent or legal guardian, as appropriate) must agree to proceed with treatment.

4.4 Teduglutide Treatment Inclusion Criteria

1. Subject is teduglutide-naïve, receiving PS, and unable to significantly reduce PS or advance enteral feeds (eg, 10% or less change in PS or advance in feeds) for at least 3 months prior to and during the teduglutide pre-treatment visit, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PS returns to within 10% of baseline prior to the event.
2. Subject was previously treated with teduglutide and at least 1 of the following criteria is satisfied:
    a. Increasing PS requirements following teduglutide discontinuation.
    b. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
    c. Deteriorating nutritional status eg, weight loss or growth failure) despite maximal tolerated enteral nutrition following teduglutide discontinuation.
    d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
    e. Severe diarrhea related to teduglutide discontinuation.

4.5 Teduglutide Treatment Exclusion Criteria

1. Body weight <10 kg at the pre-treatment visit.
2. Unresected GI polyp, known polyposis condition, pre-malignant change, or malignancy, in the GI tract
3. History of cancer in the previous 5 years except surgically curative skin cancers
4. Serial transverse enteroplasty or other major intestinal surgery within 3 months preceding the teduglutide pre-treatment visit. Insertion of a feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, and endoscopic procedures are allowed.
5. Intestinal or other major surgery planned or scheduled to occur during the 28-week cycle
6. Clinically significant intestinal stricture or obstruction
7. Clinically significant, active or recurrent pancreatic or biliary disease
8. Active, severe, or unstable, clinically significant hepatic impairment or injury, including the following laboratory values at the pre-treatment visit:
    a. Total bilirubin ≥2 × upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7 × ULN
    c. Alanine aminotransferase (ALT) ≥7 × ULN
9. Renal dysfunction shown by results of an estimated glomerular filtration rate (eGFR) below 50 mL/min/1.73 m^2 at the pre-treatment visit
10. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, or patent ductus arteriosus (PDA) ligation
11. Participation in a clinical study using an experimental drug (other than glutamine, Omegaven, or Smoflipid) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to the pre-treatment visit and for the duration of the 28-week cycle
12. Treatment with analogs of glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2) (not including teduglutide), insulin-like growth factor-1 (IGF-1), or growth hormone, within 3 months preceding the teduglutide pretreatment visit.
13. Treatment with octreotide or dipeptidyl peptidase 4 (DPP-4) inhibitors within 3 months prior to the pre-treatment visit
14. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients
15. Known history of alcohol or other substance abuse within 1 year prior to the pre-treatment visit
16. Pregnant or lactating female subjects
17. Sexually active female subjects of child-bearing potential unwilling to use approved contraception during teduglutide treatment and for 30 days after the treatment period

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.

4.6 Follow-up Period Escape Criteria

At the discretion of the investigator, the follow-up period may be interrupted and the subject may proceed directly to the pre-treatment visit, if ≥1 of the following criteria is met:

1. Increasing PS requirements following teduglutide discontinuation.
2. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition 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.

4.7 Reproductive Potential

4.7.1 Female Contraception

To be eligible for treatment with teduglutide, sexually active females of child-bearing potential must use an acceptable form of contraception throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used, they should be administered according to the package insert. Females of child-bearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of investigational product.

To be eligible for treatment with teduglutide, female pediatric subjects and adolescent subjects should be either:

- Pre-menarchal and either Tanner Stage 1 or less than age 9 years, or
- Females of child-bearing potential (FOCBP) with a negative serum beta-human chorionic gonadotropin (β-HCG) pregnancy test at the teduglutide pre-treatment visit**.** Females of child-bearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- True abstinence: Abstention of sexual activity that is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).
- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)

- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the pre-treatment visit, plus condoms. Note: if subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.8 Discontinuation of Subjects

4.8.1 Teduglutide Discontinuation

If the investigational product is discontinued prematurely during a teduglutide treatment cycle and the subject wishes to remain in the study, the evaluations listed for the EOT visit are to be performed. A 4-week follow-up period will ensue, consisting of weekly telephone visits (CxW25-27) and the week 28 clinic visit (CxW28). The subject would then enter a no-teduglutide treatment (NTT) period and could be evaluated for subsequent teduglutide treatment eligibility according to the study schedules. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for permanent treatment discontinuation, dates of investigational product administered (including last date of treatment), and amount of investigational product taken must be recorded in the electronic case report form (eCRF) and source documents, as described in Section 4.8.3. The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor, when possible.

4.8.2 Study Withdrawal

At any time during the study, the investigator or sponsor may withdraw a subject, or a subject may withdraw from the study, for any reason, without prejudice to their future medical care by the physician or at the institution.

If a subject withdraws from the study during a teduglutide cycle, the evaluations listed for the EOT visit are to be performed as completely as possible. Whenever possible, the subject will then be asked to return 4 weeks later for the early termination (ET) visit, and will be contacted weekly by phone during the interim period between EOT and ET for safety follow-up.

If a subject withdraws from the study during a NTT period, the evaluations listed for the ET visit are to be performed as soon and completely as possible.

Subjects who withdraw from the study will not be replaced.

4.8.3 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
- Protocol deviation

- Lack of efficacy
- Physician decision
- Withdrawal by subject
- Withdrawal by parent/guardian
- Lost to follow-up
- Pregnancy (Discontinuation of treatment only)
- Death
- Other

4.8.3.1 Subjects 'Lost to Follow-up' Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact 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 CONCOMITANT TREATMENT

5.1 Concomitant Medications and GI Procedures

Concomitant treatment refers to all treatment taken between the dates of informed consent and EOS, inclusive. Concomitant treatment information must be recorded on the appropriate eCRF page. Concomitant treatments will be assessed at each site visit, and include all non-study treatments (medications, herbal treatments, vitamins, invasive and diagnostic procedures). Concomitant GI procedures include (but are not limited to) endoscopy, radiographic studies, GI and liver biopsies and associated pathology results. Concomitant treatment information must be recorded on the appropriate eCRF page. Details of medication changes and/or dosages will be recorded on the eCRF.

The mechanism of action of teduglutide may increase absorption of drugs (eg, motility medication including narcotics and opioids used for the management of SBS, warfarin, psychotropics, metronidazole, and digoxin). Accordingly, due consideration should be given to modifying concomitant medication regimens. Down-titration of concomitant medications should be considered when drugs, especially those with a narrow therapeutic range, are prescribed at dosages that are higher than usual.

5.1.1 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.1.2 Prohibited Treatment

The mechanism of action of teduglutide may increase enteral absorption of drugs (eg, motility medication including narcotics and opioids used for the management of SBS, warfarin, psychotropics, metronidazole, digoxin), so consideration should be given to modifying concomitant enteral medication regimens. Down-titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic range, are given at dosages that are higher than usual.

The following medications are prohibited during teduglutide treatment and within the provided timeframe prior to the pre-treatment visit:

Table 5-1: Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pre-Treatment Visit
Native/synthetic glucagon-like peptide-2 (not-including teduglutide)	Any
Glucagon-like peptide-1 analog or human growth hormone	3 months
Octreotide or dipeptidyl peptidase 4 inhibitors	3 months
Biological therapy (eg, antitumor necrosis factor)	6 months

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is teduglutide, which 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 SHP633 investigator's brochure.

6.1.1 Blinding the Treatment Assignment

Not applicable for this open-label study.

6.2 Administration of Investigational Product(s)

6.2.1 Interactive Response Technology for Investigational Product Management

An interactive web-based response system (IWRS) will be used for screening and enrolling subjects, recording subject visits, investigational product supply dispensation and management, inventory management and supply ordering, investigational product expiration tracking and management, and return of investigational product. Please refer to the Study Manual for additional details regarding the IWRS.

The IWRS will also be used for creating, tracking, and confirming investigational product shipments. A user manual with specific functions and instructions for the IWRS will be provided to the site, and site personnel will receive training.

6.2.2 Allocation of Subjects to Treatment

This is an open-label study. Subjects will retain their assigned subject number from the TED-C14-006 study. Assessment of need for teduglutide treatment should be guided by the teduglutide treatment inclusion criteria. If the investigator, subject, and/or parent/guardian agree to proceed with treatment, a formal evaluation of teduglutide inclusion and exclusion criteria will be performed at the pre-treatment visit (Table 1-3).

6.2.3 Dosing

If teduglutide treatment eligibility is established at the pre-treatment visit and again, confirmed at the CxD1 visit, the subject will start a teduglutide treatment period, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily. The initial dose will be calculated based on body weight measured at the teduglutide pre-treatment visit, and adjusted as needed, based on body weight measured at Week 12 (CxW12). 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 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 rotated.

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 each 24-week teduglutide 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. At any time during the follow-up period, if escape criteria are met, the subject may proceed directly to another Pre-Treatment visit to assess treatment eligibility for another cycle (Section 4.6). Following the completion of the 4-week follow-up, the subject will continue in the study off teduglutide. Additional 28-week cycles may be repeated if treatment eligibility is established each time.

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification will be applied to the investigational product(s) container.

The study drug will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of study drug will be supplied and these will be labeled in accordance with applicable regulatory requirements. Sterile water for injection syringes and other ancillary components will be provided separately and will be labeled in accordance with the applicable regulatory requirements.

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

6.3.2 Packaging

Investigational product is packaged in the following conditions:

Teduglutide will be provided in a sterile, single-use, glass vial as a lyophilized powder, to be reconstituted with 0.5 mL sterile water for injection provided as the diluent in a prefilled syringe.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 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.

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

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. The investigator is to keep a current record of the inventory and dispensation of all clinical supplies. This record will be made available to the sponsor's site monitor for the purpose of accounting for all clinical supplies. Any discrepancy or deficiency will be recorded and will include an explanation. All supplies sent to the investigator must be accounted for and in no case will clinical supplies be used in any unauthorized situation.

The investigator has overall responsibility for administering/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 (as documented by the investigator in the applicable study delegation of authority form) will dispense the investigational product only to subjects eligible

for teduglutide treatment following the procedures set out in the study protocol. All dispensed study medication will be documented in the interactive response technology system and/or other investigational product record (eg, investigation product accountability form). The investigator is responsible for assuring the retrieval of all study supplies from subjects.

All used and unused study drug vials must be returned by the subjects and/or parent/guardian, and will be retained at the site. If deemed appropriate, the investigator or his/her designee may dispense the unused study drug vials to the same subject. All original containers, whether empty or containing study drug will be returned to the pharmacy. Returned study drugs will NOT be relabeled or reassigned for use by other subjects. Contents of the study drug containers will not be combined. All used and unused vials must be returned to the distribution center according to the sponsor's instruction. No vial/kit may be destroyed on site without approval by the sponsor.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

Subjects will be instructed to bring their unused investigational product and empty/used investigational product packaging to every visit. Drug accountability will be assessed 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. The pharmacist/nominated person will record details on the drug accountability form.

Of those subjects eligible for teduglutide treatment, 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 Schedule of Assessments (Table 1-1, Table 1-2, and Table 1-3) and must be referred to in conjunction with the instructions provided in this section.

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 (and assent, as applicable) from the subject. A subject will have approximately 7 days, after completion of the TED-C14-006 study, to sign consent to participate in the SHP633-304 study. The first visit after screening must occur within 12 weeks of screening for a pre-treatment visit, and within 2 to 12 weeks of screening for an NTx visit.

The screening visit (Scr) assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1-1, and as detailed below:

- Informed consent, and informed assent (if applicable), is obtained
- Study eligibility is determined. A screen failure is a subject who has given informed consent and failed to meet the Study Inclusion Eligibility Criteria. Subjects cannot be rescreened once they have been designated as a screen failure.
- Demographics, updates to medical history and SBS history
- Intake and output diaries are dispensed
- Evaluate teduglutide treatment inclusion criteria
- Adverse events, concomitant medications and concomitant GI procedures

7.1.2 Visits for Subjects Not Receiving Teduglutide

While outside of the 28-week teduglutide-treatment cycle, subjects will be followed approximately every 12 weeks for safety and efficacy assessments. No-teduglutide treatment visits are numbered sequentially (NT1, NT2, etc.), even if interrupted by the treatment cycles. The visit window (±7 days) is relative to the first NTx visit in the current NTT period. Assessments will be performed as outlined in Table 1-2 and described below.

- Intake and output diaries are dispensed
- Evaluate teduglutide treatment inclusion criteria
- Adverse events, concomitant medications and concomitant GI procedures
- Physical examination and vital signs, including weight

- Height and head circumference
- Review intake and output diaries
- Record PS prescription and adjust as needed
- Safety Laboratory Tests (ie, clinical chemistry, hematology, and urinalysis)
- PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales
- Antibodies to teduglutide, if and when required
- Fecal occult blood testing, as indicated (Section 7.2.9.1)
- Colonoscopy/sigmoidoscopy, as indicated (see Section 7.2.9.2)
- Serum sample, as indicated

Teduglutide treatment may be considered at any time during the NTT period. If the investigator and the subject (and parent or legal guardian, as appropriate) agrees to proceed with treatment if the subject is eligible, the subject may proceed to the pre-treatment visit immediately to determine eligibility.

7.1.3 Visits for Subjects Receiving Teduglutide

7.1.3.1 Pre-treatment Visit

Subjects who meet at least 1 of the teduglutide treatment inclusion criteria during the screening visit or during the NTT period may proceed to the pre-treatment visit immediately if the investigator, subject and parent agree to proceed with teduglutide therapy. Similarly, subjects who meet escape criteria during the teduglutide follow-up period may proceed to the pre-treatment visit immediately.

The pre-treatment visit may also be combined with screening visit, and if the pre-treatment visit assessments occur within 7 days of the TED-C14-006 EOS visit (Week 28), both sets of assessments can be combined. A subject must have 2 weeks of intake diary data collected, prior to the first dose administration (CxD1) during any teduglutide treatment cycle. In general, pre-treatment assessments may occur over a period of up to 21 days. The teduglutide pre-treatment visit (Px) assessments and procedures will be performed as in Table 1-3 and as described below:

- Evaluate teduglutide eligibility (treatment inclusion/exclusion criteria)
- Dispense intake and output diaries
- Adverse events, concomitant medications and concomitant GI procedures
- Fecal occult blood testing

- Gastrointestinal-specific testing, including colonoscopy or sigmoidoscopy as indicated
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries
- Record PS prescription and adjust as needed.
- Safety Laboratory Tests
  (In addition to clinical chemistry, hematology, and urinalysis, labs at this visit include prothrombin time [PT] international normalized ratio [INR]. Subsequent prothrombin time/international normalized ratio (PT/INR) measurement is only required to evaluate for suspected drug-induced liver injury [DILI]).
- Serum pregnancy testing (when the pre-treatment and screening visits are combined, the serum pregnancy test should be performed at the local laboratory)
- Serum sample

7.1.3.2 Teduglutide Treatment Period (CxD1-CxW24)

The open-label teduglutide treatment period will comprise 24 weeks, during which all assessments and procedures listed for Visits CxD1-CxW24 in Table 1-3 shall be completed. Cycles are numbered sequentially, such that the first visit of the first cycle is C1D1, and the first visit of the second cycle is C2D1, etc. Visit windows are calculated based upon the date of first investigational product administration (Visit CxD1).

Visit CxD1

Assessments and procedures at this visit will be performed as outlined Table 1-3 and as described below.

Two weeks of intake diary data are required before drug is administered at CxD1.

- Confirm teduglutide treatment eligibility
- Dispense intake and output diaries
- Adverse events, concomitant medications and concomitant GI procedures
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries
- Record PS prescription and adjust as needed

- Safety laboratory tests
- Quality of life measurements
- Antibodies to teduglutide
- Pregnancy testing (urine)
- Dispense study drug

Site Visits during Teduglutide Treatment Period

Subjects will return for clinic visits on cycle weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24/EOT. Assessments and procedures at these visits will be performed as outlined in Table 1-3 and as described below:

- Dispense/review intake and output diaries (every effort should be made to complete 2 weeks of intake diary entries prior to each clinic visit and to complete 48 hours of output diary entries during a period of nutritional stability prior to each clinic visit)
- Physical examination and vital signs, including weight
- Record PS prescription and adjust as needed
- Safety laboratory tests
- Urine pregnancy testing for FOCBP (CxW4, CxW9, CxW12, CxW16, CxW20, CxW24)
- Study drug dispensation (except for CxW24)
- Adverse events, concomitant medications and concomitant GI procedures

In addition, at CxW12 and CxW24 Visits **ONLY**, the following procedures will be performed:

- Height and head circumference
- Antibodies to teduglutide
- Fecal occult blood testing (FOBT)
- GI-specific testing, including colonoscopy or sigmoidoscopy as indicated
- Quality of life measurements

At CxW24 **ONLY**, a serum sample is collected and stored for future analysis. This sample will not be used for genetic testing and lack of collection will not constitute a protocol deviation.

PHONE VISITS

Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period. Phone visit assessments and procedures are outlined in Table 1-3 and described below:

- Review intake and output diaries
- Safety laboratory tests (clinical chemistry and urinalysis)
- Record PS prescription and adjust as needed
- Obtain AEs, concomitant medications, and concomitant GI procedures
- Evaluate escape criteria

7.1.4 Teduglutide Follow-up Period

The safety follow-up period for this protocol is 4 weeks (Weeks 25 – 28 of the cycle). Phone visits will occur on cycle weeks 25, 26, and 27 for all subjects. Phone visit assessments and procedures at weeks 25-27 will be the same as for telephone visits performed during the teduglutide treatment period. In addition, subjects will be evaluated for follow-up period escape criteria. If escape criteria are met at any time during the follow-up period, the subject may proceed directly to another pre-treatment visit at the investigator's discretion. The investigator may combine the CxW28 visit with the next pre-treatment visit if at least one escape criterion is met at the CxW28 visit, and the pre-treatment assessments occur within 7 days of the CxW28 visit. If a subject is completing the study at the CxW28 visit, the EOS/ET visit (Section 7.1.5) will take place in lieu of the CxW28 visit. Otherwise, following completion of the 28-week treatment cycle, the subject will proceed to an NTT visit within approximately 12 weeks.

At cycle week 28 (CxW28), subjects will return to the study site. In addition to the assessments performed at weeks 25-27, the following procedures will be performed at **CxW28 ONLY:**

- Dispense intake and output diaries
- Physical examination and vital signs, including weight
- Antibodies to teduglutide
- Pregnancy testing (urine)
- Evaluate escape criteria

7.1.5 Study Completion/Early Termination Visit (EOS/ET Visit)

All subjects will return to the study site for the end of study/early termination visit (EOS/ET). Assessments and procedures at this visit will be performed as outlined in Table 1-1 and as described here. If a subject discontinues the study prematurely, the assessments for the EOS/ET Visit are to be performed as completely as possible (see Section 4.8.2).

- Adverse events, concomitant medications and concomitant GI procedures
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries (the intake diary should be completed daily for a minimum of 2 weeks prior to the EOS/ET visit. The output diary should be completed daily over a 48-hour period of nutritional stability before the EOS/ET visit)
- Record PS prescription and adjust as needed
- Safety laboratory tests
- Fecal occult blood testing, as indicated
- Gastrointestinal-specific testing, including colonoscopy or sigmoidoscopy as indicated.
- Quality of life measurements
- Antibodies to teduglutide
- Pregnancy testing, as needed

7.2 Study Evaluations and Procedures

7.2.1 Demographics, Medical History, and SBS History

Demographics, medical history, and SBS history will be obtained at screening. Medical history for purposes of this extension study will consist of the following:

- Adverse events that were ongoing at the time of completion of TED-C14-006
- Events that occurred during the period between completion of TED-C14-006 and informed consent to SHP-633-304

This medical history information will supplement the medical history information collected at the start of the TED-C14-006 core study. If the subject has any changes to the SBS history collected at the baseline visit of the TED-C14-006 study, that information (updated SBS history) will be collected.

7.2.2 Physical Examination

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

7.2.3 Vital Signs, Body Weight, Height, Head Circumference and Body Mass Index (BMI)

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 cuff (using the same method, the same arm, and in the same position throughout the study).

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Height (or length) and head circumference (for subjects ≤36 months of age) will be measured at selected visits. A height z-score, weight z-score, BMI, and BMI z-score will be calculated by the sponsor using the site-provided height and weight data collected at each site visit

New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

7.2.4 Clinical Laboratory Tests

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 1-1, Table 1-2, and Table 1-3) 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 teduglutide treatment period, subjects will also have safety labs within approximately 5-7 days after a PS adjustment. Safety labs performed after PS 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 8.1). Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

New clinically significant labs should be reported as AEs.

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

Table 7-1: List of Laboratory Tests

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

Coagulation:
Prothrombin time/International normalized ratio

Urinalysis:
- Blood
- Glucose
- Leukocytes
- Microscopic analysis
- pH
- Protein
- Specific gravity

Pregnancy tests (females of childbearing potential):
- Serum β-HCG (screening)
- Urine β-HCG (all other visits)

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
- Uric acid

7.2.5 Serum Sampling

Serum samples will be collected and stored for future analysis at the following times:

- At the pre-treatment visit. If the subject met a follow-up period escape criterion, the serum sample will not be collected at the pre-treatment visit
- At the CxW24 (EOT) visit
- During NTT: Approximately every 24 weeks

The serum sample will not be used for genetic testing. Lack of collection will not constitute a protocol deviation.

The sponsor, sponsor's representatives, biorepositories, and any specialty laboratories will be blinded to the subject's identity. The sample and/or extracted material will otherwise be stored for up to 15 years from the end of the study after which time it will be destroyed. Upon written request, subjects will be permitted to withdraw their sample from the analysis and have their

sample and/or extracted material destroyed. Any results already generated from the samples will not be removed from any analyses that have already been performed.

7.2.6 Pregnancy Testing

A serum pregnancy test is performed on all FOCBP at the teduglutide pre-treatment visit (when the pre-treatment and screening visits are combined, the serum pregnancy test should be performed at the local laboratory). Urine pregnancy tests will be administered at all other visits according to the study schedules, or if pregnancy is suspected, or as specified per protocol upon withdrawal of the subject from the study.

7.2.7 Antibody Testing

Blood samples will be drawn for the analysis of antibodies to teduglutide according to the Schedule of Assessments (Table 1-1, Table 1-2, and Table 1-3). Blood samples for antibodies may be drawn from a central line or from peripheral access. The sample drawn on CxD1 must be drawn prior to administration of the first dose of teduglutide. Once the subject has started teduglutide treatment, samples must be drawn at least 14 hours after dosing. Subjects who test positive for antibodies to teduglutide will also be tested for neutralizing antibody. Subjects who have been previously treated with teduglutide, and who test positive for antibodies to teduglutide, will have follow-up blood draws for antibodies to teduglutide every 12 weeks while on study until a negative result is obtained.

7.2.8 Volume of Blood

Efforts will be made to minimize the amount of blood drawn from all pediatric subjects enrolled 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 annually are shown in Table 7-2.

Table 7-2: Approximate Volume of Blood to be Drawn from Each Subject Annually

Assessment		Sample Volume (mL)	No. Samples per two 28-week Teduglutide Cycles	Total Volume (mL)
Subjects Receiving Teduglutide Treatment				
Safety	Biochemistry and β-hCG[a]	2.5	24	60
	Hematology	2	24	48
	Coagulation Parameters	1	2	2
	Antibodies	2	8	16
	Serum storage samples	3	4	12
Total mL per 2, 28-week Treatment Cycles (Approximate Annual Volume):				**138**
Subjects Not Receiving Teduglutide Treatment[b]				
Assessment		**Sample Volume (mL)**	**No. Samples per 4 NTT Visits**	**Total Volume (mL)**
Safety	Biochemistry	2.5	4	10
	Hematology	2	4	8
	Serum storage samples	3	2	6
Total mL per 4 "No-Teduglutide Treatment" Visits 48-week period:				**24**

Abbreviations: β-hCG=beta-human chorionic gonadotropin; NTT=no-teduglutide treatment

[a] β-hCG testing will only be administered to females who are eligible for teduglutide treatment.

Table 7-2: Approximate Volume of Blood to be Drawn from Each Subject Annually

Assessment	Sample Volume (mL)	No. Samples per two 28-week Teduglutide Cycles	Total Volume (mL)

[b] Subjects not receiving teduglutide treatment, but who were exposed to it previously and tested positive for anti-teduglutide antibodies will require blood samples for antibody testing every 12 weeks until they test negative.

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 PS adjustment, and anti-teduglutide antibody testing during no-teduglutide treatment.

7.2.9 Gastrointestinal-specific Testing

7.2.9.1 Fecal Occult Blood Testing

Fecal occult blood testing must be performed on all subjects at the pre-treatment visit, week 12, and week 24 of the teduglutide cycle. During NTT periods, FOBT must be performed on teduglutide-exposed subjects (subjects who have received teduglutide any time in the past and are therefore not teduglutide-naïve) on a roughly annual basis (approximately every 48-60 weeks). Actions to be taken in response to a positive FOBT are described below.

7.2.9.2 Colonoscopy or Sigmoidoscopy

Teduglutide-naïve subjects age 12 and older will undergo colonoscopy or sigmoidoscopy at the pre-treatment visit if one has not been performed within 1 year.

Subjects of any age with newly positive FOBT results at the pre-treatment visit for which a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy or sigmoidoscopy prior to receiving teduglutide. If newly positive FOBT results (for which a readily detectable cause cannot be identified) are obtained at the end of a teduglutide treatment cycle (CxW24/EOT), colonoscopy or sigmoidoscopy will be performed. The need for colonoscopy or sigmoidoscopy in response to positive FOBTs at any other point during the study, or to re-evaluate persistently positive FOBTs is at the discretion of the investigator.

Teduglutide-exposed subjects who have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) will undergo colonoscopy or sigmoidoscopy. While receiving additional teduglutide treatment, subjects will undergo colonoscopy or sigmoidoscopy at 5 year intervals or more often as needed.

Upper endoscopy may be performed along with any colonoscopy or sigmoidoscopy at the investigator's discretion. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. Subjects with unresected GI polyps, polyposis conditions, pre-malignant change or malignancy in the GI tract will be excluded from teduglutide treatment.

7.2.10 Nutritional Support

Nutritional support includes PS, enteral nutrition, and other food and fluids. Advances in enteral nutrition and/or reductions to PS will be based on clinical status, including weight, linear growth, hydration status, and safety laboratory results. Intake and output diaries will include data to be

considered in the adjustment of each subject's nutritional support. Guidelines for nutritional support management and weaning algorithms are provided in Appendix 2.

7.2.11 Diaries

7.2.11.1 Study Drug Administration Diary

A study drug administration diary will record administration of teduglutide. This diary should be completed by the subject (or parent/legal guardian, as applicable) daily during the teduglutide treatment period (between visits CxD1 and CxW24).

7.2.11.2 Intake Diary

Intake diaries will be used to collect and evaluate each subject's nutritional support. The subject/parent/guardian will complete the appropriate fields of the PS section of the intake diary 2 weeks prior to ALL scheduled site visits (except at pre-treatment visit). During the 24-week teduglutide treatment period, the intake diary will also be completed for 1 week following PS adjustments. The intake diary will also be completed daily during the 4-week follow-up period. The following data will be captured in the intake diaries:

- Parenteral support volume and infusion duration
- Site personnel will determine the actual PS daily calories based on diary entries.

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 PS reduction and advance in feeds.

7.2.11.3 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 that are in a teduglutide treatment cycle within 1 week of implementing a change in the PS prescription, regardless of previous teduglutide exposure.

Urine data:

- Toilet-trained subjects (who do not wear diapers)
  Measure and record all urine output in mL or cc
- Nontoilet-trained subjects (who wear diapers)
  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 may be asked to collect the first void after the daily PS infusion to measure specific gravity

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

- Toilet-trained subjects (who do not wear diapers)
  Record the occurrence of each bowel movement and score the stool consistency using the Bristol Stool Form Scale (see Output diary)

- Nontoilet-trained subjects (who wear diapers)
  Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency using the Bristol Stool Form Scale (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. Ostomy output will not be scored using the Bristol scale.

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 PS reduction and advance in feeds.

7.2.12 Health-related Quality of Life Assessments

Throughout the study, health-related quality of life assessments will be performed using the PedsQL Generic Core Scales. Each PedsQL age-appropriate form takes less than 4 minutes to complete. The scales include self-reports for pediatric subjects and adolescents aged 5 to 18 years and proxy-reports from parents of pediatric subjects aged 2 to 18 years.

Field trials have shown that the internal consistency reliability of the PedsQL was excellent, with alphas for the generic core scales in both self- and proxy-report greater than the 0.70 standard, and alphas for the full 23-item scale approaching 0.90 for self- and proxy-report. Missing data were minimal. Item response distributions were across the full scale range, with no floor effects, and minimal ceiling effects.

The validity of the PedsQL Generic Core Scales was demonstrated through known group comparisons, and correlations with other measures of disease burden. The PedsQL self- and proxy-report distinguished between pediatric subjects with and without a chronic health condition, and within the group of pediatric subjects with a chronic condition, between those who did or did not have an overnight hospital visit in the last 12 months. Further, both child self-report and parent proxy-report correlated significantly with the number of days the child was too ill to pursue normal activities, needed someone to care for him or her, missed school in the last month, the number of days the parent missed from work in the last month, and parent-report of problems pursuing their normal work routine and concentrating at work. The PedsQL Generic Core Scales are also responsive to clinical change, as demonstrated in field trials.

7.2.12.1 Pediatric Quality of Life Generic Core Scale (PedsQL™), Acute version

The PedsQL Generic Core Scale is designed to measures health-related quality of life (HRQoL) in pediatric subjects and adolescents (2-18 years of age). The developmentally appropriate PedsQL Generic Core Scale will be completed by either the parent or legal guardian and subject as indicated in Table 7-3 at the time points as outlined in Table 1-1, Table 1-2, and Table 1-3.

Table 7-3: Developmentally Appropriate PedsQL™ Generic Core Scales

Report	Completed by
Parent Report for Toddlers (ages 2-4)	Parent or Legal Guardian
Child Self Report and Parent Proxy-Report for Young Pediatric subjects (ages 5-7)	Subject and Parent or Legal Guardian

Table 7-3: Developmentally Appropriate PedsQL™ Generic Core Scales

Report	Completed by
Child Self Report and Parent Proxy-Report for Pediatric subjects (ages 8-12)	Subject and Parent or Legal Guardian
Child Self Report and Parent Proxy-Report for Teens (ages 13-18)[a]	Subject and Parent or Legal Guardian

Abbreviations: PedsQL=Pediatric Quality of Life Inventory

[a] The Child Self Report and Parent Proxy-Report for Teens (ages 13-18) will also be completed for subjects older than 18 years of age

The Parent Report for Toddlers (ages 2-4) of the PedsQL Generic Core Scale is composed of 21 items comprising 4 dimensions as follows: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), 4) School Functioning (3 items).

The Child and Parent Reports of the PedsQL Generic Core Scale for Young Pediatric subjects (ages 5-7), Pediatric subjects (ages 8-12), and Teens (ages 13-18) are composed of 23 items comprising 4 dimensions as follows: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), 4) School Functioning (5 items).

7.2.12.2 Pediatric Quality of Life Family Impact Module (PedsQL™), Acute version

The PedsQL Family Impact Module is a parent-report multidimensional instrument that will be completed by the parent or legal guardian, as outlined in Table 1-1, Table 1-2, and Table 1-3.

The PedsQL Family Impact Module is a specific module of the PedsQL that is used to measure the impact of pediatric chronic health conditions on parents and the family (Varni et al., 2004). The 36-item PedsQL Family Impact Module consists of 6 scales measuring parent self-reported functioning as follows: 1) Physical Functioning (6 items), 2) Emotional Functioning (5 items), 3) Social Functioning (4 items), 4) Cognitive Functioning (5 items; worries about treatment and disease), 5) Communication (3 items), 6) Worry (5 items). Two additional scales measure parent-reported family functioning as follows: 1) Daily Activities (3 items), and 2) Family Relationships (5 items). The PedsQL Family Impact Module should take the parent or legal guardian approximately 5 to 10 minutes to complete.

7.2.12.3 PedsQL Gastrointestinal Symptoms Module (PedsQL™), Acute version

The PedsQL Gastrointestinal Symptom Module is a disease-specific 58-item module, comprised of 10 different symptom scales that assess gastrointestinal symptom-related quality of life: food and drink limits, trouble swallowing, heartburn and reflux, nausea and vomiting, gas and bloating, constipation, blood in poop, and diarrhea. The PedsQL Gastrointestinal Symptoms Module was designed to allow the selection and scoring of individual scales from the Module. The scales of Food and Drink Limits (6 items) and Diarrhea (7 items) were identified as clinically relevant and appropriate for the symptoms experienced in this pediatric study population, and therefore, are the only scales used in this study. The scales will be completed by either the parent or legal guardian and subject as indicated in Table 7-3 at the time points outlined in Table 1-1, Table 1-2, and Table 1-3.

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 7.1.4. 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.

In consideration of whether a treatment-emergent adverse event (TEAE) might lead to dose interruption (Section 8.4.1) or early termination of the study (Section 8.5), severe TEAEs will also be graded according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) severity grading criteria (US Department of Health and Human Services et al., 2010).

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 study drug that are not resolved at EOT 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 in 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.

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 (eg, 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

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.4.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Global Drug Safety Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the Shire Medical Monitor using the details specified in the emergency contact information section of the protocol. In the event a subject becomes pregnant during the study, teduglutide administration must be discontinued immediately.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Adverse Event Form for Serious Adverse Events (SAEs) and Non-serious AEs as Required by the Protocol. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by the Protocol as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or will determine the pregnancy onset date.

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 study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.4, 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 of Individual Subjects

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

Study drug must be discontinued if any of the following events occur:

- Pregnancy
- Severe hypersensitivity, such as anaphylaxis determined by the investigator to be related to study drug. This does not include the presence of anti-teduglutide antibodies, mild injection site reactions or mild symptoms that according to the investigator do not pose a significant risk to the subject.
- An AE that is of NCI CTCAE severity Grade 3 or 4 and considered to be related to study drug administration
- Confirmed drug-induced liver injury (DILI) related to teduglutide (see Section 8.4.2)

8.4.1 Dose Interruption Criteria Based on Adverse Event Severity and Relationship to Investigational Product

The investigational product must be discontinued if the subject experienced an AE that is of severity ≥Grade 3 per the NCI CTCAE and is reported as related to the investigational product.

In consideration of whether a TEAE might lead to dose interruption, severe TEAEs will also be graded according to the NCI CTCAE severity grading criteria (US Department of Health and Human Services et al., 2010). All such TEAEs should be discussed with the Shire Medical Monitor or designee as soon as possible. The length of the dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

8.4.2 Dose Interruption Criteria Based on Drug-Induced Liver Injury

Teduglutide administration for an individual subject may need to be interrupted if the subject has clinical and laboratory evidence of potential DILI, in the absence of an alternative explanation, as identified by the following criteria:

- ALT or AST >8x ULN
- ALT or AST >5x ULN and >2x baseline value for more than 2 weeks
- (ALT or AST >3x ULN and >2x baseline value) and (total bilirubin >2x ULN or INR>1.5)
- ALT or AST >3x ULN and >2x baseline value with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

All laboratory values suggestive of potentially new DILI should be repeated and verified within 3 days. International normalized ratio should be measured with this set of verification laboratory assessments 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 to evaluate the cause of liver injury. This evaluation may include, as clinically indicated, consideration of sepsis, acute viral hepatitis (eg, hepatitis A immunoglobulin [IgM], hepatitis B surface antigen, hepatitis C antibodies, cytomegalovirus IgM, Epstein-Barr virus antibody panel), hepatobiliary obstruction (ultrasound), autoimmune hepatitis (anti-nuclear, anti-smooth muscle, anti-actin, or anti-liver kidney microsomal antibodies), intestinal failure associated liver disease, cardiovascular causes such as ischemic hepatitis, and concomitant hepatotoxic treatments.

Additional evaluations may be performed at the discretion of the investigator in consultation with the Shire medical monitor.

Teduglutide administration must be permanently discontinued if DILI is confirmed and deemed related to study drug.

8.5 Early Termination of the Clinical Study

The DMC may recommend stopping the study if any of the following conditions are met:

- ≥2 subjects develop the same event of CTCAE severity Grade 3 that is reported as related to the investigational product

  or

- 1 subject develops an event of CTCAE severity Grade 4 that is reported as related to the investigational product.

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol in 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 in 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. Unscheduled safety follow up assessments (including visits conducted after EOS) are not to be collected unless requested.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management process. 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 its agent. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, USA) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the statistical methods and definitions 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.

9.4 Planned Interim Analysis, and Data Monitoring Committee

An interim analysis is planned when 6 months of safety data have been collected.

A 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.

9.5 Sample Size Calculation and Power Considerations

The number of subjects in this study is not based on statistical power considerations as this is an extension study of the core study, TED-C14-006. The maximum number of subjects was determined by the enrollment in TED-C14-006.

9.6 Study Population

The safety population includes all enrolled subjects in the study. Safety population will be used for both safety and efficacy analyses.

9.7 Efficacy Analyses

No claims of statistical significance will be made; however, 95% confidence intervals will be provided, if applicable. Continuous variables, including those assessed on a discrete scale, 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.

9.7.1 Efficacy Endpoints

Efficacy endpoints will be analyzed at the end of each teduglutide treatment period (Week 24 or EOT), and at each study visit, relative to the baseline of the core study (TED-C14-006) and/or first exposure to teduglutide. The following efficacy endpoints will be analyzed:

- Reduction in PS volume of at least 20%
- Absolute and relative change in PS volume
- Complete weaning off PS
- Change in days per week of PS

9.8 Safety Analyses

9.8.1 Safety Endpoints

The following safety endpoints will be analyzed:

- Adverse events
- Vital signs, including temperature, heart rate, and blood pressure

- Laboratory safety data (ie, clinical chemistry, hematology, and urinalysis)
- Urine output
- Stool output
- Antibodies to teduglutide
- Gastrointestinal-specific testing , including fecal occult blood testing and colonoscopy or sigmoidoscopy
- Z-scores for weight, height (or length), head circumference (up to 36 months of age), and body mass index

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number of events, incidence, and percentage of AEs will be calculated overall, by System Organ Class (SOC) and by preferred term. SAEs will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) with regard to drug class and drug name. The number and percentage of subjects with specific prior medications will be summarized. Medical history (including surgical/procedural history) will be coded using MedDRA. The number and percentage of subjects with specific histories will be summarized by system organ class and preferred term.

For clinical laboratory tests, vital signs, body weight, and fluid balance variables, descriptive statistics (mean, median, standard deviation, minimum and maximum values, the number and percentage of subjects in specified categories) will be calculated to summarize the observed values and change from baseline at each scheduled visit.

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

Additional safety parameters and measures will include change in body weight, height (or length) and head circumference (up to 36 months of age). Derived variables will include height z-score, weight z-score, BMI, and BMI z-score. Descriptive statistics (mean, median, standard deviation, minimum and maximum values, the number and percentage of subjects in specified categories) will be calculated to summarize the absolute values and change from baseline at each scheduled visit.

9.9 Other Analyses

9.9.1 Health-related Quality of Life Analyses

Health economics and outcomes research endpoints will be analyzed at approximately 12-week intervals (Weeks 12 and 24 of each teduglutide treatment cycle, and every 12 weeks for subjects not on teduglutide), relative to the study baseline. The beginning of each treatment cycle (CxD1) will be an additional baseline.

- Change in Pediatric Quality of Life Inventory (PedsQL) score

- Change in PedsQL Family Impact Module score
- Change in PedsQL Gastrointestinal Symptoms Module Sub-Scales scores:
    - Food and Drink Limits
    - Diarrhea

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 to the CRO 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 (CSR) 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 EOS 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 is appointed to review the final CSR for multicenter studies. Agreement with the final CSR 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 products, 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 international 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 Case Report Forms

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded into eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. 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 into the eCRF.

eCRFs should be approved by the investigator per study specifications and data deliverable requirements.

The clinical research associate (CRA)/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 diary cards, original clinical laboratory reports, and histology and pathology 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 CRA/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 subject 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 Food and Drug Administration (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 and assent, where applicable, from 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 or the subject's legally-authorized representative, as applicable, 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 (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or 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.

Within the source documents, site personnel should document instruction of and understanding by the parent/legally-authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

The principal investigator provides the sponsor with a copy of the consent form, and assent form where applicable, which was reviewed by the IRB/EC and which 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.

For sites within the EU, the applicant for an EC opinion can be the sponsor, the investigator, or for multicenter studies 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 (or 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; for sites within the EU, this can be done by the sponsor, the investigator or for multicenter studies 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 (or 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 review 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 SHP633; national or local regulatory authorities; and the IRBs/ECs 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 2-4 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 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	08 April 2016	Global
Amendment 1	22 Nov 2016	Global
Amendment 2	23 Mar 2017	Global

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date 22 Nov 2016**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Title of the Shire medical monitor has been changed to [redacted] for clarity.		Protocol Signature Page Emergency Contact Information
Clarification has been made that during the no-teduglutide treatment period, visits will take place *approximately* every 12 weeks.		Synopsis Sections 3.1, 7.1.2 Figure 3-1
The study design flow chart has been edited for clarity.		Synopsis Figure 3-1
The collection of all actual and prescribed enteral nutrition data has been removed to reduce the burden on the subjects and investigators. Enteral nutrition data are not required as the efficacy endpoints are limited to parenteral support parameters.		Synopsis Table 1-1, Table 1-2, Table 1-3 Sections 7.1.2, 7.1.3.1, 7.1.3.2, 7.1.5, 7.2.11.2, 7.2.11.3
Exclusion criterion 11 has been revised to add Smoflipid as other experimental drugs that are allowed prior and during the study. Like glutamine and Omegaven, Smoflipid is not expected to interfere with the assessments of safety and efficacy of teduglutide and many subjects may already be receiving the treatments off-label as part of standard medical therapy.		Synopsis Section 4.5
Exclusion criterion 12 and prohibited treatment have been refined: exclusion/prohibition of treatment with growth hormone has been extended to 3 months for consistency with other teduglutide studies.		Synopsis Section 4.5 Table 5-1
The language on escape criteria has been corrected for consistency within the protocol.		Synopsis Section 4.6
Language in efficacy and safety endpoints has been clarified.		Synopsis Sections 9.7.1, 9.8.1
Completion and review of intake and output diaries have been clarified.		Table 1-2, Table 1-3 Sections 7.1.3.2, 7.1.5
When the screening and pre-treatment visits are combined, the serum pregnancy test required at the pre-treatment visit should be performed at the local laboratory instead of the central laboratory. This will ensure timely results prior to starting treatment with teduglutide.		Table 1-3 Sections 7.1.3.1, 7.2.6
The requirement for urine specimen collection has been revised so that a lack of urinalysis will not constitute a protocol deviation for any pediatric		Table 1-1, Table 1-2, Table 1-3 Section 7.2.4

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **22 Nov 2016**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
subjects (not only for subjects wearing diapers).		
Clarification has been made that the first no-teduglutide treatment visit after the screening visit will occur within 2 to 12 weeks of the screening (formerly within 12 weeks of screening).		Synopsis Table 1-2 Section 7.1.1
Windows have been clarified for visits during the no-teduglutide and teduglutide treatment periods.		Table 1-2, Table 1-3 Section 7.1.2
'Specific' has been deleted from 'positive/specific anti-teduglutide antibodies' to eliminate the redundancy. By definition, positive samples must be specific (as assessed in the confirmatory assay), or otherwise considered negative.		Table 1-2 Sections 7.2.7, 9.8.1
Parental height and gestational age at birth have been removed from medical history.		Table 1-1 (footnote b) Section 7.2.1
For consistency within the protocol, sigmoidoscopy has been added as the alternate to colonoscopy throughout the protocol.		Table 1-1, Table 1-2, Table 1-3 Sections 3.1, 7.1.2, 7.2.9.2
Removal of former footnote i on fecal occult blood test for clarity.		Table 1-3
Clarification has been made on circumstances when the CxW28 visit may be combined with the next pre-treatment or EOS/ET visit.		Table 1-3 Section 7.1.4
The text on PS support requirements over time in pediatric subjects with SBS has been clarified, and text on intestinal adaptation has been refined.		Section 1.1
Status of current teduglutide approvals for use has been updated.		Section 1.2, 3.1
The term 're-challenge' has been replaced with 'additional teduglutide treatment' for clarity and consistency with other studies.		Section 3.1
Number of subjects enrolled has been corrected for consistency with protocol synopsis.		Section 3.1
Definition of a subject's completion of the study has been corrected for consistency within the protocol.		Section 3.2
Evaluations to be performed when a subject discontinues teduglutide or when withdraws from the study have been clarified.		Sections 4.8.1, 4.8.2
Withdrawal by parent/guardian has been added as reason for discontinuation.		Section 4.8.3
COUMADIN has been changed to warfarin for clarity.		Sections 5.1, 5.1.2
Clarification has been made on handling of study drug, which is for single use only and should be used within 3 hours following reconstitution.		Section 6.3.3
The investigator or designee may now dispense the unused study drug vials to the same subject if deemed appropriate to ensure sufficient supplies between visits. Also, documentation of all dispensed study medication has been clarified.		Section 6.4
Clarification has been made that local laboratory results are not required to be entered in the eCRFs.		Section 7.2.4
Collection of urine sodium and urine osmolality has been removed.		Section 7.2.4

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **22 Nov 2016**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Clarification has been made that the serum sample will not be collected at the pre-treatment visit if the subject met a follow-up period escape criterion.		Section 7.2.5
Intake and output diaries (formerly in Sections 7.2.11 and 7.2.12, respectively) have been moved under a new Section 7.2.11 'Diaries' for clarity, and are now Sections 7.2.11.2 and 7.2.11.3, respectively. Information on study drug administration diary has been added in Section 7.2.11.1. Clarification has been made that only available diary data will be reviewed at each clinic and telephone visit.		Sections 7.2.11, 7.2.11.1, 7.2.11.2, 7.2.11.3
Performance of dipstick specific gravity tests by the subject at home on the first urine produced after the daily infusions of PS has been removed. It is now at the discretion of the investigator for all subjects, not just those in diapers. This change is to align with standard medical practice.		Section 7.2.11.3
Clarifications have been made to the language on dose interruption.		Sections 8.4, 8.4.1
Unscheduled safety follow up assessments (including visits conducted after EOS) are not to be recorded. However, clarification has been made that they are to be collected where requested.		Section 9.1
The protocol now refers to the data monitoring committee (DMC) Charter for the schedule of DMC reviews.		Section 9.4
Changes have been made to the Health economics and outcomes research endpoints to include the beginning of each treatment cycle (CxD1) as additional baseline. These changes are for clarity and consistency with other teduglutide studies.		Synopsis Section 9.9.1
Minor corrections have been made to the guidelines for nutritional support management during the study.		Appendix 2

APPENDIX 2 GUIDELINES FOR NUTRITIONAL SUPPORT MANAGEMENT DURING THE STUDY

Nutritional support adjustment in volume and calories should be considered at all planned visits. Please consider the following clinical parameters identified as markers for adequate management of pediatric SBS. These parameters should also be considered for managing nutritional support (PS and/or oral/enteral feeding) in terms of volume and calories during the treatment period.

- Growth trajectory, including weight, height (or length), and head circumference (for pediatric subjects up to 36 months of age)
- Other clinical evaluations
  - Serum electrolytes
  - Blood urea nitrogen /creatinine levels
  - Changes in stool frequency or volume, including mixed output
  - Stool consistency (ie, Bristol Stool Scale)
  - Urine specific gravity
- General consideration to possible clinical deterioration in SBS
  - Inability to maintain weight and growth velocity
  - Diarrhea (≥10 bowel movements per day, ≥80 mL/kg/day from an ostomy, or ≥75 mL/kg/day mixed output)
  - Colic/vomiting frequency increased
  - Electrolyte changes or imbalance
  - Skin breakdown
- 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.
- Nutritional support constituents may be adjusted at the discretion of the investigator.
- 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.
- If there is a change in enteral nutrition (EN) or other food or fluid intake, the investigator should consider this when adjusting the PS/EN support in volume and calories.

Figure A-1 Weaning Algorithm for Subjects Who are NOT Toilet Trained and in Diapers

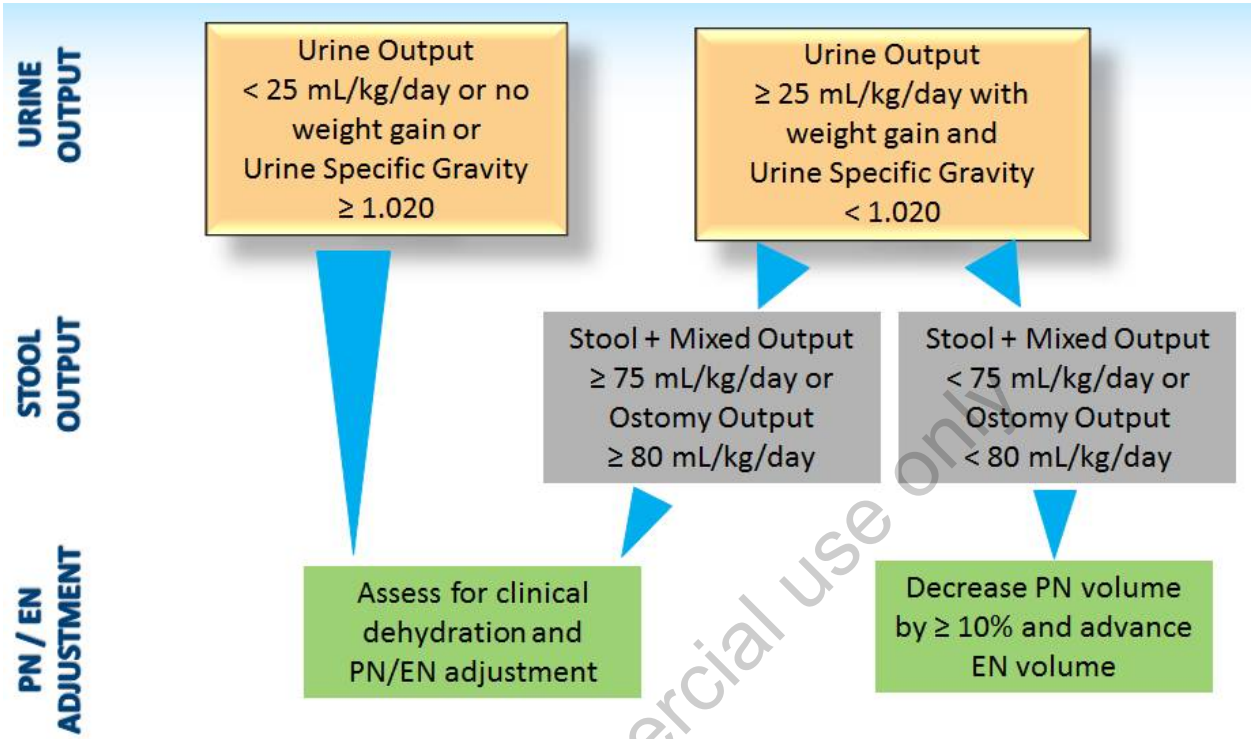


Figure A-2 Weaning Algorithm for Subjects Who are Toilet Trained and NOT in Diapers

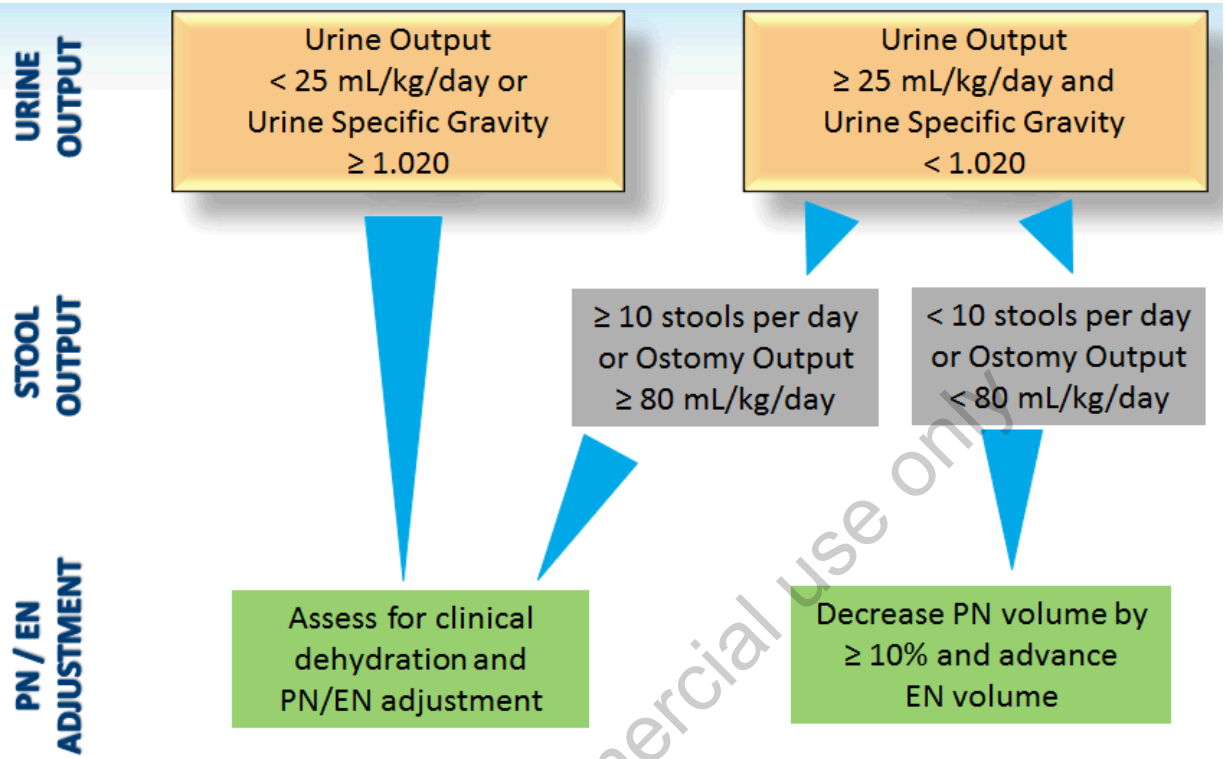
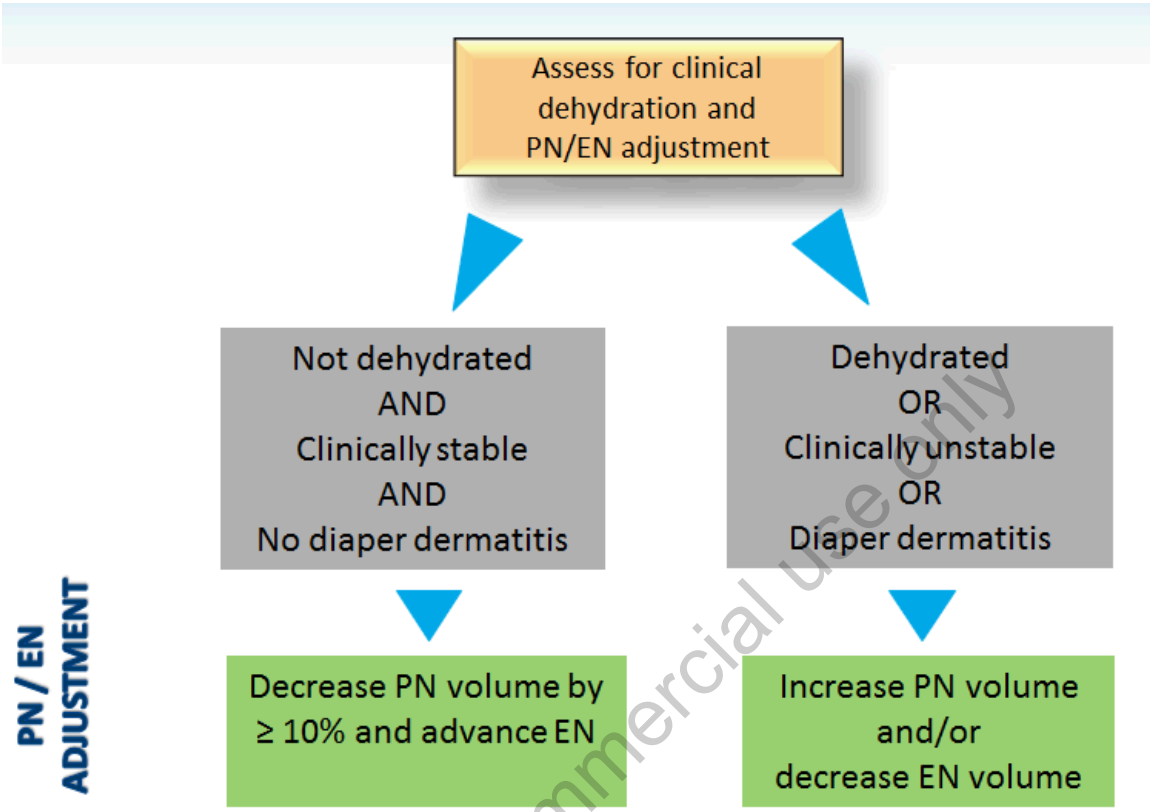


Figure A-3 Clinical Dehydration Assessment and PS/EN Adjustment



PROTOCOL: SHP633-304

TITLE:	A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome Who Completed TED-C14-006 or SHP633-301
DRUG:	Teduglutide
IND:	IND# 058213
EUDRACT NO.:	2016-000849-30
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way, Lexington, MA 02421 USA
PROTOCOL HISTORY:	Amendment 3: 16 May 2018 Amendment 2: 23 Mar 2017 Amendment 1: 22 Nov 2016 Original Protocol: 08 April 2016

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

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

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP633-304.

Title: A prospective, open label, long-term safety and efficacy study of teduglutide in pediatric patients with short bowel syndrome who completed TED-C14-006 or SHP633-301

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 Conference on Harmonization (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)

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3	**Amendment Date** **16 May 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
The primary contact for EU and backup contact for NA was updated to [redacted].		Emergency Contact Information
To allow the enrollment of subjects who completed SHP633-301 where SHP633-301 was registered and approved by the local Health Authorities. The study title and eligibility criteria have been modified to accommodate younger children completing SHP633-301. SHP633-304 will evaluate long-term safety and efficacy in subjects who completed SHP633-301 and will provide a mechanism for subjects who complete SHP633-301 to receive additional teduglutide treatment if clinically indicated.		Synopsis; Table 1-1; Section 2; Section 3.1; Section 4.1; Section 4.5; Section 6.2.2; Section 7.1.1; Section 7.1.3.1; Section 7.2.1; Section 9.5; Section 9.7.1
To minimize risk to subjects, a new escape criterion was added, allowing those who had escaped during the follow-up period of a previous teduglutide treatment to omit the follow-up period during subsequent teduglutide treatment cycles. For subjects who previously escaped the follow-up period, CxW24 assessments can be combined with the next pretreatment visit assessments.		Synopsis; Table 1-3; Figure 3-1; Section 3.1; Section 4.6; Section 6.2.3; Section 7.1.3.1; Section 7.1.3.2; Section 7.1.4; Section 7.2.5
Added the recording of parenteral support prescription at screening.		Table 1-1
Clarified language that all concomitant procedures are to be captured, not just gastrointestinal procedures.		Table 1-1; Table 1-2; Table 1-3, Section 5.1; Section 7.1.1; Section 7.1.2; Section 7.1.3.1; Section 7.1.3.2; Section 7.1.5
Updated the information on the clinical studies with teduglutide in pediatric subjects to include the results of TED-C14-006 and a description of the additional core study, SHP633-301.		Section 1.3
Added new PK simulation data to further support dosing.		Section 3.1
Deleted text that was duplicated in other sentences of sections.		Section 5.1
Deleted biological therapy (eg, antitumor necrosis factor) from the table of prohibited treatments as it was included in error.		Table 5-1
Clarified that compliance with study drug is calculated from subject diaries		Section 6.5
Added direct bilirubin to the list of laboratory tests.		Table 7-1
Specified that blood pressure should be collected in the same extremity rather than in the same arm as blood pressure is not collected using the arm in small children.		Section 7.2.3
Specified that saved serum samples should be omitted for subjects weighing less than 10 kg and whenever local blood volume limitations are exceeded.		Section 7.2.8
Clarified that if a child is under 2 years of age or unable to complete a quality of life questionnaire (due to developmental delay or other illness) it will not constitute a protocol deviation.		Section 7.2.12

Specified that an interim analysis is planned when 6 months of safety data have been collected for subjects entering from TED-C14-006. Additional interim analyses may be conducted as needed.	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 protocol

See Appendix 1 for protocol history, including all amendments.

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 using the details below.

[redacted], MD PhD

Email: [redacted]

Fax: [redacted]

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

Primary contact for North America (NA) and backup contact for European Union (EU)

[redacted], MD, [redacted]

Mobile: [redacted]

US Toll Free number: [redacted]

Phone: [redacted] (medical emergencies – NA)

Email: [redacted]

Primary contact for EU and backup contact for NA

[redacted], MD, [redacted]

Mobile: [redacted]

Phone: [redacted]

Phone: [redacted] (medical emergencies – EU)

Email: [redacted]

In addition, the investigator may also contact the Shire Medical Monitor:

[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 (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 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):
[redacted] Shire (USA)

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ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-HCG	beta-human chorionic gonadotropin
BMI	body mass index
CRA	clinical research associate
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced livery injury
DMC	data monitoring committee
DPP-4	dipeptidyl peptidase 4
EC	ethics committee
eCRF	electronic case report form
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FOBT	fecal occult blood test
FOCBP	female of child-bearing potential
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
GLP-2	glucagon-like peptide 2
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IGF-1	insulin-like growth factor 1
IRB	institutional review board
IV	intravenous
IWRS	interactive web-based response system

MedDRA	Medical Dictionary for Regulatory Activities
NA	North America
NCI	National Cancer Institute
NDA	new drug application
NTT	no-teduglutide treatment
PedsQL	Pediatric Quality of Life inventory
PS	parenteral support
PT/INR	prothrombin time/international normalized ratio
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
SOC	standard of care
$t_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
UK	United Kingdom
ULN	upper limit of normal
US	United States
WHO-DD	World Health Organization – Drug Dictionary

STUDY SYNOPSIS

Protocol number: SHP633-304	**Drug:** Teduglutide
Title of the study: A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome (SBS) Who Completed TED-C14-006 or SHP633-301	
Number of subjects (total and for each treatment arm): Approximately 65 subjects who completed the TED-C14-006 or SHP633-301 studies, including subjects in the standard of care treatment arms, are expected to enroll in this extension study. This study will enroll up to as many subjects as complete the TED-C14-006 and SHP633-301 studies.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 28 investigational sites in North America and Europe will participate in this extension study	
Study period (planned): October 2016 – September 2019	**Clinical phase:** 3 Extension
Objectives: **Primary:** To evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with SBS. **Secondary:** To evaluate long-term efficacy of teduglutide treatment in pediatric subjects with SBS.	
Rationale: This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects with short bowel syndrome (SBS) who completed either the TED-C14-006 or SHP633-301 studies (the core studies). In addition to evaluating the long-term safety and durability of efficacy after 24-weeks of treatment, this extension study will evaluate the need for additional teduglutide treatment in these subjects, and will allow the study of first-time treatment of teduglutide-naïve subjects who participated in the standard of care (SOC) treatment arms in TED-C14-006 or SHP633-301.	
Investigational product, dose, and mode of administration: This study will allow repeat doses of teduglutide 0.05 mg/kg subcutaneous (SC) once daily (QD) injection for eligible pediatric subjects. There is no active comparator or reference product.	
Methodology: This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects who completed the TED-C14-006 or SHP633-301 studies (core studies). Once the informed consent (and if applicable, informed assent) have been reviewed and signed, demographics, and updates to medical history and short bowel syndrome history will be obtained. Subjects not receiving teduglutide treatment (ie, in a no-teduglutide treatment [NTT] period), will be seen approximately every 12 weeks for safety, parenteral support (PS) requirements, and quality of life. The first NTT visit after the screening visit will occur within 2 to 12 weeks of the screening visit. At any point after screening, including during a NTT period, subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed **immediately** to the pretreatment visit if the investigator, subject, and parent agree to proceed with teduglutide therapy. After the pretreatment visit, subjects who meet ≥1 of the teduglutide treatment inclusion criteria, and meet none of the teduglutide treatment exclusion criteria, will start a 28-week cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily, followed by a 4-week follow-up period (during which no teduglutide is administered) (Figure 3-1). During the 28-week cycle, clinic visits will occur at weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period (between weeks 1 and 24), and weekly during the teduglutide follow-up period (between weeks 24 and 28). Safety and PS requirements will be evaluated at every visit, and quality of life assessments will be made approximately every 12 weeks. If a subject meets 1 of the follow-up period escape criteria between cycle week 24	

and 28, the subject may "escape" the follow-up period early and proceed immediately to another pretreatment visit. Following completion of the 28-week treatment cycle, the subject will proceed to an NTT visit or another pretreatment visit within approximately 12 weeks.

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, all attempts should be made to follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) for decisions regarding PS support reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines, however, is not considered a protocol deviation. (Appendix 2).

Study Design Flow Chart

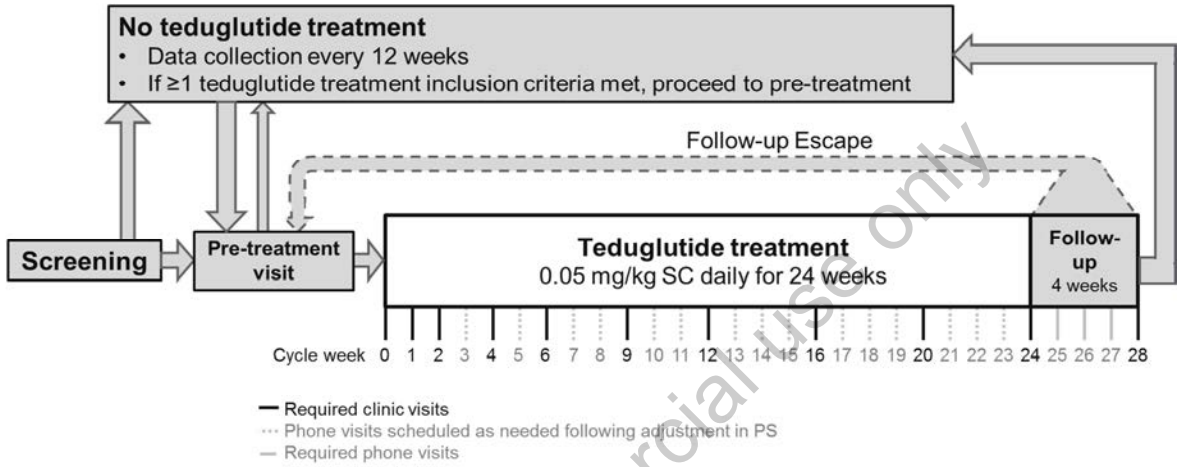

Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pretreatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects will enter a 28-week teduglutide cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24 (**solid black lines**). Phone visits are required approximately 1 week after adjustments in PS during the intervening weeks between weeks 2 and 24 (**dashed grey lines**). Subjects discontinue teduglutide at week 24 and enter a 4-week follow-up (no-treatment) period, during which phone visits will be performed weekly (**solid grey lines**). If an escape criterion is met at week 24 or during the follow-up period, subjects may proceed directly to another pretreatment visit.

Study Inclusion Criteria:

The subject will be considered eligible for the study if they meet **all** of the study inclusion criteria. Teduglutide treatment eligibility does not impact study eligibility.

1. Subject provides written informed consent (subject, parent or legal guardian and, as appropriate, informed assent) to participate in the study before completing any study-related procedures.
2. Subject completed the TED-C14-006 or SHP633-301 studies (including subjects in the standard of care treatment arms). Subjects are considered to have completed SHP633-301 if they completed study assessments through week 24.
3. Subject understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Study Exclusion Criteria: There are no exclusion criteria for this study.

Teduglutide Eligibility Criteria: Subjects are eligible for teduglutide treatment if at least one (≥1) of the teduglutide treatment inclusion criteria, and none of the teduglutide treatment exclusion criteria, are met. In addition, the investigator and the subject (and/or parent or legal guardian, as appropriate) must agree to proceed with treatment.

***Teduglutide Treatment Inclusion Criteria*:**

1. Subject is teduglutide-naïve, receiving PS, and unable to significantly reduce PS or advance enteral feeds (eg, 10% or less change in PS or advance in feeds) for at least 3 months prior to and during the teduglutide pretreatment visit, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PS returns to within 10% of baseline prior to the event.
2. Subject was previously treated with teduglutide and at least one of the following criteria is satisfied:
    a. Increasing PS requirements following teduglutide discontinuation.
    b. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
    c. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.
    d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
    e. Severe diarrhea related to teduglutide discontinuation.

Teduglutide Treatment Exclusion Criteria:

1. Body weight <5 kg at the pretreatment visit.
2. Unresected gastrointestinal (GI) polyp, known polyposis condition, premalignant change, or malignancy, in the GI tract.
3. History of cancer in the previous 5 years except surgically curative skin cancers.
4. Serial transverse enteroplasty or other major intestinal surgery within 3 months preceding the teduglutide pretreatment visit. Insertion of a feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, and endoscopic procedures are allowed.
5. Intestinal or other major surgery planned or scheduled to occur during the 28-week cycle.
6. Clinically significant intestinal stricture or obstruction.
7. Clinically significant, active or recurrent pancreatic or biliary disease.
8. Active, severe, or unstable, clinically significant hepatic impairment or injury, including the following laboratory values at the pretreatment visit:
    a. Total bilirubin ≥2 × upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7 × ULN
    c. Alanine aminotransferase (ALT) ≥7 × ULN
9. Renal dysfunction shown by results of an estimated glomerular filtration rate below 50 mL/min/1.73 m^2 at the pretreatment visit.
10. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, or patent ductus arteriosus ligation.
11. Participation in a clinical study using an experimental drug (other than glutamine, Omegaven, or Smoflipid) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to the pretreatment visit and for the duration of the 28-week cycle.
12. Treatment with analogs of glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2) (not including teduglutide), insulin-like growth factor-1 (IGF-1), or growth hormone, within 3 months preceding the teduglutide pretreatment visit.
13. Treatment with octreotide or dipeptidyl peptidase 4 (DPP-4) inhibitors within 3 months prior to the pretreatment visit.
14. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.
15. Known history of alcohol or other substance abuse within 1 year prior to the pretreatment visit.

16. Pregnant or lactating female subjects.
17. Sexually active female subjects of child-bearing potential unwilling to use approved contraception during teduglutide treatment and for 30 days after the treatment period.
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.

Follow-up Period Escape Criteria: At the discretion of the investigator, the follow-up period may be interrupted or omitted and the subject may proceed directly to the pretreatment visit, if ≥1 of the following criteria is met:

1. Increasing PS 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.
5. The subject escaped during the follow-up period of SHP633-301 or during the follow-up period of a previous teduglutide treatment cycle within SHP633-304.

Maximum duration of subject involvement in the study:

A subject will be considered enrolled in the study once the subject has provided signed consent, and meets all of the Study Inclusion Criteria. Subjects may participate in multiple NTT periods and/or multiple 28-week treatment cycles. The study will continue for at least 1 year, and until each subject has access (as needed) to teduglutide. The subject's maximum duration of participation is expected to be approximately 3 years. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing End of Study (EOS) visit.

- **Planned duration of no-teduglutide treatment periods**: variable, depending on disease course
- **Planned duration of the teduglutide pretreatment visit:** 1 to 21 days
- **Planned cycle duration**: 28 weeks. Each cycle consists of 24 weeks of teduglutide treatment followed by a 4-week follow-up period (no treatment)

Endpoints and statistical analysis:

- The **safety population** will consist of all enrolled subjects. The safety population will be used for both safety and efficacy analysis.

Efficacy Endpoints

Efficacy endpoints will be analyzed at the end of each teduglutide treatment period (week 24 or end of treatment [EOT]), and at each study visit, relative to the baseline of the core study (TED-C14-006 or SHP633-301) and/or first exposure to teduglutide. The following efficacy endpoints will be analyzed:

- Reduction in PS volume of at least 20%
- Absolute and relative change in PS volume
- Complete weaning off PS
- Change in days per week of PS

Health Economics and Outcomes Research Endpoints

Health economics and outcomes research endpoints will be analyzed at approximately 12-week intervals (weeks 12 and 24 of each teduglutide treatment cycle, and every 12 weeks for subjects not on teduglutide), relative to the study baseline. The beginning of each treatment cycle (CxD1) will be an additional baseline.

- Change in Pediatric Quality of Life Inventory (PedsQL) score
- Change in PedsQL Family Impact Module score
- Change in PedsQL Gastrointestinal Symptoms Module Sub-Scales scores:
  - Food and Drink Limits
  - Diarrhea

Safety Endpoints

The following safety endpoints will be analyzed:

- Adverse events
- Vital signs, including temperature, heart rate, blood pressure
- Laboratory safety data (ie, clinical chemistry, hematology, and urinalysis)
- Urine output
- Stool output
- Antibodies to teduglutide
- Gastrointestinal-specific testing, including fecal occult blood testing and colonoscopy or sigmoidoscopy
- Z-scores for weight, height (or length), head circumference (up to 36 months of age), and body mass index

Statistical Methodology for Efficacy Analysis

No claims of statistical significance will be made; however, 95% confidence intervals will be provided, if applicable. Continuous variables, including those assessed on a discrete scale, 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.

Statistical Methodology for Safety Analysis

Safety data, including laboratory tests and vital signs assessments, will be summarized by visit. AEs will also be collected and summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data.

Sample Size Justification

As this is an extension study, the maximum number of subjects was determined by enrollment in TED-C14-006 and SHP633-301.

STUDY SCHEDULE(S)

Table 1-1: Schedule of Events Required for All Subjects

Period	Screening	End of Study or Early Termination
	Scr	EOS/ET
Visit Type	**Site**	**Site**
Informed consent/assent[a]	X	
Study eligibility	X	
Demographics, medical history[b], SBS history[c]	X	
Dispense intake and output diaries	X	
Evaluate teduglutide treatment inclusion criteria[d]	X	
Adverse events	X	X
Concomitant medications and procedures	X	X
Physical examination and vital signs, including weight		X
Height and head circumference[e]		X
Review intake and output diaries[f]		X
Record PS prescription and adjust as needed[g]	X	X
Safety laboratory tests[h]		X
PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales		X
Antibodies to teduglutide[i]		X
Fecal occult blood testing[j]		(X)
Colonoscopy or sigmoidoscopy[k]		(X)
Pregnancy testing[l]		(X)

FOBT = fecal occult blood testing; FOCBP = female of child-bearing potential; EOS =end of study; ET=early termination; GI=gastrointestinal; NTx=no treatment; PedsQL=Pediatric Quality of Life Inventory; PS=parenteral support; SBS=Short Bowel Syndrome; Scr =Screening.

[a] Informed Consent (and informed assent, if applicable) must be obtained prior to performing any study-related procedures; consent (and informed assent, if applicable) may be obtained anytime during the EOS visit for the TED-C14-006 or SHP633-301 studies. Subject will have approximately 7 days after completion of the TED-C14-006 or SHP633-301 studies to sign consent to participate in the SHP633-304 study.

[b] Updates to the medical history will be collected, consisting of adverse events that were ongoing at the time of completion of TED-C14-006 or SHP633-301, and events that occurred during the period between completion of TED-C14-006 or SHP633-301 and informed consent to SHP-633-304.

[c] If the subject has any changes to the SBS history that had been collected at the baseline of the TED-C14-006 or SHP633-301, then the updated SBS history will be collected.

[d] Subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed to the pretreatment visit if the investigator, subject, and parent or legal guardian agrees to proceed with teduglutide therapy (Table 1-3).

[e] Head circumference will be measured in subjects 36 months of age and younger.

[f] The intake diary should be completed daily for a minimum of 2 weeks prior to the EOS/ET visit. The output diary should be completed daily over a 48-hour period of nutritional stability before the EOS/ET visit.

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

[h] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

[i] Required for all teduglutide-exposed subjects

[j] FOBT should be performed on teduglutide-exposed subjects on an annual basis, approximately every 48-60 weeks at a minimum.

[k] The need for colonoscopy/sigmoidoscopy in response to a positive FOBT during a no-teduglutide treatment period is at the discretion of the investigator, but all teduglutide-exposed subjects will undergo colonoscopy/sigmoidoscopy after they have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure), and subjects who continue to receive teduglutide will undergo colonoscopy/sigmoidoscopy at 5 year intervals or more often as needed. See Section 7.2.9 for details.

[l] Pregnancy testing is required for FOCBP at an ET visit if the subject has not had a pregnancy test at least 30 days after study drug discontinuation.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

Table 1-2: Schedule of Events for Subjects Not Receiving Teduglutide

Visit Number	**NTx**
Visit Type	**Site**
Visit Frequency[a]	**Every 12 weeks**
Window (days)[b]	**±7**
Dispense intake and output diaries	X
Evaluate teduglutide treatment inclusion criteria[c]	X
Adverse events	X
Concomitant medications and procedures	X
Physical examination and vital signs, including weight	X
Height and head circumference[d]	X
Review intake and output diaries[e]	X
Record PS prescription and adjust as needed[f]	X
Safety laboratory tests[g]	X
PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales	X
Antibodies to teduglutide[h]	(X)
Fecal occult blood testing[i]	Annually
Colonoscopy or sigmoidoscopy[j]	(X)
Serum sample[k]	Every 24 weeks

FOBT = fecal occult blood testing; NTT = no-teduglutide treatment; PedsQL = Pediatric Quality of Life Inventory; PS= parenteral support; TED = teduglutide.

[a] The first NTx visit following the screening visit must occur within 2 to 12 weeks of screening.

[b] Window is relative to the first NTx visit in the current no-teduglutide treatment period.

[c] Subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed to the pretreatment visit if the investigator, subject, and parent or guardian agree to proceed with teduglutide therapy (Table 1-3).

[d] Head circumference will be measured in subjects 36 months of age and younger.

[f] Intake diaries will collect actual PS volume and hours per day, completed daily for a minimum of 2 weeks prior to each study visit (see Section 7.2.11.2). Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit (see Section 7.2.11.3 for more detail).

[f] PS 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.

[g] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

[h] Subjects who have been treated previously and test positive for teduglutide antibodies should have follow-up samples collected every 12 weeks during the study until a negative result is obtained.

[i] FOBT should be performed on teduglutide-exposed subjects on an annual basis, approximately every 48-60 weeks at a minimum.

[j] The need for colonoscopy/sigmoidoscopy in response to a positive FOBT during a no-teduglutide treatment period is at the discretion of the investigator, but all teduglutide-exposed subjects will undergo colonoscopy/sigmoidoscopy after they have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) and subjects who continue to receive teduglutide will undergo colonoscopy/sigmoidoscopy at 5 year intervals or more often as needed. See Section 7.2.9 for details.

[k] Lack of collection of serum samples will not constitute a protocol deviation.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	**Pre-treatment**	**Teduglutide Treatment**															**Follow-up**	
Visit Number	**Px[a]**	**Cx D1**	**Cx W1**	**Cx W2**	Phone contact is required approximately 1 week after PS adjustment	**Cx W4**	Phone contact is required approximately 1 week after PS adjustment	**Cx W6**	Phone contact is required approximately 1 week after PS adjustment	**Cx W9**	Phone contact is required approximately 1 week after PS adjustment	**Cx W12**	Phone contact is required approximately 1 week after PS adjustment	**Cx W16**	Phone contact is required approximately 1 week after PS adjustment	**Cx W20**	Phone contact is required approximately 1 week after PS adjustment	**CxW24 (EOT)**	**CxW25 CxW26 CxW27**	**CxW28[c]**
Visit Type	**Site**	**Site**	**Site**	**Site**		**Site**		**Site**		**Site**		**Site**		**Site**		**Site**		**Site**	**Phone[b]**	**Site**
Cycle Day	**-21 to 0**	**1**	**8**	**15**		**29**		**43**		**64**		**85**		**113**		**141**		**169**	**176 183 190**	**197**
Window (days)[d]	-21 to 0		**±2**	**±2**		**±2**		**±2**		**±4**		**±4**		**±4**		**±4**		**±4**	**±2**	**±2**
Evaluate teduglutide eligibility (inclusion and exclusion) criteria	X	X[e]																		
Dispense intake and output diaries	X	X	X	X		X		X		X		X		X		X		X		X
Adverse events	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
Physical examination and vital signs, including weight	X	X	X	X		X		X		X		X		X		X		X		X
Height and head circumference[f]	X	X										X						X		
Review intake and output diaries[g]	X	X	X	X		X		X		X		X		X		X		X	X	X
Record PS Rx and adjust as needed[h]	X	X	X	X		X		X		X		X		X		X		X	X	X
Safety laboratory testsi	X[i]	X	X	X		X		X		X		X		X		X		X	(X)	X
PedsQL Generic Core Scale/ Family Impact Module/ GI Symptoms Module Sub-Scales		X										X						X		
Antibodies to teduglutide[j]		X										X						X		X
Fecal occult blood testing	X											X						X		
Colonoscopy/ sigmoidoscopy[k]	(X)											(X)						(X)		

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	Pre-treatment	Teduglutide Treatment																Follow-up	
Pregnancy testing[l]	X	X				X				X		X				X			X
Serum sample[m]	X															X			
Evaluate escape criteria[n]																X[p]		X	X
Dispense study drug[o]		X	X	X		X		X		X		X		X					

EOS = end of study; EOT = end of treatment; ET = early termination; FOBT = fecal occult blood test; FOCBP = female of child-bearing potential; FU = follow-up; GI = gastrointestinal; PedsQL = Pediatric Quality of Life Inventory; PS= parenteral support; SBS = Short Bowel Syndrome; SC = subcutaneous; Scr = Screening; TED = teduglutide; Tx = treatment.

[a] If the first pretreatment visit (P1) follows the screening visit, it must occur within 12 weeks of screening.

[b] Phone visits are required approximately 1 week after adjustments in PS. The assessments to be performed at phone visits are the same as those described for CxW25-27 (except for evaluation of escape criteria).

[c] The investigator may combine the CxW28 visit with the next pretreatment visit if at least one escape criterion is met at the CxW28 visit, and the pretreatment assessments occur within 7 days of the CxW28 visit. If a subject is completing the study at the CxW28 visit, the EOS/ET visit (Table 1-1) will take place in lieu of the CxW28 visit.

[d] Visit windows are relative to the CxD1 visit.

[e] Eligibility will need to be re-confirmed prior to the first dose in the cycle. Negative urine pregnancy test is required prior to the first dose of teduglutide, but results of other labs obtained at the CxD1 visit are not required to determine teduglutide treatment eligibility.

[f] Head circumference will be measured in subjects 36 months of age and younger.

[g] Intake diaries will collect actual PS volume and hours per day. Intake diaries should be completed daily for a minimum of 2 weeks immediately prior to each clinic visit (except at pretreatment visit), for 1 week following PS adjustment, and daily during the 4-week follow-up period. 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 PS prescription. See Section 7.2.11 for more detail.

[h] PS 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] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Clinical chemistry and urinalysis must also be performed within approximately 5-7 days of any adjustment to the PS prescription. Safety labs performed between clinic visits may be performed locally. Unscheduled lab results will not be captured in the eCRFs. If abnormal results are considered an adverse event, an AE form will be completed. Collect PT/INR at the pretreatment visit. Additional collection will occur if a potential drug-induced liver injury signal is observed. Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

[j] Samples collected on CxD1 must be drawn prior to first administration of teduglutide. Samples collected while subjects are receiving teduglutide (CxW12 and CxW24) must be drawn at least 14 hours after dosing.

[k] The teduglutide-naïve subjects age 12 and older will undergo colonoscopy/sigmoidoscopy at the pretreatment visit if one has not been performed within 1 year. Subjects of any age with newly positive FOBT results at the pretreatment visit for which a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy/sigmoidoscopy prior to receiving teduglutide. If newly positive FOBT results (for which a readily detectable cause cannot be identified) are obtained at the end of a teduglutide treatment cycle (CxW24/EOT), colonoscopy/sigmoidoscopy will be performed. The need for colonoscopy/sigmoidoscopy in response to positive FOBTs at CxW12 is at the discretion of the investigator. Teduglutide-exposed subjects who have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) will undergo colonoscopy/sigmoidoscopy. See Section 7.2.9 for details.

[l] A serum pregnancy test is performed on all FOCBP at the teduglutide pretreatment visit (when the pretreatment and screening visits are combined, the serum pregnancy test should be performed at the local laboratory). Urine pregnancy tests will be administered at all other visits according to the study schedules, or if pregnancy is suspected, or as specified per protocol upon withdrawal of the subject from the study.

[m] Lack of collection of serum samples will not constitute a protocol deviation.

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	Pre-treatment	Teduglutide Treatment	Follow-up

[n] If escape criteria are met, the subject may proceed directly to another pretreatment visit at the discretion of the investigator.
[o] The first SC injection of teduglutide in treatment-naïve subjects will be administered under the supervision of the investigator/designee after which the subject will be observed for hypersensitivity reactions for at least 4 hours. The site of administration (arm, thigh, abdomen) of the first teduglutide dose must be specified and recorded in the eCRF. See Section 6.2.3 for dose adjustment.
[p] Escape criteria will be assessed for subjects who escaped during the follow-up period of a previous teduglutide treatment cycle at CxW24. The investigator may combine the CxW24 visit with the next pretreatment visit if at least 1 escape criterion is met at the CxW24 visit. In order to combine assessments, the pretreatment assessments must occur within 7 days of the CxW24 visit.
Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

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. It is estimated that, at most, there are a few hundred pediatric subjects 1 year and older with SBS (Khan et al., 2015; Wales et al., 2004). 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. Although the small intestine is capable of remarkable adaptation, excessive loss of absorptive surface area or specialized functions can lead to dependence on parenteral nutrition or intravenous (IV) fluids (parenteral support [PS]). Treatment of both pediatric and adult patients is focused on achieving adequate intestinal absorption to allow for minimization or discontinuation of PS. About 30% of infants with SBS become independent of PS requirements within 12 months of the initial insult, and an additional 10% wean off PS within 24 months. After this time, linear intestinal growth slows. About 60% of pediatric subjects with SBS are able to become independent of PS within 5 years of the initial diagnosis (Khan et al., 2015). Nevertheless, despite optimal medical management, many pediatric subjects remain dependent on PS. Complications of long-term PS include liver disease, catheter-related blood stream infections, central line-associated venous thrombosis and dwindling central venous access. Sepsis is the leading cause of death in these patients and quality of life is poor (Squires et al., 2012). Accelerating the adaptive process and achieving enteral autonomy is an urgent goal for all patients with SBS who are dependent on PS (Khan et al., 2015; Squires et al., 2012).

Intestinal adaptation is driven by hormonal cues in response to nutrient malabsorption (Drucker and Yusta, 2014). Chief among these is hormones glucagon-like peptide 2 (GLP-2), which is secreted from L-type enteroendocrine cells that reside in the intestinal epithelium in the ileum and colon. Resection of these regions may impair the adaptive response by limiting endogenous production of GLP-2.

1.2 Product Background

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-IV (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$) in adults of approximately 2 hours 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). The European Commission granted a centralized marketing authorization valid throughout the European Union (EU) for teduglutide (Revestive™) on 30 August 2012 and a New Drug Application (NDA) for teduglutide (Gattex®) was approved by the United States (US) Food and Drug Administration (FDA) on 21 December 2012 for the treatment of adult patients with SBS who are dependent on PS. Teduglutide has also been approved for use in adult patients with SBS in Canada and Switzerland. On 29 Jun 2016, the

European Commission granted an extension of the Market Authorization for teduglutide (REVESTIVE™) for the treatment of patients aged 1 year and above with SBS; patients should be stable following a period of intestinal adaptation.

1.3 Clinical Studies with Teduglutide in Pediatric Subjects

One Phase 3 study, TED-C13-003, was completed in pediatric SBS subjects in the US and United Kingdom (UK). In this study, teduglutide was administered to 3 cohorts of pediatric subjects from ages 1-17. 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 PS volume at week 12 of 37%, including complete independence from PS 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 PS volume at week 12 of 39%, including complete independence from PS 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 (TESAEs) related to teduglutide were reported. No discontinuations from study were due to adverse events (AEs).

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 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.

SHP633-301 is an ongoing study in the United Kingdom, Italy, Finland, and France to evaluate the safety, efficacy, and PK of teduglutide treatment in infants 4 to 12 months of age with SBS. Like TED-C14-006, this study has a teduglutide treatment arm and a SOC arm. Subjects in both arms will participate in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the 24-week treatment period, subjects in the SOC treatment

arm will receive standard medical therapy for SBS; while those in the teduglutide treatment arm will receive daily SC injections of 0.05 mg/kg teduglutide in addition to standard medical therapy. Similar to the treatment cycles in SHP633-304, subjects in SHP633-301 may escape from the 4-week follow-up period and proceed directly to the SHP633-304 study, if they meet an escape criterion specified in the SHP633-301 protocol. It is expected the subjects entering SHP633-304 from SHP633-301 will be 11 to 19 months of age when enrolling in SHP633-304.

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 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects with SBS who completed the TED-C14-006 or SHP633-301 studies. In addition to evaluating the long-term safety and durability of efficacy after 24 weeks of treatment, this extension study will evaluate the need for additional teduglutide treatment in these subjects, and will allow for the first-time treatment of teduglutide-naïve subjects who participated in the SOC treatment arms in TED-C14-006 or SHP633-301.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objective of the study is to evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with SBS who completed TED-C14-006 or SHP633-301.

2.2.2 Secondary Objectives

The secondary objective of this study is to evaluate the long-term efficacy of teduglutide treatment in pediatric subjects with SBS who completed TED-C14-006 or SHP633-301.

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects who completed the TED-C14-006 or SHP633-301 studies (the "core studies"). At the time of entry into TED-C14-006, subjects were less than 18 years of age, were dependent on parenteral nutrition to provide at least 30% of their caloric or fluid needs, and had not been able to significantly reduce PS for at least 3 months prior to enrollment. During TED-C14-006, some subjects elected to receive standard of care instead of teduglutide treatment. Subjects who elected to receive teduglutide were randomized to 0.025 mg/kg or 0.05 mg/kg once daily (QD) dosing in a double-blinded manner.

At the time of entry into SHP633-304, subjects were 4 to 12 months corrected gestational age, were dependent on parenteral nutrition to provide at least 35% of their caloric or fluid needs, and had not been able to significantly reduce PS for at least 1 month prior to enrollment. During SHP633-301, subjects were randomized to receive standard of care or teduglutide 0.05 mg/kg SC QD.

Approximately 65 subjects who complete the core studies are expected to enroll in this extension study. All subjects who completed either core study, including those who received standard of care, may be eligible to enter SHP633-304. To be eligible to receive teduglutide treatment within SHP633-304, subjects must meet ≥1 of the teduglutide treatment inclusion criteria and none of the teduglutide treatment exclusion criteria.

Additional Teduglutide Treatment

Subjects not receiving teduglutide treatment (ie, in a “no-teduglutide treatment period”), will be seen approximately every 12 weeks for safety, parenteral support (PS) requirements, and quality of life. At any point during a no-teduglutide treatment period, subjects who meet ≥1 *teduglutide treatment inclusion* may proceed directly to the pretreatment visit if the investigator, subject, and parent agree to proceed with teduglutide therapy.

Rationale: Some pediatric subjects may have a durable beneficial effect after 24 weeks of teduglutide treatment and thus long-term follow-up without additional teduglutide treatment may be appropriate. However, there may be some pediatric subjects who deteriorate or stop improving after discontinuation of teduglutide treatment. In these pediatric subjects, additional teduglutide treatment may be beneficial.

Dose Selection

Analysis suggested that pediatric patients, ages 1 to 17 years old, are likely to require the same dose as used in adults, namely 0.05 mg/kg/day (Mouksassi et al., 2009). In this extension study, all subjects who enter a teduglutide treatment cycle will receive 0.05 mg/kg SC QD.

Rationale: Teduglutide is approved for adult use in the US and EU, and for pediatric use in the EU, at a dose of 0.05 mg/kg SC once daily. The completed pediatric studies (TED-C13-003 and TED-C14-006) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit/risk profile. In addition, population pharmacokinetic modeling and simulations were conducted to determine the effective 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 the pediatric study (TED- C13- 003) and suggested that the dose in pediatric subjects is likely to be same as the dose in adults (O'Keefe et al., 2006).

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 infants (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 of 0.05 mg/kg since AUC_{ss} was previously shown not to correlate with efficacy. Thus, the 0.05 mg/kg dose is proposed for testing in all age groups.

Duration of Treatment

The duration of teduglutide treatment in this study mirrors that of the TED-C14-006 and SHP633-301 studies, consisting of 24 weeks of teduglutide treatment, followed by a 4-week follow-up period. The follow-up period is a mechanism to evaluate whether continued teduglutide is needed. If a subject deteriorates during the follow-up period, the subject may be evaluated immediately for additional teduglutide treatment. Subjects who clinically deteriorate or stop improving at any time after the end of the follow-up period will also be assessed for additional treatment.

Rationale: During the teduglutide treatment cycle, visit frequency is similar to frequencies performed in TED-C13-003, TED-C14-006, and SHP633-301 to ensure sufficient safety monitoring and weaning of PS. During the no-teduglutide treatment, visits occur every 12 weeks, a frequency that is consistent with standard medical practices. To minimize risk to subjects, those who have deteriorated quickly after treatment interruption (ie, escaped from a prior follow-up period) may be evaluated immediately for eligibility for additional treatment when they reach the week 24 visit.

Measures and Parameters

Following the review and signing of the informed consent (and informed assent, if applicable), screening visit procedures will begin including demographics, and updates to medical history and SBS history. Subjects who meet ≥1 of the teduglutide treatment inclusion criteria may proceed to the pretreatment visit.

After the pretreatment visit, subjects who still meet ≥1 of the teduglutide treatment inclusion criteria, and meet none of the teduglutide treatment exclusion criteria, will start a 28-week cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily, followed by a 4-week follow-up (no treatment) period (Figure 3-1). During the 28-week cycle, clinic visits will occur at weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. Phone visits are required approximately

1 week after adjustments in PS during the teduglutide treatment period (between weeks 1-24), and weekly during the teduglutide follow-up period (between weeks 24 and 28).

Safety and PS requirements will be evaluated on a weekly basis, and quality of life assessments will be made approximately every 12 weeks. 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, all attempts should be made to follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) for decisions regarding PS reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines, however, is not considered a protocol deviation (Appendix 2).

Rationale: Measures of long term safety will include adverse events, growth parameters and anti-drug antibodies. Measure of long term efficacy will include durability of effect as measured by reduction in PS and improvement in pediatric quality of life measures (PedsQL, PedsQL Family Impact Module). A reduction in PS volume of at least 20% at end of treatment (EOT) was used as the primary endpoint in pivotal phase 3 adult clinical trials and the completed phase 3 pediatric study (TED-C13-003), and will be used as an endpoint in this extension study. In previous clinical studies, a reduction of this magnitude was associated with a reduction in the number of days per week of PS, and increases in enteral intake. Reduction in volume and time of PS due to improved enteral absorption may provide a pediatric subject with opportunities for more age-appropriate activities including oral rehabilitation. Quality of life assessments will be performed in this study to quantitate this effect.

Teduglutide has been found to have a targeted intestinotrophic effect. Taking into account the patient population and the pharmacologic effect of teduglutide, GI-specific screening tests, including fecal occult blood testing and colonoscopy/sigmoidoscopy, which are commonly part of the routine care of these subjects, will be performed to ensure safety. This study captures long-term safety data on polyps and other colonic mucosal changes in teduglutide-exposed subjects using the surveillance strategy proposed in Section 7.2.9.

Figure 3-1: Study Design Flow Chart

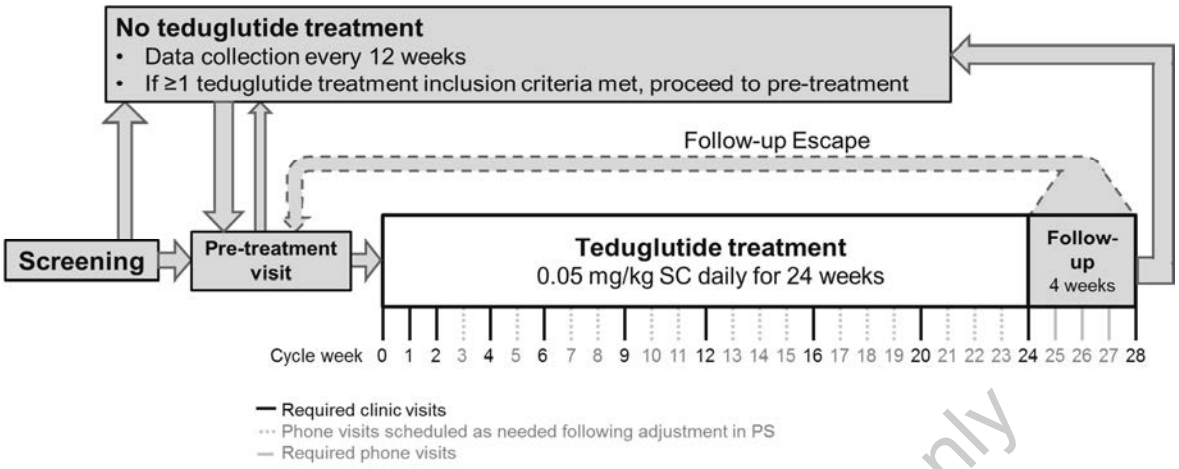

Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pretreatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects will enter a 28-week teduglutide cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24 (**solid black lines**). Phone visits are required approximately 1 week after adjustments in PS during the intervening weeks between weeks 2 and 24 (**dashed grey lines**). Subjects discontinue teduglutide at week 24 and enter a 4-week follow-up (no-treatment) period, during which phone visits will be performed weekly (**solid grey lines**). If an escape criterion is met at week 24 or during the follow-up period, subjects may proceed directly to another pretreatment visit.

3.2 Duration and Study Completion Definition

A subject will be considered enrolled in the study once the subject has provided signed consent, and meets all of the Inclusion Criteria. The study will continue for at least 1 year and until each subject has access, as needed, to teduglutide. The subject's maximum duration of participation is expected to be approximately 3 years. The study will be completed in approximately 40 months. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing the End of Study (EOS) visit.

The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact (last safety contact), whichever is later. The study completion date will be used to ascertain timing for study results posting and reporting.

4 STUDY POPULATION

Each subject must review and sign the informed consent (and informed assent, if applicable) before any study-related procedures specified in the protocol are performed. Teduglutide treatment eligibility does not impact study eligibility.

4.1 Study Inclusion Eligibility Criteria

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

1. Subject provides written informed consent (subject, parent or legal guardian and, as appropriate, subject informed assent) to participate in the study before completing any study-related procedures.
2. Subject completed the TED-C14-006 or SHP633-301 studies (including subjects in the standard of care treatment arms). Subjects are considered to have completed SHP633-301 if they completed study assessments through week 24.
3. Subject understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.2 Study Exclusion Eligibility Criteria

There are no exclusion criteria for this study.

4.3 Teduglutide Eligibility Criteria

Subjects are eligible for teduglutide treatment if at least 1 (≥1) of the teduglutide treatment inclusion criteria, and none of the teduglutide treatment exclusion criteria are met. In addition, the investigator and the subject (and/or parent or legal guardian, as appropriate) must agree to proceed with treatment.

4.4 Teduglutide Treatment Inclusion Criteria

1. Subject is teduglutide-naïve, receiving PS, and unable to significantly reduce PS or advance enteral feeds (eg, 10% or less change in PS or advance in feeds) for at least 3 months prior to and during the teduglutide pretreatment visit, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PS returns to within 10% of baseline prior to the event.
2. Subject was previously treated with teduglutide and at least 1 of the following criteria is satisfied:
    a. Increasing PS requirements following teduglutide discontinuation.
    b. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
    c. Deteriorating nutritional status eg, weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.
    d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.

e. Severe diarrhea related to teduglutide discontinuation.

4.5 Teduglutide Treatment Exclusion Criteria

1. Body weight <5 kg at the pretreatment visit.
2. Unresected GI polyp, known polyposis condition, premalignant change, or malignancy, in the GI tract
3. History of cancer in the previous 5 years except surgically curative skin cancers
4. Serial transverse enteroplasty or other major intestinal surgery within 3 months preceding the teduglutide pretreatment visit. Insertion of a feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, and endoscopic procedures are allowed.
5. Intestinal or other major surgery planned or scheduled to occur during the 28-week cycle
6. Clinically significant intestinal stricture or obstruction
7. Clinically significant, active or recurrent pancreatic or biliary disease
8. Active, severe, or unstable, clinically significant hepatic impairment or injury, including the following laboratory values at the pretreatment visit:
    a. Total bilirubin ≥2 × upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7 × ULN
    c. Alanine aminotransferase (ALT) ≥7 × ULN
9. Renal dysfunction shown by results of an estimated glomerular filtration rate below 50 mL/min/1.73 m^2 at the pretreatment visit
10. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, or patent ductus arteriosus ligation
11. Participation in a clinical study using an experimental drug (other than glutamine, Omegaven, or Smoflipid) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to the pretreatment visit and for the duration of the 28-week cycle
12. Treatment with analogs of glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2) (not including teduglutide), insulin-like growth factor-1 (IGF-1), or growth hormone, within 3 months preceding the teduglutide pretreatment visit.
13. Treatment with octreotide or dipeptidyl peptidase 4 (DPP-4) inhibitors within 3 months prior to the pretreatment visit
14. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients
15. Known history of alcohol or other substance abuse within 1 year prior to the pretreatment visit
16. Pregnant or lactating female subjects
17. Sexually active female subjects of child-bearing potential unwilling to use approved contraception during teduglutide treatment and for 30 days after the treatment period

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.

4.6 Follow-up Period Escape Criteria

At the discretion of the investigator, the follow-up period may be interrupted or omitted and the subject may proceed directly to the pretreatment visit, if ≥1 of the following criteria is met:

1. Increasing PS 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.
5. The subject escaped during the follow-up period of SHP633-301 or during the follow-up period of a previous teduglutide treatment cycle within SHP633-304.

4.7 Reproductive Potential

4.7.1 Female Contraception

To be eligible for treatment with teduglutide, sexually active females of child-bearing potential must use an acceptable form of contraception throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used, they should be administered according to the package insert. Females of child-bearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of investigational product.

To be eligible for treatment with teduglutide, female pediatric subjects and adolescent subjects should be either:

- Pre-menarchal and either Tanner Stage 1 or less than age 9 years, or
- Females of child-bearing potential (FOCBP) with a negative serum beta-human chorionic gonadotropin (β-HCG) pregnancy test at the teduglutide pretreatment visit**.** Females of child-bearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- True abstinence: Abstention of sexual activity that is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).
- Intrauterine devices plus condoms

- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)

- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the pretreatment visit, plus condoms. Note: if subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.8 Discontinuation of Subjects

4.8.1 Teduglutide Discontinuation

If the investigational product is discontinued prematurely during a teduglutide treatment cycle and the subject wishes to remain in the study, the evaluations listed for the EOT visit are to be performed. A 4-week follow-up period will ensue, consisting of weekly telephone visits (CxW25-27) and the week 28 clinic visit (CxW28). The subject would then enter a no-teduglutide treatment (NTT) period and could be evaluated for subsequent teduglutide treatment eligibility according to the study schedules. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for permanent treatment discontinuation, dates of investigational product administered (including last date of treatment), and amount of investigational product taken must be recorded in the electronic case report form (eCRF) and source documents, as described in Section 4.8.3. The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor, when possible.

4.8.2 Study Withdrawal

At any time during the study, the investigator or sponsor may withdraw a subject, or a subject may withdraw from the study, for any reason, without prejudice to their future medical care by the physician or at the institution.

If a subject withdraws from the study during a teduglutide cycle, the evaluations listed for the EOT visit are to be performed as completely as possible. Whenever possible, the subject will then be asked to return 4 weeks later for the early termination (ET) visit, and will be contacted weekly by phone during the interim period between EOT and ET for safety follow-up.

If a subject withdraws from the study during a NTT period, the evaluations listed for the ET visit are to be performed as soon and completely as possible.

Subjects who withdraw from the study will not be replaced.

4.8.3 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
- Protocol deviation
- Lack of efficacy
- Physician decision
- Withdrawal by subject
- Withdrawal by parent/guardian
- Lost to follow-up
- Pregnancy (Discontinuation of treatment only)
- Death
- Other

4.8.3.1 Subjects 'Lost to Follow-up' Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact 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 CONCOMITANT TREATMENT

5.1 Concomitant Medications and Procedures

Concomitant treatment refers to all treatment taken between the dates of informed consent and EOS, inclusive. Concomitant medications and procedures will be assessed at each site visit, and include all non-study treatments (medications, herbal treatments, vitamins, invasive and diagnostic procedures). Concomitant treatment information must be recorded on the appropriate eCRF page. Details of medication changes and/or dosages will be recorded on the eCRF.

5.1.1 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.1.2 Prohibited Treatment

The mechanism of action of teduglutide may increase enteral absorption of drugs (eg, motility medication including narcotics and opioids used for the management of SBS, warfarin, psychotropics, metronidazole, digoxin), so consideration should be given to modifying concomitant enteral medication regimens. Down-titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic range, are given at dosages that are higher than usual.

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

Table 5-1: Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pretreatment Visit
Native/synthetic glucagon-like peptide-2 (not-including teduglutide)	Any
Glucagon-like peptide-1 analog or human growth hormone	3 months
Octreotide or dipeptidyl peptidase 4 inhibitors	3 months

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is teduglutide, which 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 SHP633 investigator's brochure.

6.1.1 Blinding the Treatment Assignment

Not applicable for this open-label study.

6.2 Administration of Investigational Product(s)

6.2.1 Interactive Response Technology for Investigational Product Management

An interactive web-based response system (IWRS) will be used for screening and enrolling subjects, recording subject visits, investigational product supply dispensation and management, inventory management and supply ordering, investigational product expiration tracking and management, and return of investigational product. Please refer to the Study Manual for additional details regarding the IWRS.

The IWRS will also be used for creating, tracking, and confirming investigational product shipments. A user manual with specific functions and instructions for the IWRS will be provided to the site, and site personnel will receive training.

6.2.2 Allocation of Subjects to Treatment

This is an open-label study. Subjects will retain their assigned subject number from the TED-C14-006 or SHP633-301 studies. Assessment of need for teduglutide treatment should be guided by the teduglutide treatment inclusion criteria. If the investigator, subject, and/or parent/guardian agree to proceed with treatment, a formal evaluation of teduglutide inclusion and exclusion criteria will be performed at the pretreatment visit (Table 1-3).

6.2.3 Dosing

If teduglutide treatment eligibility is established at the pretreatment visit and again, confirmed at the CxD1 visit, the subject will start a teduglutide treatment period, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily. The initial dose will be calculated based on body weight measured at the teduglutide pretreatment visit, and adjusted as needed, based on body weight measured at week 12 (CxW12). 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 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 rotated.

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 each 24-week teduglutide treatment period, subjects will be evaluated for the need for additional teduglutide treatment. During the 4-week follow-up, the investigator will assess the subject via weekly telephone visits. At any time during the follow-up period, if escape criteria are met, the subject may proceed directly to another Pre-Treatment visit to assess treatment eligibility for another cycle (Section 4.6). Following the completion of the 4-week follow-up, the subject will continue in the study off teduglutide until teduglutide treatment eligibility criteria are again met. Additional 28-week cycles may be repeated if treatment eligibility is established each time.

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification will be applied to the investigational product(s) container.

The study drug will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of study drug will be supplied and these will be labeled in accordance with applicable regulatory requirements. Sterile water for injection syringes and other ancillary components will be provided separately and will be labeled in accordance with the applicable regulatory requirements.

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

6.3.2 Packaging

Investigational product is packaged in the following conditions:

Teduglutide will be provided in a sterile, single-use, glass vial as a lyophilized powder, to be reconstituted with 0.5 mL sterile water for injection provided as the diluent in a prefilled syringe.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 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.

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

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. The investigator is to keep a current record of the inventory and dispensation of all clinical supplies. This record will be made available to the sponsor's site monitor for the purpose of accounting for all clinical supplies. Any discrepancy or deficiency will be recorded and will include an explanation. All supplies sent to the investigator must be accounted for and in no case will clinical supplies be used in any unauthorized situation.

The investigator has overall responsibility for administering/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 (as documented by the investigator in the applicable study delegation of authority form) will dispense the investigational product only to subjects eligible for teduglutide treatment following the procedures set out in the study protocol. All dispensed study medication will be documented in the interactive response technology system and/or other investigational product record (eg, investigation product accountability form). The investigator is responsible for assuring the retrieval of all study supplies from subjects.

All used and unused study drug vials must be returned by the subjects and/or parent/guardian, and will be retained at the site. If deemed appropriate, the investigator or his/her designee may dispense the unused study drug vials to the same subject. All original containers, whether empty or containing study drug will be returned to the pharmacy. Returned study drugs will NOT be relabeled or reassigned for use by other subjects. Contents of the study drug containers will not be combined. All used and unused vials must be returned to the distribution center according to the sponsor's instruction. No vial/kit may be destroyed on site without approval by the sponsor.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

Subjects will be instructed to bring their unused investigational product and empty/used investigational product packaging to every visit. Drug accountability will be assessed 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. The pharmacist/nominated person will record details on the drug accountability form.

Compliance with study drug is calculated from subject diaries. Of those subjects eligible for teduglutide treatment, 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 Schedule of Assessments (Table 1-1, Table 1-2, and Table 1-3) and must be referred to in conjunction with the instructions provided in this section.

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 (and assent, as applicable) from the subject. A subject will have approximately 7 days, after completion of either the TED-C14-006 or SHP633-301 studies, to sign consent to participate in the SHP633-304 study. The first visit after screening must occur within 12 weeks of screening for a pretreatment visit, and within 2 to 12 weeks of screening for an NTx visit.

The screening visit (Scr) assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1-1, and as detailed below:

- Informed consent, and informed assent (if applicable), is obtained
- Study eligibility is determined. A screen failure is a subject who has given informed consent and failed to meet the Study Inclusion Eligibility Criteria. Subjects cannot be rescreened once they have been designated as a screen failure.
- Demographics, updates to medical history and SBS history
- Intake and output diaries are dispensed
- Evaluate teduglutide treatment inclusion criteria
- Adverse events, concomitant medications and concomitant procedures

7.1.2 Visits for Subjects Not Receiving Teduglutide

While outside of the 28-week teduglutide-treatment cycle, subjects will be followed approximately every 12 weeks for safety and efficacy assessments. No-teduglutide treatment visits are numbered sequentially (NT1, NT2, etc.), even if interrupted by the treatment cycles. The visit window (±7 days) is relative to the first NTx visit in the current NTT period. Assessments will be performed as outlined in Table 1-2 and described below.

- Intake and output diaries are dispensed
- Evaluate teduglutide treatment inclusion criteria
- Adverse events, concomitant medications and concomitant procedures
- Physical examination and vital signs, including weight

- Height and head circumference
- Review intake and output diaries
- Record PS prescription and adjust as needed
- Safety Laboratory Tests (ie, clinical chemistry, hematology, and urinalysis)
- PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales
- Antibodies to teduglutide, if and when required
- Fecal occult blood testing, as indicated (Section 7.2.9.1)
- Colonoscopy/sigmoidoscopy, as indicated (see Section 7.2.9.2)
- Serum sample, as indicated

Teduglutide treatment may be considered at any time during the NTT period. If the investigator and the subject (and parent or legal guardian, as appropriate) agrees to proceed with treatment if the subject is eligible, the subject may proceed to the pretreatment visit immediately to determine eligibility.

7.1.3 Visits for Subjects Receiving Teduglutide

7.1.3.1 Pre-treatment Visit

Subjects who meet at least 1 of the teduglutide treatment inclusion criteria during the screening visit or during the NTT period may proceed to the pretreatment visit immediately if the investigator, subject and parent agree to proceed with teduglutide therapy. Similarly, subjects who meet escape criteria at cycle week 24 or during the teduglutide follow-up period may proceed to the pretreatment visit immediately.

The pretreatment visit may also be combined with screening visit, and if the pretreatment visit assessments occur within 7 days of the TED-C14-006 or SHP633-301 EOS visit, both sets of assessments can be combined. A subject must have 2 weeks of intake diary data collected, prior to the first dose administration (CxD1) during any teduglutide treatment cycle. In general, pretreatment assessments may occur over a period of up to 21 days. The teduglutide pretreatment visit (Px) assessments and procedures will be performed as in Table 1-3 and as described below:

- Evaluate teduglutide eligibility (treatment inclusion/exclusion criteria)
- Dispense intake and output diaries
- Adverse events, concomitant medications and concomitant procedures
- Fecal occult blood testing

- Gastrointestinal-specific testing, including colonoscopy or sigmoidoscopy as indicated
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries
- Record PS prescription and adjust as needed.
- Safety Laboratory Tests
  (In addition to clinical chemistry, hematology, and urinalysis, labs at this visit include prothrombin time [PT] international normalized ratio [INR]. Subsequent prothrombin time/international normalized ratio [PT/INR] measurement is only required to evaluate for suspected drug-induced liver injury [DILI]).
- Serum pregnancy testing, if applicable (when the pretreatment and screening visits are combined, the serum pregnancy test should be performed at the local laboratory)
- Serum sample

7.1.3.2 Teduglutide Treatment Period (CxD1-CxW24)

The open-label teduglutide treatment period will comprise 24 weeks, during which all assessments and procedures listed for Visits CxD1-CxW24 in Table 1-3 shall be completed. Cycles are numbered sequentially, such that the first visit of the first cycle is C1D1, and the first visit of the second cycle is C2D1, etc. Visit windows are calculated based upon the date of first investigational product administration (Visit CxD1).

Visit CxD1

Assessments and procedures at this visit will be performed as outlined Table 1-3 and as described below.

Two weeks of intake diary data are required before drug is administered at CxD1.

- Confirm teduglutide treatment eligibility
- Dispense intake and output diaries
- Adverse events, concomitant medications and concomitant procedures
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries
- Record PS prescription and adjust as needed

- Safety laboratory tests
- Quality of life measurements
- Antibodies to teduglutide
- Pregnancy testing (urine), if applicable
- Dispense study drug

Site Visits during Teduglutide Treatment Period

Subjects will return for clinic visits on cycle weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24/EOT. Assessments and procedures at these visits will be performed as outlined in Table 1-3 and as described below:

- Dispense/review intake and output diaries (every effort should be made to complete 2 weeks of intake diary entries prior to each clinic visit and to complete 48 hours of output diary entries during a period of nutritional stability prior to each clinic visit)
- Physical examination and vital signs, including weight
- Record PS prescription and adjust as needed
- Safety laboratory tests
- Urine pregnancy testing for FOCBP (CxW4, CxW9, CxW12, CxW16, CxW20, CxW24)
- Study drug dispensation (except for CxW24)
- Adverse events, concomitant medications and concomitant procedures

In addition, at CxW12 and CxW24 Visits **ONLY**, the following procedures will be performed:

- Height and head circumference
- Antibodies to teduglutide
- Fecal occult blood testing (FOBT)
- GI-specific testing, including colonoscopy or sigmoidoscopy as indicated
- Quality of life measurements

At CxW24 **ONLY**, a serum sample is collected and stored for future analysis. This sample will not be used for genetic testing and lack of collection will not constitute a protocol deviation.

Escape criteria are also evaluated at CxW24. The investigator may combine the CxW24 assessments with the next pretreatment visit assessments if at least 1 escape criterion is met at the CxW24 visit and the pretreatment assessments occur within 7 days of the CxW24 visit.

Phone Visits

Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period. Phone visit assessments and procedures are outlined in Table 1-3 and described below:

- Review intake and output diaries
- Safety laboratory tests (clinical chemistry and urinalysis)
- Record PS prescription and adjust as needed
- Obtain AEs, concomitant medications, and concomitant procedures
- Evaluate escape criteria

7.1.4 Teduglutide Follow-up Period

The safety follow-up period for this protocol is 4 weeks (weeks 25 – 28 of the cycle). Phone visits will occur on cycle weeks 25, 26, and 27 for all subjects. Phone visit assessments and procedures at weeks 25-27 will be the same as for telephone visits performed during the teduglutide treatment period. In addition, subjects will be evaluated for follow-up period escape criteria. If escape criteria are met at any time during the follow-up period, the subject may proceed directly to another pretreatment visit at the investigator's discretion. The investigator may combine the CxW24 or CxW28 visits with the next pretreatment visit if at least 1 escape criterion is met at the CxW24 or CxW28 visits, and the pretreatment assessments occur within 7 days of the CxW24 or CxW28 visit. If a subject is completing the study at the CxW28 visit, the EOS/ET visit (Section 7.1.5) will take place in lieu of the CxW28 visit. Otherwise, following completion of the 28-week treatment cycle, the subject will proceed to an NTT visit within approximately 12 weeks.

At cycle week 28 (CxW28), subjects will return to the study site. In addition to the assessments performed at weeks 25-27, the following procedures will be performed at **CxW28 ONLY:**

- Dispense intake and output diaries
- Physical examination and vital signs, including weight
- Antibodies to teduglutide
- Pregnancy testing (urine), if applicable
- Evaluate escape criteria

7.1.5 Study Completion/Early Termination Visit (EOS/ET Visit)

All subjects will return to the study site for the end of study/early termination visit (EOS/ET). Assessments and procedures at this visit will be performed as outlined in Table 1-1 and as described here. If a subject discontinues the study prematurely, the assessments for the EOS/ET Visit are to be performed as completely as possible (see Section 4.8.2).

- Adverse events, concomitant medications and concomitant procedures
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries (the intake diary should be completed daily for a minimum of 2 weeks prior to the EOS/ET visit. The output diary should be completed daily over a 48-hour period of nutritional stability before the EOS/ET visit)
- Record PS prescription and adjust as needed
- Safety laboratory tests
- Fecal occult blood testing, as indicated
- Gastrointestinal-specific testing, including colonoscopy or sigmoidoscopy as indicated.
- Quality of life measurements
- Antibodies to teduglutide
- Pregnancy testing, as needed

7.2 Study Evaluations and Procedures

7.2.1 Demographics, Medical History, and SBS History

Demographics, medical history, and SBS history will be obtained at screening. Medical history for purposes of this extension study will consist of the following:

- Adverse events that were ongoing at the time of completion of TED-C14-006 or SHP633-301
- Events that occurred during the period between completion of TED-C14-006 or SHP633-301 and informed consent to SHP-633-304

This medical history information will supplement the medical history information collected at the start of the TED-C14-006 or SHP633-301 core studies. If the subject has any changes to the SBS history collected at the baseline visit of the TED-C14-006 or SHP633-301 studies, that information (updated SBS history) will be collected.

7.2.2 Physical Examination

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

7.2.3 Vital Signs, Body Weight, Height, Head Circumference and Body Mass Index

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 cuff (using the same method, the same extremity, and in the same position throughout the study, whenever possible).

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Height (or length) and head circumference (for subjects ≤36 months of age) will be measured at selected visits. A height z-score, weight z-score, BMI, and BMI z-score will be calculated by the sponsor using the site-provided height and weight data collected at each site visit

New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

7.2.4 Clinical Laboratory Tests

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 1-1, Table 1-2, and Table 1-3) 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 teduglutide treatment period, subjects will also have safety labs within approximately 5-7 days after a PS adjustment. Safety labs performed after PS 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 8.1). Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

New clinically significant labs should be reported as AEs.

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

Table 7-1: List of Laboratory Tests

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

Coagulation:
Prothrombin time/International normalized ratio

Urinalysis:
- Blood
- Glucose
- Leukocytes
- Microscopic analysis
- pH
- Protein
- Specific gravity

Pregnancy tests (females of childbearing potential):
- Serum β-HCG (screening)
- Urine β-HCG (all other visits)

Biochemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bicarbonate
- Bilirubin (total, direct, 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
- Uric acid

7.2.5 Serum Sampling

Serum samples will be collected and stored for future analysis at the following times:

- At the pretreatment visit. If the subject arrived at the pretreatment visit by meeting an escape criterion, the serum sample will not be repeated at the pretreatment visit, because it will have been collected recently at the CxW24 visit.
- At the CxW24 (EOT) visit
- During NTT: Approximately every 24 weeks

The serum sample will not be used for genetic testing. Lack of collection will not constitute a protocol deviation.

The sponsor, sponsor's representatives, biorepositories, and any specialty laboratories will be blinded to the subject's identity. The sample and/or extracted material will otherwise be stored for up to 15 years from the end of the study after which time it will be destroyed. Upon written request, subjects will be permitted to withdraw their sample from the analysis and have their

sample and/or extracted material destroyed. Any results already generated from the samples will not be removed from any analyses that have already been performed.

7.2.6 Pregnancy Testing

A serum pregnancy test is performed on all FOCBP at the teduglutide pretreatment visit (when the pretreatment and screening visits are combined, the serum pregnancy test should be performed at the local laboratory). Urine pregnancy tests will be administered at all other visits according to the study schedules, or if pregnancy is suspected, or as specified per protocol upon withdrawal of the subject from the study.

7.2.7 Antibody Testing

Blood samples will be drawn for the analysis of antibodies to teduglutide according to the Schedule of Assessments (Table 1-1, Table 1-2, and Table 1-3). Blood samples for antibodies may be drawn from a central line or from peripheral access. The sample drawn on CxD1 must be drawn prior to administration of the first dose of teduglutide. Once the subject has started teduglutide treatment, samples must be drawn at least 14 hours after dosing. Subjects who test positive for antibodies to teduglutide will also be tested for neutralizing antibody. Subjects who have been previously treated with teduglutide, and who test positive for antibodies to teduglutide, will have follow-up blood draws for antibodies to teduglutide every 12 weeks while on study until a negative result is obtained.

7.2.8 Volume of Blood

Efforts will be made to minimize the amount of blood drawn from all pediatric subjects enrolled 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 annually are shown in Table 7-2.

Table 7-2: Approximate Volume of Blood to be Drawn from Each Subject Annually

Assessment		Sample Volume (mL)	No. Samples per two 28-week Teduglutide Cycles	Total Volume (mL)
Subjects Receiving Teduglutide Treatment				
Safety	Biochemistry and β-hCG[a]	2.5	24	60
	Hematology	2	24	48
	Coagulation Parameters	1	2	2
	Antibodies	2	8	16
	Serum storage samples	3	4	12
Total mL per 2, 28-week Treatment Cycles (Approximate Annual Volume):				**138**
Subjects Not Receiving Teduglutide Treatment[b]				
Assessment		**Sample Volume (mL)**	**No. Samples per 4 NTT Visits**	**Total Volume (mL)**
Safety	Biochemistry	2.5	4	10
	Hematology	2	4	8
	Serum storage samples	3	2	6
Total mL per 4 "No-Teduglutide Treatment" Visits 48-week period:				**24**

Abbreviations: β-hCG=beta-human chorionic gonadotropin; NTT=no-teduglutide treatment
[a] β-hCG testing will only be administered to females who are eligible for teduglutide treatment.
[b] Subjects not receiving teduglutide treatment, but who were exposed to it previously and tested positive for anti-teduglutide antibodies will require blood samples for antibody testing every 12 weeks until they test negative.

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 PS adjustment, and anti-teduglutide antibody testing during no-teduglutide treatment. Saved serum samples should be omitted for subjects weighing less than 10 kg and whenever local blood volume limitations are exceeded.

7.2.9 Gastrointestinal-specific Testing

7.2.9.1 Fecal Occult Blood Testing

Fecal occult blood testing must be performed on all subjects at the pretreatment visit, week 12, and week 24 of the teduglutide cycle. During NTT periods, FOBT must be performed on teduglutide-exposed subjects (subjects who have received teduglutide any time in the past and are therefore not teduglutide-naïve) on a roughly annual basis (approximately every 48-60 weeks). Actions to be taken in response to a positive FOBT are described below.

7.2.9.2 Colonoscopy or Sigmoidoscopy

Teduglutide-naïve subjects age 12 and older will undergo colonoscopy or sigmoidoscopy at the pretreatment visit if one has not been performed within 1 year.

Subjects of any age with newly positive FOBT results at the pretreatment visit for which a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy or sigmoidoscopy prior to receiving teduglutide. If newly positive FOBT results (for which a readily detectable cause cannot be identified) are obtained at the end of a teduglutide treatment cycle (CxW24/EOT), colonoscopy or sigmoidoscopy will be performed. The need for colonoscopy or sigmoidoscopy in response to positive FOBTs at any other point during the study, or to re-evaluate persistently positive FOBTs is at the discretion of the investigator.

Teduglutide-exposed subjects who have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) will undergo colonoscopy or sigmoidoscopy. While receiving additional teduglutide treatment, subjects will undergo colonoscopy or sigmoidoscopy at 5 year intervals or more often as needed.

Upper endoscopy may be performed along with any colonoscopy or sigmoidoscopy at the investigator's discretion. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. Subjects with unresected GI polyps, polyposis conditions, premalignant change or malignancy in the GI tract will be excluded from teduglutide treatment.

7.2.10 Nutritional Support

Nutritional support includes PS, EN, and other food and fluids. Advances in EN and/or reductions to PS will be based on clinical status, including weight, linear growth, hydration status, and safety laboratory results. Intake and output diaries will include data to be considered in the adjustment of each subject's nutritional support. Guidelines for nutritional support management and weaning algorithms are provided in Appendix 2.

7.2.11 Diaries

7.2.11.1 Study Drug Administration Diary

A study drug administration diary will record administration of teduglutide. This diary should be completed by the subject (or parent/legal guardian, as applicable) daily during the teduglutide treatment periods (between visits CxD1 and CxW24).

7.2.11.2 Intake Diary

Intake diaries will be used to collect and evaluate each subject's nutritional support. The subject/parent/guardian will complete the appropriate fields of the PS section of the intake diary 2 weeks prior to ALL scheduled site visits (except at pretreatment visit). During the 24-week teduglutide treatment period, the intake diary will also be completed for 1 week following PS adjustments. The intake diary will also be completed daily during the 4-week follow-up period. The following data will be captured in the intake diaries:

- Parenteral support volume and infusion duration
- Site personnel will determine the actual PS daily calories based on diary entries.

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 PS reduction and advance in feeds.

7.2.11.3 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 that are in a teduglutide treatment cycle within 1 week of implementing a change in the PS prescription, regardless of previous teduglutide exposure.

Urine data:

- Toilet-trained subjects (who do not wear diapers)
  Measure and record all urine output in mL or cc
- Nontoilet-trained subjects (who wear diapers)
  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 may be asked to collect the first void after the daily PS infusion to measure specific gravity

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

- Toilet-trained subjects (who do not wear diapers)
  Record the occurrence of each bowel movement and score the stool consistency using the Bristol Stool Form Scale (see Output diary)
- Nontoilet-trained subjects (who wear diapers)
  Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency using the Bristol Stool Form Scale

(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. Ostomy output will not be scored using the Bristol scale.

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 PS reduction and advance in feeds.

7.2.12 Health-related Quality of Life Assessments

Throughout the study, health-related quality of life assessments will be performed using the PedsQL Generic Core Scales. Each PedsQL age-appropriate form takes less than 4 minutes to complete. The scales include self-reports for pediatric subjects and adolescents aged 5 to 18 years and proxy-reports from parents of pediatric subjects aged 2 to 18 years. The PedsQL Generic Core Scales will not be performed for subjects younger than 2 years of age. If a child is unable to complete the age-appropriate questionnaire (eg, due to developmental delay or other illness) it will not constitute a protocol deviation, but the parent should continue to complete the appropriate parent-specific forms.

Field trials have shown that the internal consistency reliability of the PedsQL was excellent, with alphas for the generic core scales in both self- and proxy-report greater than the 0.70 standard, and alphas for the full 23-item scale approaching 0.90 for self- and proxy-report. Missing data were minimal. Item response distributions were across the full scale range, with no floor effects, and minimal ceiling effects.

The validity of the PedsQL Generic Core Scales was demonstrated through known group comparisons, and correlations with other measures of disease burden. The PedsQL self- and proxy-report distinguished between pediatric subjects with and without a chronic health condition, and within the group of pediatric subjects with a chronic condition, between those who did or did not have an overnight hospital visit in the last 12 months. Further, both child self-report and parent proxy-report correlated significantly with the number of days the child was too ill to pursue normal activities, needed someone to care for him or her, missed school in the last month, the number of days the parent missed from work in the last month, and parent-report of problems pursuing their normal work routine and concentrating at work. The PedsQL Generic Core Scales are also responsive to clinical change, as demonstrated in field trials.

7.2.12.1 Pediatric Quality of Life Generic Core Scale (PedsQL™), Acute version

The PedsQL Generic Core Scale is designed to measures health-related quality of life (HRQoL) in pediatric subjects and adolescents (2-18 years of age). The developmentally appropriate PedsQL Generic Core Scale will be completed by either the parent or legal guardian and subject as indicated in Table 7-3 at the time points as outlined in Table 1-1, Table 1-2, and Table 1-3.

Table 7-3: Developmentally Appropriate PedsQL™ Generic Core Scales

Report	Completed by
Parent Report for Toddlers (ages 2-4)	Parent or Legal Guardian
Child Self Report and Parent Proxy-Report for Young Pediatric subjects (ages 5-7)	Subject and Parent or Legal Guardian
Child Self Report and Parent Proxy-Report for Pediatric subjects (ages 8-12)	Subject and Parent or Legal Guardian
Child Self Report and Parent Proxy-Report for Teens (ages 13-18)[a]	Subject and Parent or Legal Guardian

Abbreviations: PedsQL=Pediatric Quality of Life Inventory

[a] The Child Self Report and Parent Proxy-Report for Teens (ages 13-18) will also be completed for subjects older than 18 years of age

The Parent Report for Toddlers (ages 2-4) of the PedsQL Generic Core Scale is composed of 21 items comprising 4 dimensions as follows: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), 4) School Functioning (3 items).

The Child and Parent Reports of the PedsQL Generic Core Scale for Young Pediatric subjects (ages 5-7), Pediatric subjects (ages 8-12), and Teens (ages 13-18) are composed of 23 items comprising 4 dimensions as follows: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), 4) School Functioning (5 items).

7.2.12.2 Pediatric Quality of Life Family Impact Module (PedsQL™), Acute version

The PedsQL Family Impact Module is a parent-report multidimensional instrument that will be completed by the parent or legal guardian, as outlined in Table 1-1, Table 1-2, and Table 1-3.

The PedsQL Family Impact Module is a specific module of the PedsQL that is used to measure the impact of pediatric chronic health conditions on parents and the family (Varni et al., 2004). The 36-item PedsQL Family Impact Module consists of 6 scales measuring parent self-reported functioning as follows: 1) Physical Functioning (6 items), 2) Emotional Functioning (5 items), 3) Social Functioning (4 items), 4) Cognitive Functioning (5 items; worries about treatment and disease), 5) Communication (3 items), 6) Worry (5 items). Two additional scales measure parent-reported family functioning as follows: 1) Daily Activities (3 items), and 2) Family Relationships (5 items). The PedsQL Family Impact Module should take the parent or legal guardian approximately 5 to 10 minutes to complete.

7.2.12.3 PedsQL Gastrointestinal Symptoms Module (PedsQL™), Acute version

The PedsQL Gastrointestinal Symptom Module is a disease-specific 58-item module, comprised of 10 different symptom scales that assess gastrointestinal symptom-related quality of life: food and drink limits, trouble swallowing, heartburn and reflux, nausea and vomiting, gas and bloating, constipation, blood in poop, and diarrhea. The PedsQL Gastrointestinal Symptoms Module was designed to allow the selection and scoring of individual scales from the Module. The scales of Food and Drink Limits (6 items) and Diarrhea (7 items) were identified as clinically relevant and appropriate for the symptoms experienced in this pediatric study population, and therefore, are the only scales used in this study. The scales will be completed by either the parent or legal guardian and subject as indicated in Table 7-3 at the time points outlined in Table 1-1, Table 1-2, and Table 1-3.

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 7.1.4. 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 pretreatment 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.

In consideration of whether a treatment-emergent adverse event (TEAE) might lead to dose interruption (Section 8.4.1) or early termination of the study (Section 8.5), severe TEAEs will also be graded according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) severity grading criteria (US Department of Health and Human Services et al., 2010).

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 study drug that are not resolved at EOT 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 in 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.

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 (eg, 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

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.4.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Global Drug Safety Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the Shire Medical Monitor using the details specified in the emergency contact information section of the protocol. In the event a subject becomes pregnant during the study, teduglutide administration must be discontinued immediately.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Adverse Event Form for Serious Adverse Events and Non-serious AEs as Required by the Protocol. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by the Protocol as well as the Shire Investigational and Marketed

Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or will determine the pregnancy onset date.

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 serious adverse event (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 7.1.4, 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 of Individual Subjects

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

Study drug must be discontinued if any of the following events occur:

- Pregnancy
- Severe hypersensitivity, such as anaphylaxis determined by the investigator to be related to study drug. This does not include the presence of anti-teduglutide antibodies, mild injection site reactions or mild symptoms that according to the investigator do not pose a significant risk to the subject.
- An AE that is of NCI CTCAE severity Grade 3 or 4 and considered to be related to study drug administration
- Confirmed DILI related to teduglutide (see Section 8.4.2)

8.4.1 Dose Interruption Criteria Based on Adverse Event Severity and Relationship to Investigational Product

The investigational product must be discontinued if the subject experienced an AE that is of severity ≥Grade 3 per the NCI CTCAE and is reported as related to the investigational product.

In consideration of whether a TEAE might lead to dose interruption, severe TEAEs will also be graded according to the NCI CTCAE severity grading criteria (US Department of Health and Human Services et al., 2010). All such TEAEs should be discussed with the Shire Medical Monitor or designee as soon as possible. The length of the dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

8.4.2 Dose Interruption Criteria Based on Drug-Induced Liver Injury

Teduglutide administration for an individual subject may need to be interrupted if the subject has clinical and laboratory evidence of potential DILI, in the absence of an alternative explanation, as identified by the following criteria:

- ALT or AST >8x ULN
- ALT or AST >5x ULN and >2x baseline value for more than 2 weeks
- (ALT or AST >3x ULN and >2x baseline value) and (total bilirubin >2x ULN or INR>1.5)
- ALT or AST >3x ULN and >2x baseline value with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

All laboratory values suggestive of potentially new DILI should be repeated and verified within 3 days. International normalized ratio should be measured with this set of verification laboratory assessments 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 to evaluate the cause of liver injury. This evaluation may include, as clinically indicated, consideration of sepsis, acute viral hepatitis (eg, hepatitis A immunoglobulin [IgM], hepatitis B surface antigen, hepatitis C antibodies, cytomegalovirus IgM, Epstein-Barr virus antibody panel), hepatobiliary obstruction (ultrasound), autoimmune hepatitis (anti-nuclear, anti-smooth muscle, anti-actin, or anti-liver kidney microsomal antibodies), intestinal failure associated liver disease, cardiovascular causes such as ischemic hepatitis, and concomitant hepatotoxic treatments.

Additional evaluations may be performed at the discretion of the investigator in consultation with the Shire medical monitor.

Teduglutide administration must be permanently discontinued if DILI is confirmed and deemed related to study drug.

8.5 Early Termination of the Clinical Study

The data monitoring committee (DMC) may recommend stopping the study if any of the following conditions are met:

- ≥2 subjects develop the same event of CTCAE severity Grade 3 that is reported as related to the investigational product

  or

- 1 subject develops an event of CTCAE severity Grade 4 that is reported as related to the investigational product.

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol in 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 in 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. Unscheduled safety follow up assessments (including visits conducted after EOS) are not to be collected unless requested.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management process. 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 its agent. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, USA) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the statistical methods and definitions 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.

9.4 Planned Interim Analysis, and Data Monitoring Committee

An interim analysis is planned when 6 months of safety data have been collected for subjects entering from TED-C14-006. Additional interim analyses may be conducted as needed.

A 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.

9.5 Sample Size Calculation and Power Considerations

The number of subjects in this study is not based on statistical power considerations as this is an extension study of the core studies, TED-C14-006 and SHP633-301. The maximum number of subjects was determined by the enrollment in TED-C14-006 and SHP633-301.

9.6 Study Population

The safety population includes all enrolled subjects in the study. Safety population will be used for both safety and efficacy analyses.

9.7 Efficacy Analyses

No claims of statistical significance will be made; however, 95% confidence intervals will be provided, if applicable. Continuous variables, including those assessed on a discrete scale, 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.

9.7.1 Efficacy Endpoints

Efficacy endpoints will be analyzed at the end of each teduglutide treatment period (week 24 or EOT), and at each study visit, relative to the baseline of the core study (TED-C14-006 or SHP633-301) and/or first exposure to teduglutide. The following efficacy endpoints will be analyzed:

- Reduction in PS volume of at least 20%
- Absolute and relative change in PS volume
- Complete weaning off PS
- Change in days per week of PS

9.8 Safety Analyses

9.8.1 Safety Endpoints

The following safety endpoints will be analyzed:

- Adverse events
- Vital signs, including temperature, heart rate, and blood pressure
- Laboratory safety data (ie, clinical chemistry, hematology, and urinalysis)
- Urine output
- Stool output
- Antibodies to teduglutide
- Gastrointestinal-specific testing , including fecal occult blood testing and colonoscopy or sigmoidoscopy
- Z-scores for weight, height (or length), head circumference (up to 36 months of age), and BMI

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number of events, incidence, and percentage of AEs will be calculated overall, by System Organ Class (SOC) and by preferred term. SAEs will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) with regard to drug class and drug name. The number and percentage of subjects with specific prior medications will be summarized. Medical history (including surgical/procedural history) will be coded using MedDRA. The number and percentage of subjects with specific histories will be summarized by system organ class and preferred term.

For clinical laboratory tests, vital signs, body weight, and fluid balance variables, descriptive statistics (mean, median, standard deviation, minimum and maximum values, the number and percentage of subjects in specified categories) will be calculated to summarize the observed values and change from baseline at each scheduled visit.

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

Additional safety parameters and measures will include change in body weight, height (or length) and head circumference (up to 36 months of age). Derived variables will include height z-score, weight z-score, BMI, and BMI z-score. Descriptive statistics (mean, median, standard deviation, minimum and maximum values, the number and percentage of subjects in specified categories) will be calculated to summarize the absolute values and change from baseline at each scheduled visit.

9.9 Other Analyses

9.9.1 Health-related Quality of Life Analyses

Health economics and outcomes research endpoints will be analyzed at approximately 12-week intervals (weeks 12 and 24 of each teduglutide treatment cycle, and every 12 weeks for subjects not on teduglutide), relative to the study baseline. The beginning of each treatment cycle (CxD1) will be an additional baseline.

- Change in Pediatric Quality of Life Inventory (PedsQL) score
- Change in PedsQL Family Impact Module score
- Change in PedsQL Gastrointestinal Symptoms Module Sub-Scales scores:
    - Food and Drink Limits
    - Diarrhea

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 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 to the CRO 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 EOS 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 is appointed to review the final CSR for multicenter studies. Agreement with the final CSR 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 products, 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 Case Report Forms

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded into eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. 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 into the eCRF.

eCRFs should be approved by the investigator per study specifications and data deliverable requirements.

The clinical research associate (CRA)/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 diary cards, original clinical laboratory reports, and histology and pathology 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 CRA/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 subject 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 and assent, where applicable, from 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 or the subject's legally-authorized representative, as applicable, 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 (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or 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.

Within the source documents, site personnel should document instruction of and understanding by the parent/legally-authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

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 which 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.

For sites within the EU, the applicant for an EC opinion can be the sponsor, the investigator, or for multicenter studies 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 (or 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; for sites within the EU, this can be done by the sponsor, the investigator or for multicenter studies 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 (or 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 review 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 SHP633; national or local regulatory authorities; and the IRBs/ECs 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 2-4 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 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	08 April 2016	Global
Amendment 1	22 Nov 2016	Global
Amendment 2	23 Mar 2017	Global
Amendment 3	16 May 2018	Global

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	**Amendment Date 23 Mar 2017**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Updated emergency contact information		Emergency Contact Information; Section 8.1.6; Section 8.2.2; Section 8.2.4
To allow for approximately 7 days for subjects to transfer from Study TED-C14-006 to Study SHP633-304 (instead of up to 7 days).		Table 1-1; Section 7.1.1
A footnote was added at the pretreatment visit in the Schedule of Events for Subjects While Receiving Teduglutide to underscore that, when the first pretreatment visit (P1) follows the screening visit, it must occur within 12 weeks of screening.		Table 1-3
Revised the language on abstinence as a contraceptive method for consistency with the Medicines and Healthcare Products Regulatory Agency (MHRA) Clinical Trial Facilitation Group's "Recommendations related to contraception and pregnancy testing in clinical trials."		Section 4.7.1
Clarification that ancillary components, in addition to sterile water for injection syringes, will also be provided and labeled in accordance with the applicable regulatory requirements.		Section 6.3.1
A footnote was added in Table 7-2 to clarify that subjects older than 18 years of age will continue to use the Child Self Report and Parent Proxy-Report for Teens (ages 13-18) when completing the Pediatric Quality of Life Generic Core Scale (PEDSQL™).		Section 7.2.12.1 (Table 7-3)
Revised the text on severity categorization to specify that a severe treatment-emergent adverse event (TEAE) that might lead to dose interruption (Section 8.4.1) or early termination of the study (Section 8.5) will also be graded according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) severity grading criteria, in addition to the standard severity categorization. These events are no longer limited to only the events described in Table 8-1, entitled "CTCAE Criteria for Adverse Events that May Lead to Dose Interruption (Prospective Period of Observation Only)." Therefore, Table 8-1 has been deleted.		Section 8.1.1; Section 8.4; Section 8.4.1 Table 8-1 (deleted)

Revised the criteria for early termination of the study: stopping criteria were extended to all NCI CTCAE Grade 3 and 4 severity events reported as related to the investigational product, and no longer limited to the events described in Table 8-1, entitled "CTCAE Criteria for Adverse Events that May Lead to Dose Interruption (Prospective Period of Observation Only)."	Section 8.5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **22 Nov 2016**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Title of the Shire medical monitor has been changed to [redacted] for clarity.		Protocol Signature Page Emergency Contact Information
Clarification has been made that during the no-teduglutide treatment period, visits will take place *approximately* every 12 weeks.		Synopsis Sections 3.1, 7.1.2 Figure 3-1
The study design flow chart has been edited for clarity.		Synopsis Figure 3-1
The collection of all actual and prescribed enteral nutrition data has been removed to reduce the burden on the subjects and investigators. Enteral nutrition data are not required as the efficacy endpoints are limited to parenteral support parameters.		Synopsis Table 1-1, Table 1-2, Table 1-3 Sections 7.1.2, 7.1.3.1, 7.1.3.2, 7.1.5, 7.2.11.2, 7.2.11.3
Exclusion criterion 11 has been revised to add Smoflipid as other experimental drugs that are allowed prior and during the study. Like glutamine and Omegaven, Smoflipid is not expected to interfere with the assessments of safety and efficacy of teduglutide and many subjects may already be receiving the treatments off-label as part of standard medical therapy.		Synopsis Section 4.5
Exclusion criterion 12 and prohibited treatment have been refined: exclusion/prohibition of treatment with growth hormone has been extended to 3 months for consistency with other teduglutide studies.		Synopsis Section 4.5 Table 5-1
The language on escape criteria has been corrected for consistency within the protocol.		Synopsis Section 4.6
Language in efficacy and safety endpoints has been clarified.		Synopsis Sections 9.7.1, 9.8.1
Completion and review of intake and output diaries have been clarified.		Table 1-2, Table 1-3 Sections 7.1.3.2, 7.1.5
When the screening and pretreatment visits are combined, the serum pregnancy test required at the pretreatment visit should be performed at the local laboratory instead of the central laboratory. This will ensure timely results prior to starting treatment with teduglutide.		Table 1-3 Sections 7.1.3.1, 7.2.6
The requirement for urine specimen collection has been revised so that a lack of urinalysis will not constitute a protocol deviation for any pediatric subjects (not only for subjects wearing diapers).		Table 1-1, Table 1-2, Table 1-3 Section 7.2.4

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **22 Nov 2016**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Clarification has been made that the first no-teduglutide treatment visit after the screening visit will occur within 2 to 12 weeks of the screening (formerly within 12 weeks of screening).		Synopsis Table 1-2 Section 7.1.1
Windows have been clarified for visits during the no-teduglutide and teduglutide treatment periods.		Table 1-2, Table 1-3 Section 7.1.2
'Specific' has been deleted from 'positive/specific anti-teduglutide antibodies' to eliminate the redundancy. By definition, positive samples must be specific (as assessed in the confirmatory assay), or otherwise considered negative.		Table 1-2 Sections 7.2.7, 9.8.1
Parental height and gestational age at birth have been removed from medical history.		Table 1-1 (footnote b) Section 7.2.1
For consistency within the protocol, sigmoidoscopy has been added as the alternate to colonoscopy throughout the protocol.		Table 1-1, Table 1-2, Table 1-3 Sections 3.1, 7.1.2, 7.2.9.2
Removal of former footnote i on fecal occult blood test for clarity.		Table 1-3
Clarification has been made on circumstances when the CxW28 visit may be combined with the next pretreatment or EOS/ET visit.		Table 1-3 Section 7.1.4
The text on PS support requirements over time in pediatric subjects with SBS has been clarified, and text on intestinal adaptation has been refined.		Section 1.1
Status of current teduglutide approvals for use has been updated.		Section 1.2, 3.1
The term 're-challenge' has been replaced with 'additional teduglutide treatment' for clarity and consistency with other studies.		Section 3.1
Number of subjects enrolled has been corrected for consistency with protocol synopsis.		Section 3.1
Definition of a subject's completion of the study has been corrected for consistency within the protocol.		Section 3.2
Evaluations to be performed when a subject discontinues teduglutide or when withdraws from the study have been clarified.		Sections 4.8.1, 4.8.2
Withdrawal by parent/guardian has been added as reason for discontinuation.		Section 4.8.3
COUMADIN has been changed to warfarin for clarity.		Sections 5.1, 5.1.2
Clarification has been made on handling of study drug, which is for single use only and should be used within 3 hours following reconstitution.		Section 6.3.3
The investigator or designee may now dispense the unused study drug vials to the same subject if deemed appropriate to ensure sufficient supplies between visits. Also, documentation of all dispensed study medication has been clarified.		Section 6.4
Clarification has been made that local laboratory results are not required to be entered in the eCRFs.		Section 7.2.4
Collection of urine sodium and urine osmolality has been removed.		Section 7.2.4

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **22 Nov 2016**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Clarification has been made that the serum sample will not be collected at the pretreatment visit if the subject met a follow-up period escape criterion.		Section 7.2.5
Intake and output diaries (formerly in Sections 7.2.11 and 7.2.12, respectively) have been moved under a new Section 7.2.11 'Diaries' for clarity, and are now Sections 7.2.11.2 and 7.2.11.3, respectively. Information on study drug administration diary has been added in Section 7.2.11.1. Clarification has been made that only available diary data will be reviewed at each clinic and telephone visit.		Sections 7.2.11, 7.2.11.1, 7.2.11.2, 7.2.11.3
Performance of dipstick specific gravity tests by the subject at home on the first urine produced after the daily infusions of PS has been removed. It is now at the discretion of the investigator for all subjects, not just those in diapers. This change is to align with standard medical practice.		Section 7.2.11.3
Clarifications have been made to the language on dose interruption.		Sections 8.4, 8.4.1
Unscheduled safety follow up assessments (including visits conducted after EOS) are not to be recorded. However, clarification has been made that they are to be collected where requested.		Section 9.1
The protocol now refers to the data monitoring committee (DMC) Charter for the schedule of DMC reviews.		Section 9.4
Changes have been made to the Health economics and outcomes research endpoints to include the beginning of each treatment cycle (CxD1) as additional baseline. These changes are for clarity and consistency with other teduglutide studies.		Synopsis Section 9.9.1
Minor corrections have been made to the guidelines for nutritional support management during the study.		Appendix 2

APPENDIX 2 GUIDELINES FOR NUTRITIONAL SUPPORT MANAGEMENT DURING THE STUDY

Nutritional support adjustment in volume and calories should be considered at all planned visits. Please consider the following clinical parameters identified as markers for adequate management of pediatric SBS. These parameters should also be considered for managing nutritional support (PS and/or oral/enteral feeding) in terms of volume and calories during the treatment period.

- Growth trajectory, including weight, height (or length), and head circumference (for pediatric subjects up to 36 months of age)
- Other clinical evaluations
  - Serum electrolytes
  - Blood urea nitrogen /creatinine levels
  - Changes in stool frequency or volume, including mixed output
  - Stool consistency (ie, Bristol Stool Scale)
  - Urine specific gravity
- General consideration to possible clinical deterioration in SBS
  - Inability to maintain weight and growth velocity
  - Diarrhea (≥10 bowel movements per day, ≥80 mL/kg/day from an ostomy, or ≥75 mL/kg/day mixed output)
  - Colic/vomiting frequency increased
  - Electrolyte changes or imbalance
  - Skin breakdown
- 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.
- Nutritional support constituents may be adjusted at the discretion of the investigator.
- 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.
- If there is a change in EN or other food or fluid intake, the investigator should consider this when adjusting the PS/EN support in volume and calories.

Figure A-1 Weaning Algorithm for Subjects Who are NOT Toilet Trained and in Diapers

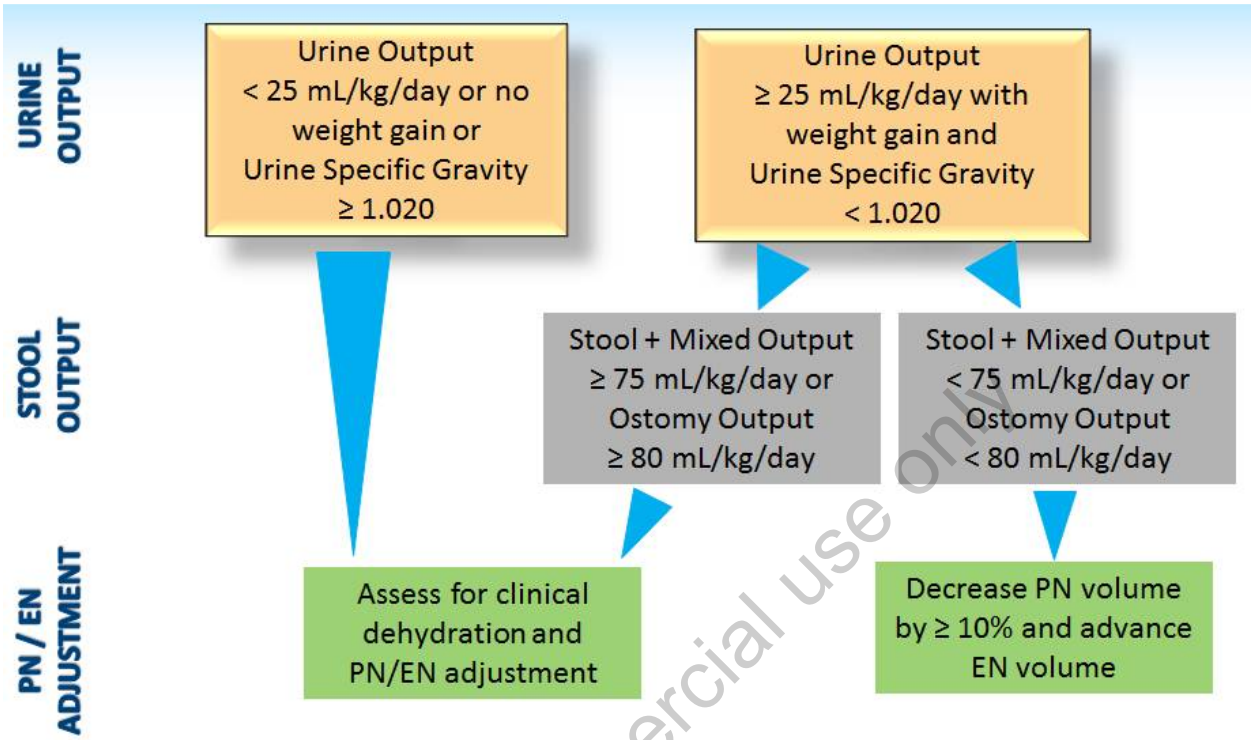


Figure A-2 Weaning Algorithm for Subjects Who are Toilet Trained and NOT in Diapers

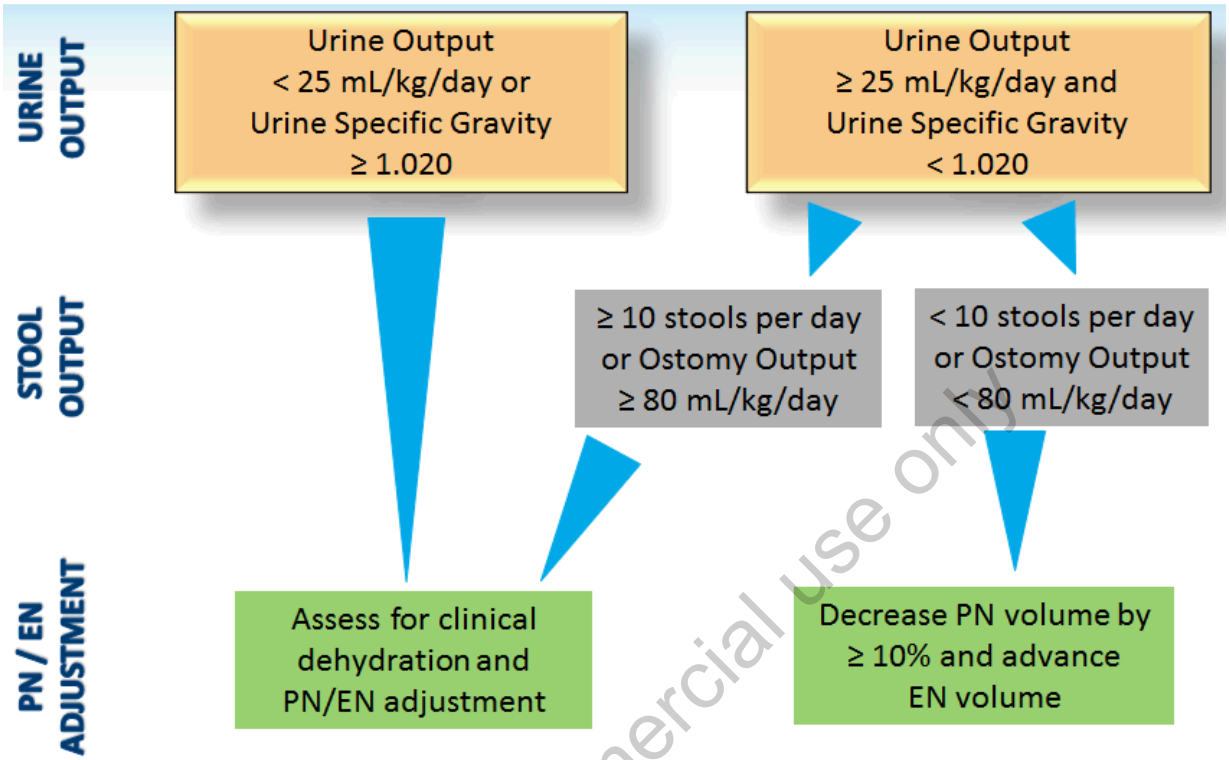
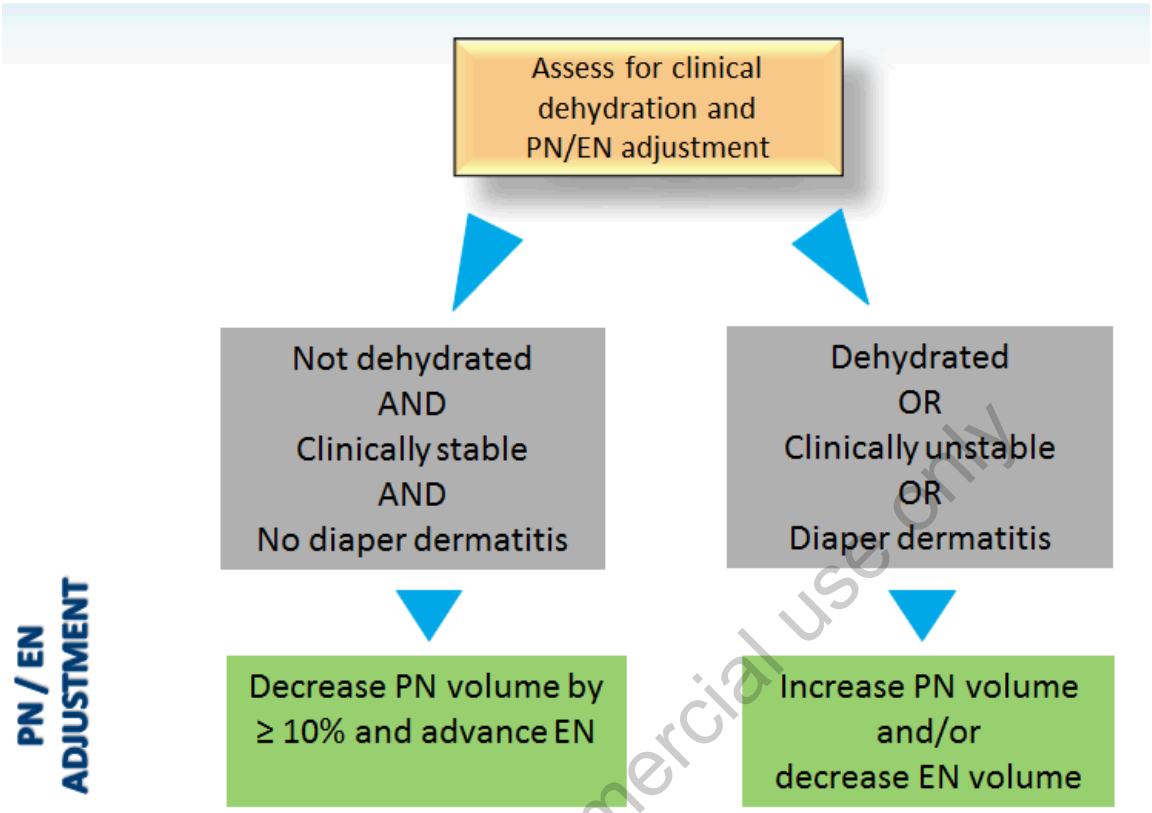


Figure A-3 Clinical Dehydration Assessment and PS/EN Adjustment



PROTOCOL: SHP633-304

TITLE:	A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome Who Completed TED-C14-006 or SHP633-301
DRUG:	Teduglutide
IND:	IND# 058213
EUDRACT NO.:	2016-000849-30
SPONSOR:	Shire Human Genetic Therapies, Inc. 300 Shire Way, Lexington, MA 02421 USA
PROTOCOL HISTORY:	Amendment 4: 01 Oct 2019 Amendment 3: 16 May 2018 Amendment 2: 23 Mar 2017 Amendment 1: 22 Nov 2016 Original Protocol: 08 Apr 2016

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 SHP633-304.

Title: A prospective, open label, long-term safety and efficacy study of teduglutide in pediatric patients with short bowel syndrome who completed TED-C14-006 or SHP633-301

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 Conference on Harmonization (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)

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 4	**Amendment Date** **01 Oct 2019**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
The name and contact information of the Sponsor [redacted] was updated to [redacted]. (Administrative letter dated 22 Oct 2018) The fax number of the Sponsor [redacted] was removed. (Administrative letter dated 15 Jan 2019)		Emergency Contact Information
The contact for medical support was updated to reflect Quintiles' current name, IQVIA, and Dr. [redacted]'s email address as [redacted]		Emergency Contact Information
Updated the Product Quality Complaints to match the current Sponsor standard		Product Quality Complaints
Extended the planned study period to December 2020.		Synopsis
Clarification of the follow-up period escape criteria and their use in combining the CxW24 and pretreatment visits was added. (Clarification Memo dated 09 Apr 2019)		Synopsis, Section 4.6
Clarified that AEs will be collected for 4 weeks after the last dose of teduglutide in the study even if the EOS/ET occurs within that timeframe.		Table 1-1, Section 7.1.5, Section 8.1
An optional qualitative interview to be conducted by phone and within 14 days after completion of the end of study/early termination visit was added. A single individual telephone interview will be conducted with English-speaking parents (or legal guardians) of subjects and subjects aged 12 years or older who provide informed consent (and if applicable, informed assent) to participate in the interview. These interviews will be performed in selected countries participating in this trial.		Table 1-1, Section 7.1.6, Section 7.2.13, Section 9.9.2, Appendix 3, Appendix 4
Noted that CRP will not be measured in subjects <10 kg due to blood volume limitations.		Table 1-2, Table 1-3, Table 7-1, Table 7-2
Noted that stored serum samples should be omitted for subjects weighing less than 15 kg and whenever local blood volume limitations are exceeded.		Table 1-2, Table 1-3, Section 7.2.5, Table 7-2
Updated the volume of blood to be drawn to be determined by subject weight.		Section 7.2.8
Clarified that serum pregnancy tests will be collected at the teduglutide pretreatment visits.		Table 7-1
Clarified that adverse event collection would include events that were reported during the qualitative interviews.		Section 8.1
The definition of an overdose was clarified as the administration of the investigational product at a dose or frequency greater than 0.05 mg/kg subcutaneous once daily. An overdose occurs if any of the following criteria are met: • More than 0.05 mg/kg is given at any one time • Consecutive doses are spaced less than 12 hours apart • Any more than 0.05 mg/kg given in one day (a day is defined as beginning at 12:00 AM and ending at 11:59 PM)		Section 8.1.7

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 4	**Amendment Date** **01 Oct 2019**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
The teduglutide dose interruption criteria were updated to specify events leading to an interruption of teduglutide treatment and events leading to a permanent discontinuation of teduglutide treatment. Investigational product must be interrupted if any of the following events occur: • An AE of special interest • An AE that is of NCI CTCAE severity Grade 3 or 4 and related to teduglutide • Intestinal obstruction • Biliary obstruction related to teduglutide • Pancreatic duct obstruction related to teduglutide • Heart failure with severe fluid overload related to teduglutide Investigational product must be permanently discontinued if any of the following events occur: • Pregnancy • Severe hypersensitivity, such as anaphylaxis determined by the investigator to be related to study drug. This does not include the presence of anti-teduglutide antibodies, mild injection site reactions or mild symptoms that according to the investigator do not pose a significant risk to the subject. • Confirmed drug-induced liver injury (DILI) related to teduglutide • Any malignancy These clarifications were made for consistency with other teduglutide studies.		Section 8.4, Section 8.4.1
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.

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 Sponsor Medical Monitor by e-mail using the details below.

[redacted], MD

Email: [redacted]

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

Primary contact for North America (NA) and backup contact for European Union (EU)

[redacted], MD, [redacted]

Mobile: [redacted]

US Toll Free number: [redacted]

Phone: [redacted] (medical emergencies – NA)

Email: [redacted]

Primary contact for EU and backup contact for NA

[redacted], MD, [redacted]

Mobile: [redacted]

Phone: [redacted]

Phone: [redacted] (medical emergencies – EU)

Email: [redacted]

In addition, the investigator may also contact the Sponsor Medical Monitor (8:00 to 20:00 US Eastern Standard Time):

[redacted], MD, [redacted]

Mobile: [redacted]

Email: [redacted]

PRODUCT QUALITY COMPLAINTS

Investigators are required to report investigational product quality complaints or non-medical complaints to Shire within 24 hours. If requested, defective product(s) will be returned to the sponsor for inspection and analysis.

A product quality complaint includes any instances where there is an allegation or report relating to Shire licensed or investigational products, received in writing, electronically, or orally, which indicates an impact to a product's strength, identity, safety, purity, or quality, or which suggests that the product did not meet the criteria defined in the regulatory applications, licenses, or marketing authorizations for the product. Examples of investigational product quality complaints include, but are not limited to, the following:

Unit issues	• Capsule fill empty or overage • Bottle/vial fill shortage or overage • Capsule/tablet damaged/broken • Syringe/vial cracked/broken	• Syringe leakage • Missing components • Product discoloration • Device malfunction
Labeling	• Label missing • Leaflet or Instructions For Use (IFU) missing • Label illegible	• Incomplete, inaccurate, or misleading labeling • Lot number or serial number missing
Packaging	• Damaged packaging (eg, secondary, primary, bag/pouch) • Tampered seals • Inadequate or faulty closure	• Missing components within package
Foreign material	• Contaminated product • Particulate in bottle/vial • Particulate in packaging	

Please report the product quality complaint using the "Product Quality Complaint Data Collection Form" via the email address:

[redacted]

Telephone number (provided for reference if needed):
Shire, Lexington, MA (USA)
[redacted]

For instruction on reporting AEs related to product complaints see Section 8.

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ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-HCG	beta-human chorionic gonadotropin
BMI	body mass index
CRA	clinical research associate
CRO	contract research organization
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced livery injury
DMC	data monitoring committee
DPP-4	dipeptidyl peptidase 4
EC	ethics committee
eCRF	electronic case report form
EMA	European Medicines Agency
EN	enteral nutrition
EOS	end of study
EOT	end of treatment
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FOBT	fecal occult blood test
FOCBP	female of child-bearing potential
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide 1
GLP-2	glucagon-like peptide 2
HIPAA	Health Insurance Portability and Accountability Act
ICF	informed consent form
ICH	International Conference on Harmonization
IGF-1	insulin-like growth factor 1
IRB	institutional review board
IV	intravenous

Abbreviation	Definition
IWRS	interactive web-based response system
MedDRA	Medical Dictionary for Regulatory Activities
NA	North America
NCI	National Cancer Institute
NDA	new drug application
NTT	no-teduglutide treatment
PedsQL	Pediatric Quality of Life inventory
PS	parenteral support
PT/INR	prothrombin time/international normalized ratio
QD	once daily
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SC	subcutaneous
SOC	standard of care
$t_{1/2}$	elimination half-life
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
UK	United Kingdom
ULN	upper limit of normal
US	United States
WHO-DD	World Health Organization – Drug Dictionary

STUDY SYNOPSIS

Protocol number: SHP633-304	**Drug:** Teduglutide
Title of the study: A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Patients with Short Bowel Syndrome (SBS) Who Completed TED-C14-006 or SHP633-301	
Number of subjects (total and for each treatment arm): Approximately 65 subjects who completed the TED-C14-006 or SHP633-301 studies, including subjects in the standard of care treatment arms, are expected to enroll in this extension study. This study will enroll up to as many subjects as complete the TED-C14-006 and SHP633-301 studies.	
Investigator(s): Multicenter study	
Site(s) and Region(s): Approximately 28 investigational sites in North America and Europe will participate in this extension study	
Study period (planned): October 2016 – December 2020	**Clinical phase:** 3 Extension
Objectives: **Primary:** To evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with SBS. **Secondary:** To evaluate long-term efficacy of teduglutide treatment in pediatric subjects with SBS.	
Rationale: This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects with short bowel syndrome (SBS) who completed either the TED-C14-006 or SHP633-301 studies (the core studies). In addition to evaluating the long-term safety and durability of efficacy after 24-weeks of treatment, this extension study will evaluate the need for additional teduglutide treatment in these subjects and will allow the study of first-time treatment of teduglutide-naïve subjects who participated in the standard of care (SOC) treatment arms in TED-C14-006 or SHP633-301.	
Investigational product, dose, and mode of administration: This study will allow repeat doses of teduglutide 0.05 mg/kg subcutaneous (SC) once daily (QD) injection for eligible pediatric subjects. There is no active comparator or reference product.	
Methodology: This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects who completed the TED-C14-006 or SHP633-301 studies (core studies). Once the informed consent (and if applicable, informed assent) have been reviewed and signed, demographics, and updates to medical history and short bowel syndrome history will be obtained. Subjects not receiving teduglutide treatment (ie, in a no-teduglutide treatment [NTT] period), will be seen approximately every 12 weeks for safety, parenteral support (PS) requirements, and quality of life. The first NTT visit after the screening visit will occur within 2 to 12 weeks of the screening visit. At any point after screening, including during a NTT period, subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed **immediately** to the pretreatment visit if the investigator, subject, and parent agree to proceed with teduglutide therapy. After the pretreatment visit, subjects who meet ≥1 of the teduglutide treatment inclusion criteria, and meet none of the teduglutide treatment exclusion criteria, will start a 28-week cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily, followed by a 4-week follow-up period (during which no teduglutide is administered) (Figure 3-1). During the 28-week cycle, clinic visits will occur at weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period (between weeks 1 and 24), and weekly during the teduglutide follow-up period (between weeks 24 and 28). Safety and PS requirements will be evaluated at every visit, and quality of life assessments will be made approximately every 12 weeks.	

If a subject meets 1 of the follow-up period escape criteria between cycle week 24 and 28, the subject may "escape" the follow-up period early and proceed immediately to another pretreatment visit. Following completion of the 28-week treatment cycle, the subject will proceed to an NTT visit or another pretreatment visit within approximately 12 weeks.

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, all attempts should be made to follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) for decisions regarding PS support reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines, however, is not considered a protocol deviation. (Appendix 2).

Study Design Flow Chart

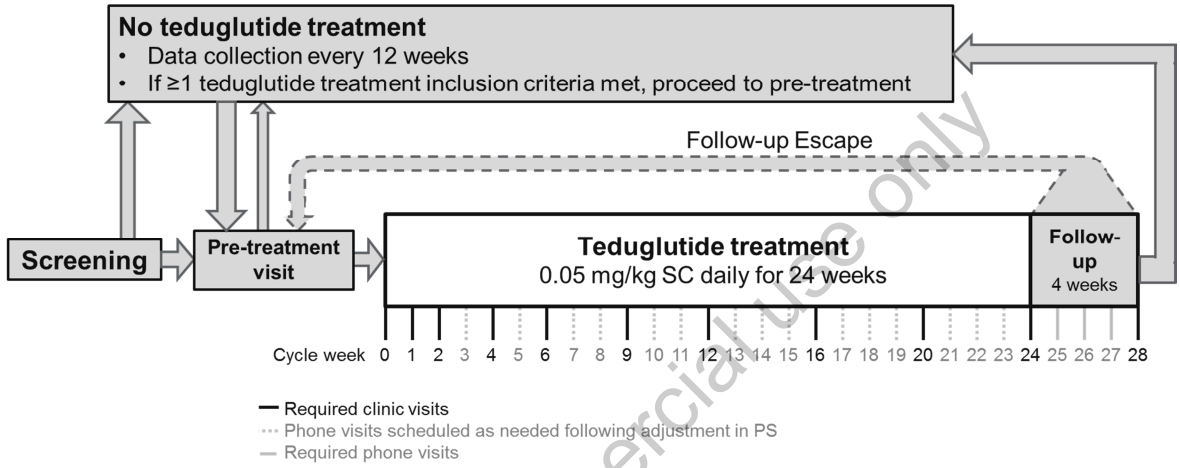

Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pretreatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects will enter a 28-week teduglutide cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24 (**solid black lines**). Phone visits are required approximately 1 week after adjustments in PS during the intervening weeks between weeks 2 and 24 (**dashed grey lines**). Subjects discontinue teduglutide at week 24 and enter a 4-week follow-up (no-treatment) period, during which phone visits will be performed weekly (**solid grey lines**). If an escape criterion is met at week 24 or during the follow-up period, subjects may proceed directly to another pretreatment visit.

Study Inclusion Criteria:

The subject will be considered eligible for the study if they meet **all** of the study inclusion criteria. Teduglutide treatment eligibility does not impact study eligibility.

1. Subject provides written informed consent (subject, parent or legal guardian and, as appropriate, informed assent) to participate in the study before completing any study-related procedures.
2. Subject completed the TED-C14-006 or SHP633-301 studies (including subjects in the standard of care treatment arms). Subjects are considered to have completed SHP633-301 if they completed study assessments through week 24.
3. Subject understands and is willing and able to fully adhere to study requirements as defined in this protocol.

Study Exclusion Criteria: There are no exclusion criteria for this study.

Teduglutide Eligibility Criteria: Subjects are eligible for teduglutide treatment if at least one (≥1) of the teduglutide treatment inclusion criteria, and none of the teduglutide treatment exclusion criteria, are met. In addition, the investigator and the subject (and/or parent or legal guardian, as appropriate) must agree to proceed with treatment.

***Teduglutide Treatment Inclusion Criteria*:**

1. Subject is teduglutide-naïve, receiving PS, and unable to significantly reduce PS or advance enteral feeds (eg, 10% or less change in PS or advance in feeds) for at least 3 months prior to and during the teduglutide pretreatment visit, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PS returns to within 10% of baseline prior to the event.
2. Subject was previously treated with teduglutide and at least one of the following criteria is satisfied:
    a. Increasing PS requirements following teduglutide discontinuation.
    b. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
    c. Deteriorating nutritional status (eg, weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.
    d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
    e. Severe diarrhea related to teduglutide discontinuation.

Teduglutide Treatment Exclusion Criteria:

1. Body weight <5 kg at the pretreatment visit.
2. Unresected gastrointestinal (GI) polyp, known polyposis condition, premalignant change, or malignancy, in the GI tract.
3. History of cancer in the previous 5 years except surgically curative skin cancers.
4. Serial transverse enteroplasty or other major intestinal surgery within 3 months preceding the teduglutide pretreatment visit. Insertion of a feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, and endoscopic procedures are allowed.
5. Intestinal or other major surgery planned or scheduled to occur during the 28-week cycle.
6. Clinically significant intestinal stricture or obstruction.
7. Clinically significant, active or recurrent pancreatic or biliary disease.
8. Active, severe, or unstable, clinically significant hepatic impairment or injury, including the following laboratory values at the pretreatment visit:
    a. Total bilirubin ≥2 × upper limit of normal (ULN)
    b. Aspartate aminotransferase (AST) ≥7 × ULN
    c. Alanine aminotransferase (ALT) ≥7 × ULN
9. Renal dysfunction shown by results of an estimated glomerular filtration rate below 50 mL/min/1.73 m^2 at the pretreatment visit.
10. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, or patent ductus arteriosus ligation.
11. Participation in a clinical study using an experimental drug (other than glutamine, Omegaven, or Smoflipid) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to the pretreatment visit and for the duration of the 28-week cycle.
12. Treatment with analogs of glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2) (not including teduglutide), insulin-like growth factor-1 (IGF-1), or growth hormone, within 3 months preceding the teduglutide pretreatment visit.
13. Treatment with octreotide or dipeptidyl peptidase 4 (DPP-4) inhibitors within 3 months prior to the pretreatment visit.
14. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients.

15. Known history of alcohol or other substance abuse within 1 year prior to the pretreatment visit.
16. Pregnant or lactating female subjects.
17. Sexually active female subjects of child-bearing potential unwilling to use approved contraception during teduglutide treatment and for 30 days after the treatment period.
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.

Follow-up Period Escape Criteria: At the discretion of the investigator, the follow-up period may be interrupted (if the subject meets 1 or more of escape criteria 1 to 4 during the follow-up period) or omitted (if the subject meets escape criterion 5 at the CxW24 visit) and the subject may proceed directly to the pretreatment visit, if ≥1 of the following criteria is met:

1. Increasing PS 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.
5. The subject escaped during the follow-up period of a previous teduglutide treatment cycle within SHP633-301 or SHP633-304. In this case, the CxW24 visit may be combined with the next cycle pretreatment visit.

Maximum duration of subject involvement in the study:

A subject will be considered enrolled in the study once the subject has provided signed consent and meets all of the Study Inclusion Criteria. Subjects may participate in multiple NTT periods and/or multiple 28-week treatment cycles. The study will continue for at least 1 year, and until each subject has access (as needed) to teduglutide. The subject's maximum duration of participation is expected to be approximately 3 years. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing End of Study (EOS) visit.

- **Planned duration of no-teduglutide treatment periods**: variable, depending on disease course
- **Planned duration of the teduglutide pretreatment visit:** 1 to 21 days
- **Planned cycle duration**: 28 weeks. Each cycle consists of 24 weeks of teduglutide treatment followed by a 4-week follow-up period (no treatment)

Endpoints and statistical analysis:

- The **safety population** will consist of all enrolled subjects. The safety population will be used for both safety and efficacy analysis.

Efficacy Endpoints

Efficacy endpoints will be analyzed at the end of each teduglutide treatment period (week 24 or end of treatment [EOT]), and at each study visit, relative to the baseline of the core study (TED-C14-006 or SHP633-301) and/or first exposure to teduglutide. The following efficacy endpoints will be analyzed:

- Reduction in PS volume of at least 20%
- Absolute and relative change in PS volume
- Complete weaning off PS
- Change in days per week of PS

Health Economics and Outcomes Research Endpoints

Health economics and outcomes research endpoints will be analyzed at approximately 12-week intervals (weeks 12 and 24 of each teduglutide treatment cycle, and every 12 weeks for subjects not on teduglutide), relative to the study baseline. The beginning of each treatment cycle (CxD1) will be an additional baseline.

- Change in Pediatric Quality of Life Inventory (PedsQL) score
- Change in PedsQL Family Impact Module score
- Change in PedsQL Gastrointestinal Symptoms Module Sub-Scales scores:
  - Food and Drink Limits
  - Diarrhea

Safety Endpoints

The following safety endpoints will be analyzed:

- Adverse events
- Vital signs, including temperature, heart rate, blood pressure
- Laboratory safety data (ie, clinical chemistry, hematology, and urinalysis)
- Urine output
- Stool output
- Antibodies to teduglutide
- Gastrointestinal-specific testing, including fecal occult blood testing and colonoscopy or sigmoidoscopy
- Z-scores for weight, height (or length), head circumference (up to 36 months of age), and body mass index

Statistical Methodology for Efficacy Analysis

No claims of statistical significance will be made; however, 95% confidence intervals will be provided, if applicable. Continuous variables, including those assessed on a discrete scale, 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.

Statistical Methodology for Safety Analysis

Safety data, including laboratory tests and vital signs assessments, will be summarized by visit. AEs will also be collected and summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data.

Sample Size Justification

As this is an extension study, the maximum number of subjects was determined by enrollment in TED-C14-006 and SHP633-301.

STUDY SCHEDULE(S)

Table 1-1: Schedule of Events Required for All Subjects

Period	Screening	End of Study or Early Termination
	Scr	EOS/ET
Visit Type	**Site**	**Site**
Informed consent/assent[a]	X	
Study eligibility	X	
Demographics, medical history[b], SBS history[c]	X	
Dispense intake and output diaries	X	
Evaluate teduglutide treatment inclusion criteria[d]	X	
Adverse events	X	X[n]
Concomitant medications and procedures	X	X
Physical examination and vital signs, including weight		X
Height and head circumference[e]		X
Review intake and output diaries[f]		X
Record PS prescription and adjust as needed[g]	X	X
Safety laboratory tests[h]		X
PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales		X
Antibodies to teduglutide[i]		X
Fecal occult blood testing[j]		(X)
Colonoscopy or sigmoidoscopy[k]		(X)
Pregnancy testing[l]		(X)
Qualitative interview[m]		X

FOBT = fecal occult blood testing; FOCBP = female of child-bearing potential; EOS =end of study; ET=early termination; GI=gastrointestinal; NTx=no treatment; PedsQL=Pediatric Quality of Life Inventory; PS=parenteral support; SBS=Short Bowel Syndrome; Scr =Screening

[a] Informed Consent (and informed assent, if applicable) must be obtained prior to performing any study-related procedures; consent (and informed assent, if applicable) may be obtained anytime during the EOS visit for the TED-C14-006 or SHP633-301 studies. Subject will have approximately 7 days after completion of the TED-C14-006 or SHP633-301 studies to sign consent to participate in the SHP633-304 study.

[b] Updates to the medical history will be collected, consisting of adverse events that were ongoing at the time of completion of TED-C14-006 or SHP633-301, and events that occurred during the period between completion of TED-C14-006 or SHP633-301 and informed consent to SHP-633-304.

[c] If the subject has any changes to the SBS history that had been collected at the baseline of the TED-C14-006 or SHP633-301, then the updated SBS history will be collected.

[d] Subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed to the pretreatment visit if the investigator, subject, and parent or legal guardian agrees to proceed with teduglutide therapy (Table 1-3).

[e] Head circumference will be measured in subjects 36 months of age and younger.

[f] The intake diary should be completed daily for a minimum of 2 weeks prior to the EOS/ET visit. The output diary should be completed daily over a 48-hour period of nutritional stability before the EOS/ET visit.

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

[h] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

[i] Required for all teduglutide-exposed subjects

[j] FOBT should be performed on teduglutide-exposed subjects on an annual basis, approximately every 48-60 weeks at a minimum.

[k] The need for colonoscopy/sigmoidoscopy in response to a positive FOBT during a no-teduglutide treatment period is at the discretion of the investigator, but all teduglutide-exposed subjects will undergo colonoscopy/sigmoidoscopy after they have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure), and subjects who continue to receive teduglutide will undergo colonoscopy/sigmoidoscopy at 5 year intervals or more often as needed. See Section 7.2.9 for details.

[l] Pregnancy testing is required for FOCBP at an ET visit if the subject has not had a pregnancy test at least 30 days after study drug discontinuation.

[m] Optional interview to be conducted by phone within 14 days after completion of the EOS/ET visit (see Section 7.2.13).

[n] AEs will be collected for 4 weeks after the last dose of teduglutide in the study even if the EOS/ET occurs within that timeframe.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

Table 1-2: Schedule of Events for Subjects Not Receiving Teduglutide

Visit Number	**NTx**
Visit Type	**Site**
Visit Frequency[a]	**Every 12 weeks**
Window (days)[b]	**±7**
Dispense intake and output diaries	X
Evaluate teduglutide treatment inclusion criteria[c]	X
Adverse events	X
Concomitant medications and procedures	X
Physical examination and vital signs, including weight	X
Height and head circumference[d]	X
Review intake and output diaries[e]	X
Record PS prescription and adjust as needed[f]	X
Safety laboratory tests[g]	X
PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales	X
Antibodies to teduglutide[h]	(X)
Fecal occult blood testing[i]	Annually
Colonoscopy or sigmoidoscopy[j]	(X)
Serum sample[k]	Every 24 weeks

FOBT = fecal occult blood testing; NTT = no-teduglutide treatment; PedsQL = Pediatric Quality of Life Inventory; PS= parenteral support; TED = teduglutide

[a] The first NTx visit following the screening visit must occur within 2 to 12 weeks of screening.

[b] Window is relative to the first NTx visit in the current no-teduglutide treatment period.

[c] Subjects who meet ≥1 teduglutide treatment inclusion criteria, may proceed to the pretreatment visit if the investigator, subject, and parent or guardian agree to proceed with teduglutide therapy (Table 1-3).

[d] Head circumference will be measured in subjects 36 months of age and younger.

[f] Intake diaries will collect actual PS volume and hours per day, completed daily for a minimum of 2 weeks prior to each study visit (see Section 7.2.11.2). Urine and stool output should be recorded in the output diary over a 48-hour period of nutritional stability before every clinic visit (see Section 7.2.11.3 for more detail).

[f] PS 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.

[g] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. CRP will not be measured in subjects <10 kg.

[h] Subjects who have been treated previously and test positive for teduglutide antibodies should have follow-up samples collected every 12 weeks during the study until a negative result is obtained.

[i] FOBT should be performed on teduglutide-exposed subjects on an annual basis, approximately every 48-60 weeks at a minimum.

[j] The need for colonoscopy/sigmoidoscopy in response to a positive FOBT during a no-teduglutide treatment period is at the discretion of the investigator, but all teduglutide-exposed subjects will undergo colonoscopy/sigmoidoscopy after they have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) and subjects who continue to receive teduglutide will undergo colonoscopy/sigmoidoscopy at 5 year intervals or more often as needed. See Section 7.2.9 for details.

[k] Lack of collection of serum samples will not constitute a protocol deviation. Stored serum samples should be omitted for subjects weighing less than 15 kg and whenever local blood volume limitations are exceeded.

Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	Pre-treatment	Teduglutide Treatment															Follow-up	
Visit Number	**Px[a]**	**Cx D1**	**Cx W1**	**Cx W2**	Phone contact is required approximately 1 week after PS adjustment	**Cx W4**	Phone contact is required approximately 1 week after PS adjustment	**Cx W6**	Phone contact is required approximately 1 week after PS adjustment	**Cx W9**	Phone contact is required approximately 1 week after PS adjustment	**Cx W12**	Phone contact is required approximately 1 week after PS adjustment	**Cx W16**	Phone contact is required approximately 1 week after PS adjustment	**Cx W20**	Phone contact is required approximately 1 week after PS adjustment	**CxW24 (EOT)**	**CxW25 CxW26 CxW27**	**CxW28[c]**
Visit Type	**Site**	**Site**	**Site**	**Site**		**Site**		**Site**		**Site**		**Site**		**Site**		**Site**		**Site**	**Phone[b]**	**Site**
Cycle Day	**-21 to 0**	**1**	**8**	**15**		**29**		**43**		**64**		**85**		**113**		**141**		**169**	**176 183 190**	**197**
Window (days)[d]	-21 to 0		**±2**	**±2**		**±2**		**±2**		**±4**		**±4**		**±4**		**±4**		**±4**	**±2**	**±2**
Evaluate teduglutide eligibility (inclusion and exclusion) criteria	X	X[e]																		
Dispense intake and output diaries	X	X	X	X		X		X		X		X		X		X		X		X
Adverse events	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
Physical examination and vital signs, including weight	X	X	X	X		X		X		X		X		X		X		X		X
Height and head circumference[f]	X	X										X						X		
Review intake and output diaries[g]	X	X	X	X		X		X		X		X		X		X		X	X	X
Record PS Rx and adjust as needed[h]	X	X	X	X		X		X		X		X		X		X		X	X	X
Safety laboratory tests[i]	X[i]	X	X	X		X		X		X		X		X		X		X	(X)	X
PedsQL Generic Core Scale/ Family Impact Module/ GI Symptoms Module Sub-Scales		X										X						X		
Antibodies to teduglutide[j]		X										X						X		X
Fecal occult blood testing	X											X						X		
Colonoscopy/ sigmoidoscopy[k]	(X)											(X)						(X)		
Pregnancy testing[l]	X	X				X				X		X		X		X		X		X

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	Pre-treatment	Teduglutide Treatment																Follow-up	
Serum sample[m]	X																X		
Evaluate escape criteria[n]																	X[p]	X	X
Dispense study drug[o]		X	X	X		X		X		X		X		X		X			

EOS = end of study; EOT = end of treatment; ET = early termination; FOBT = fecal occult blood test; FOCBP = female of child-bearing potential; FU = follow-up; GI = gastrointestinal; PedsQL = Pediatric Quality of Life Inventory; PS= parenteral support; SBS = Short Bowel Syndrome; SC = subcutaneous; Scr = Screening; TED = teduglutide; Tx = treatment

[a] If the first pretreatment visit (P1) follows the screening visit, it must occur within 12 weeks of screening.

[b] Phone visits are required approximately 1 week after adjustments in PS. The assessments to be performed at phone visits are the same as those described for CxW25-27 (except for evaluation of escape criteria).

[c] The investigator may combine the CxW28 visit with the next pretreatment visit if at least one escape criterion is met at the CxW28 visit, and the pretreatment assessments occur within 7 days of the CxW28 visit. If a subject is completing the study at the CxW28 visit, the EOS/ET visit (Table 1-1) will take place in lieu of the CxW28 visit.

[d] Visit windows are relative to the CxD1 visit.

[e] Eligibility will need to be re-confirmed prior to the first dose in the cycle. Negative urine pregnancy test is required prior to the first dose of teduglutide, but results of other labs obtained at the CxD1 visit are not required to determine teduglutide treatment eligibility.

[f] Head circumference will be measured in subjects 36 months of age and younger.

[g] Intake diaries will collect actual PS volume and hours per day. Intake diaries should be completed daily for a minimum of 2 weeks immediately prior to each clinic visit (except at pretreatment visit), for 1 week following PS adjustment, and daily during the 4-week follow-up period. 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 PS prescription. See Section 7.2.11 for more detail.

[h] PS 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] Safety laboratory assessments at site visits will consist of clinical chemistry, hematology, and urinalysis, with results processed by a central laboratory. Clinical chemistry and urinalysis must also be performed within approximately 5-7 days of any adjustment to the PS prescription. Safety labs performed between clinic visits may be performed locally. Unscheduled lab results will not be captured in the eCRFs. If abnormal results are considered an adverse event, an AE form will be completed. Collect PT/INR at the pretreatment visit. Additional collection will occur if a potential drug-induced liver injury signal is observed. Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation. CRP will not be measured in subjects <10 kg.

[j] Samples collected on CxD1 must be drawn prior to first administration of teduglutide. Samples collected while subjects are receiving teduglutide (CxW12 and CxW24) must be drawn at least 14 hours after dosing.

[k] The teduglutide-naïve subjects age 12 and older will undergo colonoscopy/sigmoidoscopy at the pretreatment visit if one has not been performed within 1 year. Subjects of any age with newly positive FOBT results at the pretreatment visit for which a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy/sigmoidoscopy prior to receiving teduglutide. If newly positive FOBT results (for which a readily detectable cause cannot be identified) are obtained at the end of a teduglutide treatment cycle (CxW24/EOT), colonoscopy/sigmoidoscopy will be performed. The need for colonoscopy/sigmoidoscopy in response to positive FOBTs at CxW12 is at the discretion of the investigator. Teduglutide-exposed subjects who have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) will undergo colonoscopy/sigmoidoscopy. See Section 7.2.9 for details.

[l] A serum pregnancy test is performed on all FOCBP at the teduglutide pretreatment visit (when the pretreatment and screening visits are combined, the serum pregnancy test should be performed at the local laboratory). Urine pregnancy tests will be administered at all other visits according to the study schedules, or if pregnancy is suspected, or as specified per protocol upon withdrawal of the subject from the study.

[m] Lack of collection of serum samples will not constitute a protocol deviation. Stored serum samples should be omitted for subjects weighing less than 15 kg and whenever local blood volume limitations are exceeded.

Table 1-3: Schedule of Events for Subjects While Receiving Teduglutide

Period	Pre-treatment	Teduglutide Treatment	Follow-up

[n] If escape criteria are met, the subject may proceed directly to another pretreatment visit at the discretion of the investigator.
[o] The first SC injection of teduglutide in treatment-naïve subjects will be administered under the supervision of the investigator/designee after which the subject will be observed for hypersensitivity reactions for at least 4 hours. The site of administration (arm, thigh, abdomen) of the first teduglutide dose must be specified and recorded in the eCRF. See Section 6.2.3 for dose adjustment.
[p] Escape criteria will be assessed for subjects who escaped during the follow-up period of a previous teduglutide treatment cycle at CxW24. The investigator may combine the CxW24 visit with the next pretreatment visit if at least 1 escape criterion is met at the CxW24 visit. In order to combine assessments, the pretreatment assessments must occur within 7 days of the CxW24 visit.
Note: (X) denotes conditional requirement for a given assessment if the subject meets certain conditions per protocol.

1 BACKGROUND INFORMATION

1.1 Indication and Current Treatment Options

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. It is estimated that, at most, there are a few hundred pediatric subjects 1 year and older with SBS (Khan et al., 2015; Wales et al., 2004). 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. Although the small intestine is capable of remarkable adaptation, excessive loss of absorptive surface area or specialized functions can lead to dependence on parenteral nutrition or intravenous (IV) fluids (parenteral support [PS]). Treatment of both pediatric and adult patients is focused on achieving adequate intestinal absorption to allow for minimization or discontinuation of PS. About 30% of infants with SBS become independent of PS requirements within 12 months of the initial insult, and an additional 10% wean off PS within 24 months. After this time, linear intestinal growth slows. About 60% of pediatric subjects with SBS are able to become independent of PS within 5 years of the initial diagnosis (Khan et al., 2015). Nevertheless, despite optimal medical management, many pediatric subjects remain dependent on PS. Complications of long-term PS include liver disease, catheter-related blood stream infections, central line-associated venous thrombosis and dwindling central venous access. Sepsis is the leading cause of death in these patients and quality of life is poor (Squires et al., 2012). Accelerating the adaptive process and achieving enteral autonomy is an urgent goal for all patients with SBS who are dependent on PS (Khan et al., 2015; Squires et al., 2012).

Intestinal adaptation is driven by hormonal cues in response to nutrient malabsorption (Drucker and Yusta, 2014). Chief among these is hormones glucagon-like peptide 2 (GLP-2), which is secreted from L-type enteroendocrine cells that reside in the intestinal epithelium in the ileum and colon. Resection of these regions may impair the adaptive response by limiting endogenous production of GLP-2.

1.2 Product Background

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-IV (DPP-4) and therefore maintains a longer elimination half-life ($t_{1/2}$) in adults of approximately 2 hours 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). The European Commission granted a centralized marketing authorization valid throughout the European Union (EU) for teduglutide (Revestive™) on 30 August 2012 and a New Drug Application (NDA) for teduglutide (Gattex®) was approved by the United States (US) Food and Drug Administration (FDA) on 21 December 2012 for the treatment of adult patients with SBS who are dependent on PS.

Teduglutide has also been approved for use in adult patients with SBS in Canada and Switzerland. On 29 Jun 2016, the European Commission granted an extension of the Market Authorization for teduglutide (REVESTIVE™) for the treatment of patients aged 1 year and above with SBS; patients should be stable following a period of intestinal adaptation.

1.3 Clinical Studies with Teduglutide in Pediatric Subjects

One Phase 3 study, TED-C13-003, was completed in pediatric SBS subjects in the US and United Kingdom (UK). In this study, teduglutide was administered to 3 cohorts of pediatric subjects from ages 1-17. 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 PS volume at week 12 of 37%, including complete independence from PS 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 PS volume at week 12 of 39%, including complete independence from PS 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 (TESAEs) related to teduglutide were reported. No discontinuations from study were due to adverse events (AEs).

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 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.

SHP633-301 is an ongoing study in the United Kingdom, Italy, Finland, and France to evaluate the safety, efficacy, and PK of teduglutide treatment in infants 4 to 12 months of age with SBS. Like TED-C14-006, this study has a teduglutide treatment arm and a SOC arm.

Subjects in both arms will participate in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the 24-week treatment period, subjects in the SOC treatment arm will receive standard medical therapy for SBS; while those in the teduglutide treatment arm will receive daily SC injections of 0.05 mg/kg teduglutide in addition to standard medical therapy. Similar to the treatment cycles in SHP633-304, subjects in SHP633-301 may escape from the 4-week follow-up period and proceed directly to the SHP633-304 study, if they meet an escape criterion specified in the SHP633-301 protocol. It is expected the subjects entering SHP633-304 from SHP633-301 will be 11 to 19 months of age when enrolling in SHP633-304.

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 STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects with SBS who completed the TED-C14-006 or SHP633-301 studies. In addition to evaluating the long-term safety and durability of efficacy after 24 weeks of treatment, this extension study will evaluate the need for additional teduglutide treatment in these subjects, and will allow for the first-time treatment of teduglutide-naïve subjects who participated in the SOC treatment arms in TED-C14-006 or SHP633-301.

2.2 Study Objectives

2.2.1 Primary Objectives

The primary objective of the study is to evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with SBS who completed TED-C14-006 or SHP633-301.

2.2.2 Secondary Objectives

The secondary objective of this study is to evaluate the long-term efficacy of teduglutide treatment in pediatric subjects with SBS who completed TED-C14-006 or SHP633-301.

3 STUDY DESIGN

3.1 Study Design and Flow Chart

This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects who completed the TED-C14-006 or SHP633-301 studies (the "core studies"). At the time of entry into TED-C14-006, subjects were less than 18 years of age, were dependent on parenteral nutrition to provide at least 30% of their caloric or fluid needs and had not been able to significantly reduce PS for at least 3 months prior to enrollment. During TED-C14-006, some subjects elected to receive standard of care instead of teduglutide treatment. Subjects who elected to receive teduglutide were randomized to 0.025 mg/kg or 0.05 mg/kg once daily (QD) dosing in a double-blinded manner.

At the time of entry into SHP633-304, subjects were 4 to 12 months corrected gestational age, were dependent on parenteral nutrition to provide at least 35% of their caloric or fluid needs, and had not been able to significantly reduce PS for at least 1 month prior to enrollment. During SHP633-301, subjects were randomized to receive standard of care or teduglutide 0.05 mg/kg SC QD.

Approximately 65 subjects who complete the core studies are expected to enroll in this extension study. All subjects who completed either core study, including those who received standard of care, may be eligible to enter SHP633-304. To be eligible to receive teduglutide treatment within SHP633-304, subjects must meet ≥1 of the teduglutide treatment inclusion criteria and none of the teduglutide treatment exclusion criteria.

Additional Teduglutide Treatment

Subjects not receiving teduglutide treatment (ie, in a “no-teduglutide treatment period”), will be seen approximately every 12 weeks for safety, parenteral support (PS) requirements, and quality of life. At any point during a no-teduglutide treatment period, subjects who meet ≥1 *teduglutide treatment inclusion* may proceed directly to the pretreatment visit if the investigator, subject, and parent agree to proceed with teduglutide therapy.

Rationale: Some pediatric subjects may have a durable beneficial effect after 24 weeks of teduglutide treatment and thus long-term follow-up without additional teduglutide treatment may be appropriate. However, there may be some pediatric subjects who deteriorate or stop improving after discontinuation of teduglutide treatment. In these pediatric subjects, additional teduglutide treatment may be beneficial.

Dose Selection

Analysis suggested that pediatric patients, ages 1 to 17 years old, are likely to require the same dose as used in adults, namely 0.05 mg/kg/day (Mouksassi et al., 2009). In this extension study, all subjects who enter a teduglutide treatment cycle will receive 0.05 mg/kg SC QD.

Rationale: Teduglutide is approved for adult use in the US and EU, and for pediatric use in the EU, at a dose of 0.05 mg/kg SC once daily. The completed pediatric studies (TED-C13-003 and TED-C14-006) demonstrated that teduglutide dosing at 0.025 and 0.05 mg/kg/day was associated with a favorable benefit/risk profile. In addition, population pharmacokinetic modeling and simulations were conducted to determine the effective 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 the pediatric study (TED- C13- 003) and suggested that the dose in pediatric subjects is likely to be same as the dose in adults (O'Keefe et al., 2006).

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 infants (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 of 0.05 mg/kg since AUC_{ss} was previously shown not to correlate with efficacy. Thus, the 0.05 mg/kg dose is proposed for testing in all age groups.

Duration of Treatment

The duration of teduglutide treatment in this study mirrors that of the TED-C14-006 and SHP633-301 studies, consisting of 24 weeks of teduglutide treatment, followed by a 4-week follow-up period. The follow-up period is a mechanism to evaluate whether continued teduglutide is needed. If a subject deteriorates during the follow-up period, the subject may be evaluated immediately for additional teduglutide treatment. Subjects who clinically deteriorate or stop improving at any time after the end of the follow-up period will also be assessed for additional treatment.

Rationale: During the teduglutide treatment cycle, visit frequency is similar to frequencies performed in TED-C13-003, TED-C14-006, and SHP633-301 to ensure sufficient safety monitoring and weaning of PS. During the no-teduglutide treatment, visits occur every 12 weeks, a frequency that is consistent with standard medical practices. To minimize risk to subjects, those who have deteriorated quickly after treatment interruption (ie, escaped from a prior follow-up period) may be evaluated immediately for eligibility for additional treatment when they reach the week 24 visit.

Measures and Parameters

Following the review and signing of the informed consent (and informed assent, if applicable), screening visit procedures will begin including demographics, and updates to medical history and SBS history. Subjects who meet ≥1 of the teduglutide treatment inclusion criteria may proceed to the pretreatment visit.

After the pretreatment visit, subjects who still meet ≥1 of the teduglutide treatment inclusion criteria, and meet none of the teduglutide treatment exclusion criteria, will start a 28-week cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily, followed by a 4-week follow-up (no treatment) period (Figure 3-1). During the 28-week cycle, clinic visits will occur at weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28. Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period (between weeks 1-24), and weekly during the teduglutide follow-up period (between weeks 24 and 28).

Safety and PS requirements will be evaluated on a weekly basis, and quality of life assessments will be made approximately every 12 weeks. 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, all attempts should be made to follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) for decisions regarding PS reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability. Departure from the guidelines, however, is not considered a protocol deviation (Appendix 2).

Rationale: Measures of long-term safety will include AEs, growth parameters and anti-drug antibodies. Measure of long-term efficacy will include durability of effect as measured by reduction in PS and improvement in pediatric quality of life measures (PedsQL, PedsQL Family Impact Module). A reduction in PS volume of at least 20% at end of treatment (EOT) was used as the primary endpoint in pivotal phase 3 adult clinical trials and the completed phase 3 pediatric study (TED-C13-003) and will be used as an endpoint in this extension study. In previous clinical studies, a reduction of this magnitude was associated with a reduction in the number of days per week of PS and increases in enteral intake. Reduction in volume and time of PS due to improved enteral absorption may provide a pediatric subject with opportunities for more age-appropriate activities including oral rehabilitation. Quality of life assessments will be performed in this study to quantitate this effect.

Teduglutide has been found to have a targeted intestinotrophic effect. Taking into account the patient population and the pharmacologic effect of teduglutide, GI-specific screening tests, including fecal occult blood testing and colonoscopy/sigmoidoscopy, which are commonly part of the routine care of these subjects, will be performed to ensure safety. This study captures long-term safety data on polyps and other colonic mucosal changes in teduglutide-exposed subjects using the surveillance strategy proposed in Section 7.2.9.

Figure 3-1: Study Design Flow Chart

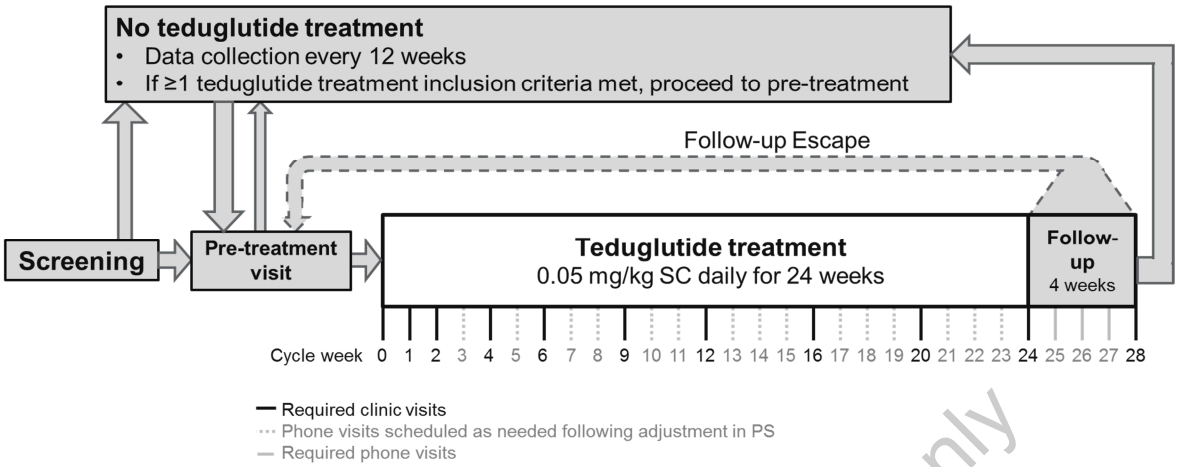

Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pretreatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects will enter a 28-week teduglutide cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24 (**solid black lines**). Phone visits are required approximately 1 week after adjustments in PS during the intervening weeks between weeks 2 and 24 (**dashed grey lines**). Subjects discontinue teduglutide at week 24 and enter a 4-week follow-up (no-treatment) period, during which phone visits will be performed weekly (**solid grey lines**). If an escape criterion is met at week 24 or during the follow-up period, subjects may proceed directly to another pretreatment visit.

3.2 Duration and Study Completion Definition

A subject will be considered enrolled in the study once the subject has provided signed consent, and meets all of the Inclusion Criteria. The study will continue for at least 1 year and until each subject has access, as needed, to teduglutide. The subject's maximum duration of participation is expected to be approximately 3 years. The study will be completed in approximately 40 months. A subject will be considered as having completed the study if the subject has not withdrawn early from the study for any reason prior to completing the End of Study (EOS) visit.

The study completion date is defined as the date the final subject, across all sites, completes their final protocol-defined assessment. Please note that this includes the follow-up visit or contact (last safety contact), whichever is later. The study completion date will be used to ascertain timing for study results posting and reporting.

4 STUDY POPULATION

Each subject must review and sign the informed consent (and informed assent, if applicable) before any study-related procedures specified in the protocol are performed. Teduglutide treatment eligibility does not impact study eligibility.

4.1 Study Inclusion Eligibility Criteria

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

1. Subject provides written informed consent (subject, parent or legal guardian and, as appropriate, subject informed assent) to participate in the study before completing any study-related procedures.
2. Subject completed the TED-C14-006 or SHP633-301 studies (including subjects in the standard of care treatment arms). Subjects are considered to have completed SHP633-301 if they completed study assessments through week 24.
3. Subject understands and is willing and able to fully adhere to study requirements as defined in this protocol.

4.2 Study Exclusion Eligibility Criteria

There are no exclusion criteria for this study.

4.3 Teduglutide Eligibility Criteria

Subjects are eligible for teduglutide treatment if at least 1 (≥1) of the teduglutide treatment inclusion criteria, and none of the teduglutide treatment exclusion criteria are met. In addition, the investigator and the subject (and/or parent or legal guardian, as appropriate) must agree to proceed with treatment.

4.4 Teduglutide Treatment Inclusion Criteria

1. Subject is teduglutide-naïve, receiving PS, and unable to significantly reduce PS or advance enteral feeds (eg, 10% or less change in PS or advance in feeds) for at least 3 months prior to and during the teduglutide pretreatment visit, as assessed by the investigator. Transient instability for events such as interruption of central access or treatment for sepsis is allowed if the PS returns to within 10% of baseline prior to the event.
2. Subject was previously treated with teduglutide and at least 1 of the following criteria is satisfied:
    a. Increasing PS requirements following teduglutide discontinuation.
    b. Decreased PS requirement during prior teduglutide treatment, followed by cessation of improvement after teduglutide discontinuation.
    c. Deteriorating nutritional status eg, weight loss or growth failure) despite maximal tolerated enteral nutrition (EN) following teduglutide discontinuation.

d. Deteriorating fluid or electrolyte status despite maximal tolerated enteral fluid and electrolyte intake following teduglutide discontinuation.
e. Severe diarrhea related to teduglutide discontinuation.

4.5 Teduglutide Treatment Exclusion Criteria

1. Body weight <5 kg at the pretreatment visit.
2. Unresected GI polyp, known polyposis condition, premalignant change, or malignancy, in the GI tract
3. History of cancer in the previous 5 years except surgically curative skin cancers
4. Serial transverse enteroplasty or other major intestinal surgery within 3 months preceding the teduglutide pretreatment visit. Insertion of a feeding tube, anastomotic ulcer repair, minor intestinal resections ≤10 cm, and endoscopic procedures are allowed.
5. Intestinal or other major surgery planned or scheduled to occur during the 28-week cycle
6. Clinically significant intestinal stricture or obstruction
7. Clinically significant, active or recurrent pancreatic or biliary disease
8. Active, severe, or unstable, clinically significant hepatic impairment or injury, including the following laboratory values at the pretreatment visit:
   a. Total bilirubin ≥2 × upper limit of normal (ULN)
   b. Aspartate aminotransferase (AST) ≥7 × ULN
   c. Alanine aminotransferase (ALT) ≥7 × ULN
9. Renal dysfunction shown by results of an estimated glomerular filtration rate below 50 mL/min/1.73 m^2 at the pretreatment visit
10. Unstable cardiac disease, congenital heart disease or cyanotic disease, with the exception of subjects who had undergone ventricular or atrial septal defect repair, or patent ductus arteriosus ligation
11. Participation in a clinical study using an experimental drug (other than glutamine, Omegaven, or Smoflipid) within 3 months or 5.5 half-lives of the experimental drug, whichever is longer, prior to the pretreatment visit and for the duration of the 28-week cycle
12. Treatment with analogs of glucagon-like peptide-1 (GLP-1), glucagon-like peptide-2 (GLP-2) (not including teduglutide), insulin-like growth factor-1 (IGF-1), or growth hormone, within 3 months preceding the teduglutide pretreatment visit.
13. Treatment with octreotide or dipeptidyl peptidase 4 (DPP-4) inhibitors within 3 months prior to the pretreatment visit
14. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients

15. Known history of alcohol or other substance abuse within 1 year prior to the pretreatment visit
16. Pregnant or lactating female subjects
17. Sexually active female subjects of child-bearing potential unwilling to use approved contraception during teduglutide treatment and for 30 days after the treatment period
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.

4.6 Follow-up Period Escape Criteria

At the discretion of the investigator, the follow-up period may be interrupted (if the subject meets 1 or more of escape criteria 1 to 4 during the follow-up period) or omitted (if the subject meets escape criterion 5 at the CxW24 visit) and the subject may proceed directly to the pretreatment visit, if ≥1 of the following criteria is met:

1. Increasing PS 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.
5. The subject escaped during the follow-up period of a previous teduglutide treatment cycle within SHP633-301 or SHP633-304. In this case, the CxW24 visit may be combined with the next cycle pretreatment visit.

4.7 Reproductive Potential

4.7.1 Female Contraception

To be eligible for treatment with teduglutide, sexually active females of child-bearing potential must use an acceptable form of contraception throughout the study period and for 30 days following the last dose of investigational product. If hormonal contraceptives are used, they should be administered according to the package insert. Females of child-bearing potential who are not currently sexually active must agree to use acceptable contraception, as defined below, if they become sexually active during the period of the study and 30 days following the last dose of investigational product.

To be eligible for treatment with teduglutide, female pediatric subjects and adolescent subjects should be either:

- Pre-menarchal and either Tanner Stage 1 or less than age 9 years, or
- Females of child-bearing potential (FOCBP) with a negative serum beta-human chorionic gonadotropin (β-HCG) pregnancy test at the teduglutide pretreatment visit.

Females of child-bearing potential must agree to abstain from sexual activity that could result in pregnancy or agree to use acceptable methods of contraception.

Acceptable methods of contraception are:

- True abstinence: Abstention of sexual activity that is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).
- Intrauterine devices plus condoms
- Double-barrier methods (eg, condoms and diaphragms with spermicidal gel or foam)
- Hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), stabilized for at least 30 days prior to the pretreatment visit, plus condoms. Note: if subject becomes sexually active during the study, they should use one of the other acceptable methods noted above in addition to the hormonal contraceptive until it has been stabilized for 30 days.

4.8 Discontinuation of Subjects

4.8.1 Teduglutide Discontinuation

If the investigational product is discontinued prematurely during a teduglutide treatment cycle and the subject wishes to remain in the study, the evaluations listed for the EOT visit are to be performed. A 4-week follow-up period will ensue, consisting of weekly telephone visits (CxW25-27) and the week 28 clinic visit (CxW28). The subject would then enter a no-teduglutide treatment (NTT) period and could be evaluated for subsequent teduglutide treatment eligibility according to the study schedules. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents. The reason for permanent treatment discontinuation, dates of investigational product administered (including last date of treatment), and amount of investigational product taken must be recorded in the electronic case report form (eCRF) and source documents, as described in Section 4.8.3. The investigator is encouraged to discuss withdrawal of a subject from investigational product with the medical monitor, when possible.

4.8.2 Study Withdrawal

At any time during the study, the investigator or sponsor may withdraw a subject, or a subject may withdraw from the study, for any reason, without prejudice to their future medical care by the physician or at the institution.

If a subject withdraws from the study during a teduglutide cycle, the evaluations listed for the EOT visit are to be performed as completely as possible. Whenever possible, the subject will then be asked to return 4 weeks later for the early termination (ET) visit, and will be contacted weekly by phone during the interim period between EOT and ET for safety follow-up.

If a subject withdraws from the study during a NTT period, the evaluations listed for the ET visit are to be performed as soon and completely as possible.

Subjects who withdraw from the study will not be replaced.

4.8.3 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
- Protocol deviation
- Lack of efficacy
- Physician decision
- Withdrawal by subject
- Withdrawal by parent/guardian
- Lost to follow-up
- Pregnancy (Discontinuation of treatment only)
- Death
- Other

4.8.3.1 Subjects 'Lost to Follow-up' Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact 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 CONCOMITANT TREATMENT

5.1 Concomitant Medications and Procedures

Concomitant treatment refers to all treatment taken between the dates of informed consent and EOS, inclusive. Concomitant medications and procedures will be assessed at each site visit, and include all non-study treatments (medications, herbal treatments, vitamins, invasive and diagnostic procedures). Concomitant treatment information must be recorded on the appropriate eCRF page. Details of medication changes and/or dosages will be recorded on the eCRF.

5.1.1 Permitted Treatment

Standard medical therapy for SBS should be continued.

5.1.2 Prohibited Treatment

The mechanism of action of teduglutide may increase enteral absorption of drugs (eg, motility medication including narcotics and opioids used for the management of SBS, warfarin, psychotropics, metronidazole, digoxin), so consideration should be given to modifying concomitant enteral medication regimens. Down-titration of concomitant enteral medications should be considered when drugs, especially those with a narrow therapeutic range, are given at dosages that are higher than usual.

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

Table 5-1: Prohibited Treatment

Prior Therapy	Time Restriction Prior to the Pretreatment Visit
Native/synthetic glucagon-like peptide-2 (not-including teduglutide)	Any
Glucagon-like peptide-1 analog or human growth hormone	3 months
Octreotide or dipeptidyl peptidase 4 inhibitors	3 months

6 INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The test product is teduglutide, which 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 SHP633 investigator's brochure.

6.1.1 Blinding the Treatment Assignment

Not applicable for this open-label study.

6.2 Administration of Investigational Product(s)

6.2.1 Interactive Response Technology for Investigational Product Management

An interactive web-based response system (IWRS) will be used for screening and enrolling subjects, recording subject visits, investigational product supply dispensation and management, inventory management and supply ordering, investigational product expiration tracking and management, and return of investigational product. Please refer to the Study Manual for additional details regarding the IWRS.

The IWRS will also be used for creating, tracking, and confirming investigational product shipments. A user manual with specific functions and instructions for the IWRS will be provided to the site, and site personnel will receive training.

6.2.2 Allocation of Subjects to Treatment

This is an open-label study. Subjects will retain their assigned subject number from the TED-C14-006 or SHP633-301 studies. Assessment of need for teduglutide treatment should be guided by the teduglutide treatment inclusion criteria. If the investigator, subject, and/or parent/guardian agree to proceed with treatment, a formal evaluation of teduglutide inclusion and exclusion criteria will be performed at the pretreatment visit (Table 1-3).

6.2.3 Dosing

If teduglutide treatment eligibility is established at the pretreatment visit and again, confirmed at the CxD1 visit, the subject will start a teduglutide treatment period, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg SC once daily. The initial dose will be calculated based on body weight measured at the teduglutide pretreatment visit, and adjusted as needed, based on body weight measured at week 12 (CxW12). 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 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 rotated.

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 each 24-week teduglutide treatment period, subjects will be evaluated for the need for additional teduglutide treatment. During the 4-week follow-up, the investigator will assess the subject via weekly telephone visits. At any time during the follow-up period, if escape criteria are met, the subject may proceed directly to another pretreatment visit to assess treatment eligibility for another cycle (Section 4.6). Following the completion of the 4-week follow-up, the subject will continue in the study off teduglutide until teduglutide treatment eligibility criteria are again met. Additional 28-week cycles may be repeated if treatment eligibility is established each time.

6.2.4 Unblinding the Treatment Assignment

Not applicable for this open-label study.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Labeling

Labels containing study information and pack identification will be applied to the investigational product(s) container.

The study drug will be packaged, labeled, and shipped to the study site by the sponsor or designee. Kits containing 7 vials of study drug will be supplied and these will be labeled in accordance with applicable regulatory requirements. Sterile water for injection syringes and other ancillary components will be provided separately and will be labeled in accordance with the applicable regulatory requirements.

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

6.3.2 Packaging

Investigational product is packaged in the following conditions:

Teduglutide will be provided in a sterile, single-use, glass vial as a lyophilized powder, to be reconstituted with 0.5 mL sterile water for injection provided as the diluent in a prefilled syringe.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 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.

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

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. The investigator is to keep a current record of the inventory and dispensation of all clinical supplies.

This record will be made available to the sponsor's site monitor for the purpose of accounting for all clinical supplies. Any discrepancy or deficiency will be recorded and will include an explanation. All supplies sent to the investigator must be accounted for and in no case will clinical supplies be used in any unauthorized situation.

The investigator has overall responsibility for administering/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 (as documented by the investigator in the applicable study delegation of authority form) will dispense the investigational product only to subjects eligible for teduglutide treatment following the procedures set out in the study protocol. All dispensed study medication will be documented in the interactive response technology system and/or other investigational product record (eg, investigation product accountability form). The investigator is responsible for assuring the retrieval of all study supplies from subjects.

All used and unused study drug vials must be returned by the subjects and/or parent/guardian, and will be retained at the site. If deemed appropriate, the investigator or his/her designee may dispense the unused study drug vials to the same subject. All original containers, whether empty or containing study drug will be returned to the pharmacy. Returned study drugs will NOT be relabeled or reassigned for use by other subjects. Contents of the study drug containers will not be combined. All used and unused vials must be returned to the distribution center according to the sponsor's instruction. No vial/kit may be destroyed on site without approval by the sponsor.

Please see the Pharmacy Manual for additional information.

6.5 Subject Compliance

Subjects will be instructed to bring their unused investigational product and empty/used investigational product packaging to every visit. Drug accountability will be assessed 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. The pharmacist/nominated person will record details on the drug accountability form.

Compliance with study drug is calculated from subject diaries. Of those subjects eligible for teduglutide treatment, 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 Schedule of Assessments (Table 1-1, Table 1-2, and Table 1-3) and must be referred to in conjunction with the instructions provided in this section.

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 (and assent, as applicable) from the subject. A subject will have approximately 7 days, after completion of either the TED-C14-006 or SHP633-301 studies, to sign consent to participate in the SHP633-304 study. The first visit after screening must occur within 12 weeks of screening for a pretreatment visit, and within 2 to 12 weeks of screening for an NTx visit.

The screening visit (Scr) assessments and procedures, beginning with informed consent, will be performed as outlined in Table 1-1, and as detailed below:

- Informed consent, and informed assent (if applicable), is obtained
- Study eligibility is determined. A screen failure is a subject who has given informed consent and failed to meet the Study Inclusion Eligibility Criteria. Subjects cannot be rescreened once they have been designated as a screen failure.
- Demographics, updates to medical history and SBS history
- Intake and output diaries are dispensed
- Evaluate teduglutide treatment inclusion criteria
- Adverse events, concomitant medications and concomitant procedures

7.1.2 Visits for Subjects Not Receiving Teduglutide

While outside of the 28-week teduglutide-treatment cycle, subjects will be followed approximately every 12 weeks for safety and efficacy assessments. No-teduglutide treatment visits are numbered sequentially (NT1, NT2, etc.), even if interrupted by the treatment cycles. The visit window (±7 days) is relative to the first NTx visit in the current NTT period. Assessments will be performed as outlined in Table 1-2 and described below.

- Intake and output diaries are dispensed
- Evaluate teduglutide treatment inclusion criteria
- Adverse events, concomitant medications and concomitant procedures
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries

- Record PS prescription and adjust as needed
- Safety Laboratory Tests (ie, clinical chemistry, hematology, and urinalysis)
- PedsQL Generic Core Scale/PedsQL Family Impact Module/ PedsQL Gastrointestinal Symptoms Module Sub-Scales
- Antibodies to teduglutide, if and when required
- Fecal occult blood testing, as indicated (Section 7.2.9.1)
- Colonoscopy/sigmoidoscopy, as indicated (see Section 7.2.9.2)
- Serum sample, as indicated

Teduglutide treatment may be considered at any time during the NTT period. If the investigator and the subject (and parent or legal guardian, as appropriate) agrees to proceed with treatment if the subject is eligible, the subject may proceed to the pretreatment visit immediately to determine eligibility.

7.1.3 Visits for Subjects Receiving Teduglutide

7.1.3.1 Pretreatment Visit

Subjects who meet at least 1 of the teduglutide treatment inclusion criteria during the screening visit or during the NTT period may proceed to the pretreatment visit immediately if the investigator, subject and parent agree to proceed with teduglutide therapy. Similarly, subjects who meet escape criteria at cycle week 24 or during the teduglutide follow-up period may proceed to the pretreatment visit immediately.

The pretreatment visit may also be combined with screening visit, and if the pretreatment visit assessments occur within 7 days of the TED-C14-006 or SHP633-301 EOS visit, both sets of assessments can be combined. A subject must have 2 weeks of intake diary data collected, prior to the first dose administration (CxD1) during any teduglutide treatment cycle. In general, pretreatment assessments may occur over a period of up to 21 days. The teduglutide pretreatment visit (Px) assessments and procedures will be performed as in Table 1-3 and as described below:

- Evaluate teduglutide eligibility (treatment inclusion/exclusion criteria)
- Dispense intake and output diaries
- Adverse events, concomitant medications and concomitant procedures
- Fecal occult blood testing
- Gastrointestinal-specific testing, including colonoscopy or sigmoidoscopy as indicated
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries
- Record PS prescription and adjust as needed

- Safety Laboratory Tests
  (In addition to clinical chemistry, hematology, and urinalysis, labs at this visit include prothrombin time [PT] international normalized ratio [INR]. Subsequent prothrombin time/international normalized ratio [PT/INR] measurement is only required to evaluate for suspected drug-induced liver injury [DILI]).
- Serum pregnancy testing, if applicable (when the pretreatment and screening visits are combined, the serum pregnancy test should be performed at the local laboratory)
- Serum sample

7.1.3.2 Teduglutide Treatment Period (CxD1-CxW24)

The open-label teduglutide treatment period will comprise 24 weeks, during which all assessments and procedures listed for Visits CxD1-CxW24 in Table 1-3 shall be completed. Cycles are numbered sequentially, such that the first visit of the first cycle is C1D1, and the first visit of the second cycle is C2D1, etc. Visit windows are calculated based upon the date of first investigational product administration (Visit CxD1).

Visit CxD1

Assessments and procedures at this visit will be performed as outlined Table 1-3 and as described below.

Two weeks of intake diary data are required before drug is administered at CxD1.

- Confirm teduglutide treatment eligibility
- Dispense intake and output diaries
- Adverse events, concomitant medications and concomitant procedures
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries
- Record PS prescription and adjust as needed
- Safety laboratory tests
- Quality of life measurements
- Antibodies to teduglutide
- Pregnancy testing (urine), if applicable
- Dispense study drug

Site Visits during Teduglutide Treatment Period

Subjects will return for clinic visits on cycle weeks 1, 2, 4, 6, 9, 12, 16, 20, and 24/EOT. Assessments and procedures at these visits will be performed as outlined in Table 1-3 and as described below:

- Dispense/review intake and output diaries (every effort should be made to complete 2 weeks of intake diary entries prior to each clinic visit and to complete 48 hours of output diary entries during a period of nutritional stability prior to each clinic visit)
- Physical examination and vital signs, including weight
- Record PS prescription and adjust as needed
- Safety laboratory tests
- Urine pregnancy testing for FOCBP (CxW4, CxW9, CxW12, CxW16, CxW20, CxW24)
- Study drug dispensation (except for CxW24)
- Adverse events, concomitant medications and concomitant procedures

In addition, at CxW12 and CxW24 Visits **ONLY**, the following procedures will be performed:

- Height and head circumference
- Antibodies to teduglutide
- Fecal occult blood testing (FOBT)
- GI-specific testing, including colonoscopy or sigmoidoscopy as indicated
- Quality of life measurements

At CxW24 **ONLY**, a serum sample is collected and stored for future analysis. This sample will not be used for genetic testing and lack of collection will not constitute a protocol deviation.

Escape criteria are also evaluated at CxW24. The investigator may combine the CxW24 assessments with the next pretreatment visit assessments if at least 1 escape criterion is met at the CxW24 visit and the pretreatment assessments occur within 7 days of the CxW24 visit.

Phone Visits

Phone visits are required approximately 1 week after adjustments in PS during the teduglutide treatment period. Phone visit assessments and procedures are outlined in Table 1-3 and described below:

- Review intake and output diaries
- Safety laboratory tests (clinical chemistry and urinalysis)
- Record PS prescription and adjust as needed

- Obtain AEs, concomitant medications, and concomitant procedures
- Evaluate escape criteria

7.1.4 Teduglutide Follow-up Period

The safety follow-up period for this protocol is 4 weeks (weeks 25 – 28 of the cycle). Phone visits will occur on cycle weeks 25, 26, and 27 for all subjects. Phone visit assessments and procedures at weeks 25-27 will be the same as for telephone visits performed during the teduglutide treatment period. In addition, subjects will be evaluated for follow-up period escape criteria. If escape criteria are met at any time during the follow-up period, the subject may proceed directly to another pretreatment visit at the investigator's discretion. The investigator may combine the CxW24 or CxW28 visits with the next pretreatment visit if at least 1 escape criterion is met at the CxW24 or CxW28 visits, and the pretreatment assessments occur within 7 days of the CxW24 or CxW28 visit. If a subject is completing the study at the CxW28 visit, the EOS/ET visit (Section 7.1.5) will take place in lieu of the CxW28 visit. Otherwise, following completion of the 28-week treatment cycle, the subject will proceed to an NTT visit within approximately 12 weeks.

At cycle week 28 (CxW28), subjects will return to the study site. In addition to the assessments performed at weeks 25-27, the following procedures will be performed at **CxW28 ONLY:**

- Dispense intake and output diaries
- Physical examination and vital signs, including weight
- Antibodies to teduglutide
- Pregnancy testing (urine), if applicable
- Evaluate escape criteria

7.1.5 Study Completion/Early Termination Visit (EOS/ET Visit)

All subjects will return to the study site for the end of study/early termination visit (EOS/ET). Assessments and procedures at this visit will be performed as outlined in Table 1-1 and as described here. If a subject discontinues the study prematurely, the assessments for the EOS/ET Visit are to be performed as completely as possible (see Section 4.8.2).

- Adverse events - AEs will be collected for 4 weeks after the last dose of teduglutide in the study even if the EOS/ET occurs within that timeframe.
- Concomitant medications and concomitant procedures
- Physical examination and vital signs, including weight
- Height and head circumference
- Review intake and output diaries (the intake diary should be completed daily for a minimum of 2 weeks prior to the EOS/ET visit. The output diary should be completed daily over a 48-hour period of nutritional stability before the EOS/ET visit)

- Record PS prescription and adjust as needed
- Safety laboratory tests
- Fecal occult blood testing, as indicated
- Gastrointestinal-specific testing, including colonoscopy or sigmoidoscopy as indicated.
- Quality of life measurements
- Antibodies to teduglutide
- Pregnancy testing, as needed

7.1.6 Qualitative Interview

An optional qualitative interview will be conducted by phone and within 14 days after completion of the EOS/ET visit (see Section 7.2.13). A single individual telephone interview will be conducted with English-speaking parents (or legal guardians) of subjects and subjects aged 12 years or older and who provide informed consent (and if applicable, informed assent) to participate in the interview. These interviews will be performed in selected countries.

7.2 Study Evaluations and Procedures

7.2.1 Demographics, Medical History, and SBS History

Demographics, medical history, and SBS history will be obtained at screening. Medical history for purposes of this extension study will consist of the following:

- Adverse events that were ongoing at the time of completion of TED-C14-006 or SHP633-301
- Events that occurred during the period between completion of TED-C14-006 or SHP633-301 and informed consent to SHP-633-304

This medical history information will supplement the medical history information collected at the start of the TED-C14-006 or SHP633-301 core studies. If the subject has any changes to the SBS history collected at the baseline visit of the TED-C14-006 or SHP633-301 studies, that information (updated SBS history) will be collected.

7.2.2 Physical Examination

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

7.2.3 Vital Signs, Body Weight, Height, Head Circumference and Body Mass Index

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 cuff (using the same method, the same extremity, and in the same position throughout the study, whenever possible).

Body weight will also be recorded in the eCRF; subjects should be weighed on the same scale at each study visit. Height (or length) and head circumference (for subjects ≤36 months of age) will be measured at selected visits. A height z-score, weight z-score, BMI, and BMI z-score will be calculated by the sponsor using the site-provided height and weight data collected at each site visit

New clinically significant vital sign abnormalities should be recorded on the appropriate AE page of the eCRF.

7.2.4 Clinical Laboratory Tests

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 1-1, Table 1-2, and Table 1-3) 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 teduglutide treatment period, subjects will also have safety labs within approximately 5-7 days after a PS adjustment. Safety labs performed after PS 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 AE (see Section 8.1). Urine specimen collection should be attempted as part of the safety labs, but lack of urinalysis will not constitute a protocol deviation.

New clinically significant labs should be reported as AEs.

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

Table 7-1: List of Laboratory Tests

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

Coagulation:
Prothrombin time/International normalized ratio

Urinalysis:
- Blood
- Glucose
- Leukocytes
- Microscopic analysis
- pH
- Protein
- Specific gravity

Pregnancy tests (females of childbearing potential):
- Serum β-HCG (teduglutide pretreatment visit)
- Urine β-HCG (all other visits)

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

[a] C-reactive protein will not be measured in subjects <10 kg.

7.2.5 Serum Sampling

Serum samples will be collected and stored for future analysis at the following times:

- At the pretreatment visit. If the subject arrived at the pretreatment visit by meeting an escape criterion, the serum sample will not be repeated at the pretreatment visit, because it will have been collected recently at the CxW24 visit.
- At the CxW24 (EOT) visit
- During NTT: Approximately every 24 weeks

Stored serum samples should be omitted for subjects weighing less than 15 kg and whenever local blood volume limitations are exceeded.

The serum sample will not be used for genetic testing. Lack of collection will not constitute a protocol deviation.

The sponsor, sponsor's representatives, biorepositories, and any specialty laboratories will be blinded to the subject's identity. The sample and/or extracted material will otherwise be stored for up to 15 years from the end of the study after which time it will be destroyed. Upon written request, subjects will be permitted to withdraw their sample from the analysis and have their sample and/or extracted material destroyed. Any results already generated from the samples will not be removed from any analyses that have already been performed.

7.2.6 Pregnancy Testing

A serum pregnancy test is performed on all FOCBP at the teduglutide pretreatment visit (when the pretreatment and screening visits are combined, the serum pregnancy test should be performed at the local laboratory). Urine pregnancy tests will be administered at all other visits according to the study schedules, or if pregnancy is suspected, or as specified per protocol upon withdrawal of the subject from the study.

7.2.7 Antibody Testing

Blood samples will be drawn for the analysis of antibodies to teduglutide according to the Schedule of Assessments (Table 1-1, Table 1-2, and Table 1-3). Blood samples for antibodies may be drawn from a central line or from peripheral access. The sample drawn on CxD1 must be drawn prior to administration of the first dose of teduglutide. Once the subject has started teduglutide treatment, samples must be drawn at least 14 hours after dosing. Subjects who test positive for antibodies to teduglutide will also be tested for neutralizing antibody. Subjects who have been previously treated with teduglutide, and who test positive for antibodies to teduglutide, will have follow-up blood draws for antibodies to teduglutide every 12 weeks while on study until a negative result is obtained.

7.2.8 Volume of Blood

Efforts will be made to minimize the amount of blood drawn from all pediatric subjects enrolled in this study. The volumes of blood to be drawn from each subject will vary depending on clinical status and subject weight. Approximate volumes of blood to be drawn from each subject annually are shown in Table 7-2.

Table 7-2: Approximate Volume of Blood to be Drawn from Each Subject Annually

Assessment		Sample Volume (mL)	No. Samples per two 28-week Teduglutide Cycles	Total Volume (mL)
Subjects ≥10 kg Receiving Teduglutide Treatment				
Safety	Biochemistry and β-hCG[a]	2.5	24	60
	Hematology	2	24	48
	Coagulation Parameters	2	2	4
	Antibodies	2	8	16
	Serum storage samples[b]	3	4	12
Total mL per 2, 28-week Treatment Cycles (Approximate Annual Volume):				**140**
Subjects <10 kg Receiving Teduglutide Treatment				
Safety	Biochemistry[c]	1	24	24
	Hematology	1	24	24
	Coagulation Parameters	2	2	4
	Antibodies	1	8	8
Total mL per 2, 28-week Treatment Cycles (Approximate Annual Volume):				**60**
Subjects ≥10 kg Not Receiving Teduglutide Treatment[d]				
Assessment		**Sample Volume (mL)**	**No. Samples per 4 NTT Visits**	**Total Volume (mL)**
Safety	Biochemistry	2.5	4	10
	Hematology	2	4	8
	Serum storage samples[b]	3	2	6
Total mL per 4 "No Teduglutide Treatment" Visits 48-week period:				**24**
Subjects <10 kg Not Receiving Teduglutide Treatment[d,]				
Assessment		**Sample Volume (mL)**	**No. Samples per 4 NTT Visits**	**Total Volume (mL)**
Safety	Biochemistry[c]	1	4	4
	Hematology	1	4	4
Total mL per 4 "No Teduglutide Treatment" Visits 48-week period:				**8**

β-hCG=beta-human chorionic gonadotropin; NTT=no-teduglutide treatment
[a] β-hCG testing will only be administered to females who are eligible for teduglutide treatment.
[b] Stored serum samples should be omitted for subjects weighing less than 15 kg and whenever local blood volume limitations are exceeded.
[c] CRP will not be measured in subjects <10 kg.
[d] Subjects not receiving teduglutide treatment, but who were exposed to it previously and tested positive for anti-teduglutide antibodies will require blood samples for antibody testing every 12 weeks until they test negative.

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 PS adjustment, and anti-teduglutide antibody testing during no-teduglutide treatment. Stored serum samples should be omitted for subjects weighing less than 15 kg and whenever local blood volume limitations are exceeded.

Maximum blood volume at any given visit occurs when the pretreatment and Week 24 visits are combined. For subjects <10 kg this is 5.0 mL and for subjects ≥10 kg this is 8.5mL.

7.2.9 Gastrointestinal-specific Testing

7.2.9.1 Fecal Occult Blood Testing

Fecal occult blood testing must be performed on all subjects at the pretreatment visit, week 12, and week 24 of the teduglutide cycle. During NTT periods, FOBT must be performed on teduglutide-exposed subjects (subjects who have received teduglutide any time in the past and are therefore not teduglutide-naïve) on a roughly annual basis (approximately every 48-60 weeks). Actions to be taken in response to a positive FOBT are described below.

7.2.9.2 Colonoscopy or Sigmoidoscopy

Teduglutide-naïve subjects age 12 and older will undergo colonoscopy or sigmoidoscopy at the pretreatment visit if one has not been performed within 1 year.

Subjects of any age with newly positive FOBT results at the pretreatment visit for which a readily detectable cause cannot be identified (eg, anal fissure) will undergo a colonoscopy or sigmoidoscopy prior to receiving teduglutide. If newly positive FOBT results (for which a readily detectable cause cannot be identified) are obtained at the end of a teduglutide treatment cycle (CxW24/EOT), colonoscopy or sigmoidoscopy will be performed. The need for colonoscopy or sigmoidoscopy in response to positive FOBTs at any other point during the study, or to re-evaluate persistently positive FOBTs is at the discretion of the investigator.

Teduglutide-exposed subjects who have received the equivalent of 2 treatment cycles (48 weeks of study drug exposure) will undergo colonoscopy or sigmoidoscopy. While receiving additional teduglutide treatment, subjects will undergo colonoscopy or sigmoidoscopy at 5 year intervals or more often as needed.

Upper endoscopy may be performed along with any colonoscopy or sigmoidoscopy at the investigator's discretion. If a polyp is found, adherence to current polyp follow-up guidelines is recommended. Subjects with unresected GI polyps, polyposis conditions, premalignant change or malignancy in the GI tract will be excluded from teduglutide treatment.

7.2.10 Nutritional Support

Nutritional support includes PS, EN, and other food and fluids. Advances in EN and/or reductions to PS will be based on clinical status, including weight, linear growth, hydration status, and safety laboratory results. Intake and output diaries will include data to be considered in the adjustment of each subject's nutritional support. Guidelines for nutritional support management and weaning algorithms are provided in Appendix 2.

7.2.11 Diaries

7.2.11.1 Study Drug Administration Diary

A study drug administration diary will record administration of teduglutide. This diary should be completed by the subject (or parent/legal guardian, as applicable) daily during the teduglutide treatment periods (between visits CxD1 and CxW24).

7.2.11.2 Intake Diary

Intake diaries will be used to collect and evaluate each subject's nutritional support. The subject/parent/guardian will complete the appropriate fields of the PS section of the intake diary 2 weeks prior to ALL scheduled site visits (except at pretreatment visit). During the 24-week teduglutide treatment period, the intake diary will also be completed for 1 week following PS adjustments. The intake diary will also be completed daily during the 4-week follow-up period. The following data will be captured in the intake diaries:

- Parenteral support volume and infusion duration
- Site personnel will determine the actual PS daily calories based on diary entries.

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 PS reduction and advance in feeds.

7.2.11.3 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 that are in a teduglutide treatment cycle within 1 week of implementing a change in the PS prescription, regardless of previous teduglutide exposure.

Urine data:

- Toilet-trained subjects (who do not wear diapers)
  Measure and record all urine output in mL or cc
- Nontoilet-trained subjects (who wear diapers)
  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 may be asked to collect the first void after the daily PS infusion to measure specific gravity

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

- Toilet-trained subjects (who do not wear diapers)
  Record the occurrence of each bowel movement and score the stool consistency using the Bristol Stool Form Scale (see Output diary)

- Nontoilet-trained subjects (who wear diapers)
  Record the weight of diapers containing stool (including diapers with mixed urine and stool) as stool output and score the stool consistency using the Bristol Stool Form Scale (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. Ostomy output will not be scored using the Bristol scale.

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 PS reduction and advance in feeds.

7.2.12 Health-related Quality of Life Assessments

Throughout the study, health-related quality of life assessments will be performed using the PedsQL Generic Core Scales. Each PedsQL age-appropriate form takes less than 4 minutes to complete. The scales include self-reports for pediatric subjects and adolescents aged 5 to 18 years and proxy-reports from parents of pediatric subjects aged 2 to 18 years. The PedsQL Generic Core Scales will not be performed for subjects younger than 2 years of age. If a child is unable to complete the age-appropriate questionnaire (eg, due to developmental delay or other illness) it will not constitute a protocol deviation, but the parent should continue to complete the appropriate parent-specific forms.

Field trials have shown that the internal consistency reliability of the PedsQL was excellent, with alphas for the generic core scales in both self- and proxy-report greater than the 0.70 standard, and alphas for the full 23-item scale approaching 0.90 for self- and proxy-report. Missing data were minimal. Item response distributions were across the full-scale range, with no floor effects, and minimal ceiling effects.

The validity of the PedsQL Generic Core Scales was demonstrated through known group comparisons, and correlations with other measures of disease burden. The PedsQL self- and proxy-report distinguished between pediatric subjects with and without a chronic health condition, and within the group of pediatric subjects with a chronic condition, between those who did or did not have an overnight hospital visit in the last 12 months. Further, both child self-report and parent proxy-report correlated significantly with the number of days the child was too ill to pursue normal activities, needed someone to care for him or her, missed school in the last month, the number of days the parent missed from work in the last month, and parent-report of problems pursuing their normal work routine and concentrating at work. The PedsQL Generic Core Scales are also responsive to clinical change, as demonstrated in field trials.

7.2.12.1 Pediatric Quality of Life Generic Core Scale (PedsQL™), Acute Version

The PedsQL Generic Core Scale is designed to measures health-related quality of life (HRQoL) in pediatric subjects and adolescents (2-18 years of age). The developmentally appropriate PedsQL Generic Core Scale will be completed by either the parent or legal guardian and subject as indicated in Table 7-3 at the time points as outlined in Table 1-1, Table 1-2, and Table 1-3.

Table 7-3: Developmentally Appropriate PedsQL™ Generic Core Scales

Report	Completed by
Parent Report for Toddlers (ages 2-4)	Parent or Legal Guardian
Child Self Report and Parent Proxy-Report for Young Pediatric subjects (ages 5-7)	Subject and Parent or Legal Guardian
Child Self Report and Parent Proxy-Report for Pediatric subjects (ages 8-12)	Subject and Parent or Legal Guardian
Child Self Report and Parent Proxy-Report for Teens (ages 13-18)[a]	Subject and Parent or Legal Guardian

Abbreviations: PedsQL=Pediatric Quality of Life Inventory

[a] The Child Self Report and Parent Proxy-Report for Teens (ages 13-18) will also be completed for subjects older than 18 years of age.

The Parent Report for Toddlers (ages 2-4) of the PedsQL Generic Core Scale is composed of 21 items comprising 4 dimensions as follows: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), 4) School Functioning (3 items).

The Child and Parent Reports of the PedsQL Generic Core Scale for Young Pediatric subjects (ages 5-7), Pediatric subjects (ages 8-12), and Teens (ages 13-18) are composed of 23 items comprising 4 dimensions as follows: 1) Physical Functioning (8 items), 2) Emotional Functioning (5 items), 3) Social Functioning (5 items), 4) School Functioning (5 items).

7.2.12.2 Pediatric Quality of Life Family Impact Module (PedsQL™), Acute Version

The PedsQL Family Impact Module is a parent-report multidimensional instrument that will be completed by the parent or legal guardian, as outlined in Table 1-1, Table 1-2, and Table 1-3.

The PedsQL Family Impact Module is a specific module of the PedsQL that is used to measure the impact of pediatric chronic health conditions on parents and the family (Varni et al., 2004). The 36-item PedsQL Family Impact Module consists of 6 scales measuring parent self-reported functioning as follows: 1) Physical Functioning (6 items), 2) Emotional Functioning (5 items), 3) Social Functioning (4 items), 4) Cognitive Functioning (5 items; worries about treatment and disease), 5) Communication (3 items), 6) Worry (5 items). Two additional scales measure parent-reported family functioning as follows: 1) Daily Activities (3 items), and 2) Family Relationships (5 items). The PedsQL Family Impact Module should take the parent or legal guardian approximately 5 to 10 minutes to complete.

7.2.12.3 PedsQL Gastrointestinal Symptoms Module (PedsQL™), Acute Version

The PedsQL Gastrointestinal Symptom Module is a disease-specific 58-item module, comprised of 10 different symptom scales that assess gastrointestinal symptom-related quality of life: food and drink limits, trouble swallowing, heartburn and reflux, nausea and vomiting, gas and bloating, constipation, blood in poop, and diarrhea. The PedsQL Gastrointestinal Symptoms Module was designed to allow the selection and scoring of individual scales from the Module. The scales of Food and Drink Limits (6 items) and Diarrhea (7 items) were identified as clinically relevant and appropriate for the symptoms experienced in this pediatric study population, and therefore, are the only scales used in this study.

The scales will be completed by either the parent or legal guardian and subject as indicated in Table 7-3 at the time points outlined in Table 1-1, Table 1-2, and Table 1-3.

7.2.13 Qualitative Interviews

The objective of the qualitative interviews is to elicit the key symptoms and impacts of importance associated with SBS as well as the effect of teduglutide in relation to symptoms and impact experienced during the clinical study as described by subjects and caregivers in their own words. In addition, the interviews with caregivers will elicit concepts on aspects of caregiver burden associated with caring for their children with SBS and the impact of teduglutide on the caregiver burden experienced during the study.

The interviews will be offered to English-speaking parents or legal guardians of subjects and subjects aged 12 years or older in selected countries. At the qualified subjects' clinic sites, subjects and caregivers will be provided with a description of the qualitative interview and be offered the opportunity to participate. Subjects and caregivers who agree to participate will be asked to provide written informed consent (for caregiver interviews) and written assent and parental permission (for subject interviews) using forms developed specifically for the interviews.

The format will be a single individual telephone interview using a semistructured interview guide. Each interview will be approximately 45 minutes and will be completed within 14 days after completion of the EOS/ET visit. Subjects and caregivers will be interviewed individually and separately and will be instructed to take the interview at a private setting.

Two interview guides have been developed, one for the caregiver interviews (Appendix 3) and one for the subject interviews (Appendix 4). Interview guides for UK sites will be reviewed by a native speaker of the local dialect. The guides will begin with a brief overview of the interview process and very general questions intended to get the participants talking about their experiences (and the impacts of these experiences) associated with SBS prior to entering the study. These questions will then be followed by a thorough probing of subject and caregiver experience during the study and the importance of the treatment outcomes. Topics included in the interview are listed below:

- Subjects: SBS-related symptoms and impacts
  - Symptoms due to SBS
  - Symptoms due to parenteral support
  - Impact of SBS on daily activities, physical functioning and social functioning
  - Impact of parenteral support on daily activities, physical functioning, and social functioning

- Subjects: experience of teduglutide treatment in relation to SBS symptoms and impacts during the study
  - Changes of SBS-related symptoms relating to teduglutide
  - Changes of parenteral support-related symptoms relating to teduglutide
  - Changes of daily activities, physical functioning, and social functioning relating to teduglutide
- Caregivers:
  - SBS-related symptoms and impacts described as an observer
    - Symptoms due to SBS
    - Symptoms due to parenteral support
    - Impact of SBS on daily activities, physical functioning, and social functioning
    - Impact of parenteral support on daily activities, physical functioning, and social functioning
  - Changes in SBS-related symptoms and impacts in relation to teduglutide treatment during the study described as an observer
    - Changes of SBS-related symptoms relating to teduglutide
    - Changes of parenteral support-related symptoms relating to teduglutide
    - Changes of daily activities, physical functioning, and social functioning relating to teduglutide
  - Description of care provided and impacts on caregivers of pediatric patients with SBS requiring parenteral support
    - Impact on ability to complete activities of daily living
    - Impact on emotional and social functioning
    - Financial impact
  - Changes of caregiver impact in relation to teduglutide treatment during the study
    - Impact on ability to complete activities of daily living
    - Impact on emotional and social functioning
    - Financial impact

To limit bias, the interviewer will begin by asking open-ended questions designed to identify the symptoms associated with SBS and their impact, as well as any perceived treatment benefits in these areas and the meaningfulness of these changes from the perspective of the parent/legal guardian and/or subject. Site personnel will obtain consent, assent, and permission for those individuals that agree to participate in the qualitative interviews.

All interviews will be conducted by experienced moderators and will be audio recorded. Interviews with subjects and caregivers from UK sites will be conducted by a moderator who is a native speaker. The content of the interview will be transcribed, and the audio recording will be destroyed to protect patient privacy. All personal information will be removed from the transcripts. Using the interview transcripts, dominant trends will be identified in each interview and then compared across the results of the other interviews to generate themes or patterns in the way subjects and caregivers describe their/their child's treatment experiences and observations during the clinical trial as well as their perceptions of treatment benefit over the trial period.

Should an interviewer become aware of any potential AE during the telephone interview, the interviewer will share the relevant information with the subject's clinical site staff within 1 day. The clinical site will be responsible for follow-up with the subject. The investigator will be responsible for determining the clinical significance of the event and the reporting of the event as outlined in Section 8.

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 4 weeks following the last dose of teduglutide in the study. This includes events occurring during the screening phase of the study and the qualitative interviews, 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 pretreatment 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.

In consideration of whether a treatment-emergent adverse event (TEAE) might lead to dose interruption (Section 8.4.1) or early termination of the study (Section 8.5), severe TEAEs will also be graded according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) severity grading criteria (US Department of Health and Human Services et al., 2010).

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 study drug that are not resolved at EOT 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 in 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.

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 (eg, 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

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.4.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Global Drug Safety Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the Sponsor Medical Monitor using the details specified in the emergency contact information section of the protocol. In the event a subject becomes pregnant during the study, teduglutide administration must be discontinued immediately.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Adverse Event Form for Serious Adverse Events and Non-serious AEs as Required by the Protocol. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Adverse Event Form for SAEs and Non-serious AEs as Required by the Protocol as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG test or will determine the pregnancy onset date.

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 the investigational product at a dose or frequency greater than 0.05 mg/kg subcutaneous once daily. An overdose occurs if any of the following criteria are met:
    - More than 0.05 mg/kg is given at any one time
    - Consecutive doses are spaced less than 12 hours apart
    - Any more than 0.05 mg/kg given in one day (a day is defined as beginning at 12:00 AM and ending at 11:59 PM)

- **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 Sponsor 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 Sponsor 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 Sponsor 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 serious adverse event (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 7.1.4, and must be reported to the Shire Global Drug Safety Department and the Sponsor 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 of Individual Subjects

The investigator is responsible for contacting the sponsor/designee when the subject's teduglutide dosing regimen is interrupted.

Attempts should be made to contact the sponsor/designee prior to dose interruption. Reasons for dosage interruptions may include but are not limited to hospitalization, AEs, a lapse in investigational product delivery, etc. The length of the 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 AE of special interest (see Section 8.3)
- An AE that is of NCI CTCAE severity Grade 3 or 4 and related to teduglutide
- Intestinal obstruction
- Biliary obstruction related to teduglutide
- Pancreatic duct obstruction related to teduglutide
- Heart failure with severe fluid overload related to teduglutide

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

- Pregnancy
- Severe hypersensitivity, such as anaphylaxis determined by the investigator to be related to study drug. This does not include the presence of anti-teduglutide antibodies, mild injection site reactions or mild symptoms that according to the investigator do not pose a significant risk to the subject.
- Confirmed DILI related to teduglutide (see Section 8.4.2)
- Any malignancy.

8.4.1 Dose Interruption Criteria Based on Adverse Event Severity and Relationship to Investigational Product

The investigational product must be interrupted if the subject experienced an AE that is of severity ≥Grade 3 per the NCI CTCAE and is reported as related to the investigational product.

In consideration of whether a TEAE might lead to dose interruption, severe TEAEs will also be graded according to the NCI CTCAE severity grading criteria (US Department of Health and Human Services et al., 2010). All such TEAEs should be discussed with the Sponsor Medical Monitor or designee as soon as possible. The length of the dose interruption, and whether teduglutide administration resumes or is permanently discontinued, depends on the clinical situation.

8.4.2 Dose Interruption Criteria Based on Drug-Induced Liver Injury

Teduglutide administration for an individual subject may need to be interrupted if the subject has clinical and laboratory evidence of potential DILI, in the absence of an alternative explanation, as identified by the following criteria:

- ALT or AST >8x ULN
- ALT or AST >5x ULN and >2x baseline value for more than 2 weeks
- (ALT or AST >3x ULN and >2x baseline value) and (total bilirubin >2x ULN or INR>1.5)
- ALT or AST >3x ULN and >2x baseline value with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

All laboratory values suggestive of potentially new DILI should be repeated and verified within 3 days. International normalized ratio should be measured with this set of verification laboratory assessments 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 to evaluate the cause of liver injury. This evaluation may include, as clinically indicated, consideration of sepsis, acute viral hepatitis (eg, hepatitis A immunoglobulin [IgM], hepatitis B surface antigen, hepatitis C antibodies, cytomegalovirus IgM, Epstein-Barr virus antibody panel), hepatobiliary obstruction (ultrasound), autoimmune hepatitis (anti-nuclear, anti-smooth muscle, anti-actin, or anti-liver kidney microsomal antibodies), intestinal failure associated liver disease, cardiovascular causes such as ischemic hepatitis, and concomitant hepatotoxic treatments.

Additional evaluations may be performed at the discretion of the investigator in consultation with the Sponsor medical monitor.

Teduglutide administration must be permanently discontinued if DILI is confirmed and deemed related to study drug.

8.5 Early Termination of the Clinical Study

The data monitoring committee (DMC) may recommend stopping the study if any of the following conditions are met:

- ≥2 subjects develop the same event of CTCAE severity Grade 3 that is reported as related to the investigational product

  or

- 1 subject develops an event of CTCAE severity Grade 4 that is reported as related to the investigational product.

9 DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol in 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 in 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. Unscheduled safety follow up assessments (including visits conducted after EOS) are not to be collected unless requested.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the CRO's data management process. 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 its agent. All statistical analyses will be performed using SAS® (SAS Institute, Cary, NC, USA) version 9.3 or higher.

The statistical analysis plan (SAP) will provide the statistical methods and definitions 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.

9.4 Planned Interim Analysis, and Data Monitoring Committee

An interim analysis is planned when 6 months of safety data have been collected for subjects entering from TED-C14-006. Additional interim analyses may be conducted as needed.

A 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.

9.5 Sample Size Calculation and Power Considerations

The number of subjects in this study is not based on statistical power considerations as this is an extension study of the core studies, TED-C14-006 and SHP633-301. The maximum number of subjects was determined by the enrollment in TED-C14-006 and SHP633-301.

9.6 Study Population

The safety population includes all enrolled subjects in the study. Safety population will be used for both safety and efficacy analyses.

9.7 Efficacy Analyses

No claims of statistical significance will be made; however, 95% confidence intervals will be provided, if applicable. Continuous variables, including those assessed on a discrete scale, 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.

9.7.1 Efficacy Endpoints

Efficacy endpoints will be analyzed at the end of each teduglutide treatment period (week 24 or EOT), and at each study visit, relative to the baseline of the core study (TED-C14-006 or SHP633-301) and/or first exposure to teduglutide. The following efficacy endpoints will be analyzed:

- Reduction in PS volume of at least 20%
- Absolute and relative change in PS volume
- Complete weaning off PS
- Change in days per week of PS

9.8 Safety Analyses

9.8.1 Safety Endpoints

The following safety endpoints will be analyzed:

- Adverse events
- Vital signs, including temperature, heart rate, and blood pressure
- Laboratory safety data (ie, clinical chemistry, hematology, and urinalysis)
- Urine output
- Stool output
- Antibodies to teduglutide
- Gastrointestinal-specific testing , including fecal occult blood testing and colonoscopy or sigmoidoscopy
- Z-scores for weight, height (or length), head circumference (up to 36 months of age), and BMI

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number of events, incidence, and percentage of AEs will be calculated overall, by System Organ Class (SOC) and by preferred term. SAEs will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed.

Prior and concomitant medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) with regard to drug class and drug name. The number and percentage of subjects with specific prior medications will be summarized. Medical history (including surgical/procedural history) will be coded using MedDRA. The number and percentage of subjects with specific histories will be summarized by system organ class and preferred term.

For clinical laboratory tests, vital signs, body weight, and fluid balance variables, descriptive statistics (mean, median, standard deviation, minimum and maximum values, the number and percentage of subjects in specified categories) will be calculated to summarize the observed values and change from baseline at each scheduled visit.

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

Additional safety parameters and measures will include change in body weight, height (or length) and head circumference (up to 36 months of age). Derived variables will include height z-score, weight z-score, BMI, and BMI z-score. Descriptive statistics (mean, median, standard deviation, minimum and maximum values, the number and percentage of subjects in specified categories) will be calculated to summarize the absolute values and change from baseline at each scheduled visit.

9.9 Other Analyses

9.9.1 Health-related Quality of Life Analyses

Health economics and outcomes research endpoints will be analyzed at approximately 12-week intervals (weeks 12 and 24 of each teduglutide treatment cycle, and every 12 weeks for subjects not on teduglutide), relative to the study baseline. The beginning of each treatment cycle (CxD1) will be an additional baseline.

- Change in Pediatric Quality of Life Inventory (PedsQL) score
- Change in PedsQL Family Impact Module score
- Change in PedsQL Gastrointestinal Symptoms Module Sub-Scales scores:
  - Food and Drink Limits
  - Diarrhea

9.9.2 Qualitative Interviews

A final report will be developed for the qualitative interviews and will be included in the CSR of the study.

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 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 to the CRO 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 EOS 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 is appointed to review the final CSR for multicenter studies. Agreement with the final CSR 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 products, 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 Case Report Forms

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded into eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. 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 into the eCRF.

eCRFs should be approved by the investigator per study specifications and data deliverable requirements.

The clinical research associate (CRA)/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 diary cards, original clinical laboratory reports, and histology and pathology 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 CRA/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 subject 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 and assent, where applicable, from 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 or the subject's legally-authorized representative, as applicable, 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 (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or 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.

Within the source documents, site personnel should document instruction of and understanding by the parent/legally-authorized representative/caregiver of the safe, responsible storage and administration of investigational product to the study subject.

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 which 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.

For sites within the EU, the applicant for an EC opinion can be the sponsor, the investigator, or for multicenter studies 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 (or 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; for sites within the EU, this can be done by the sponsor, the investigator or for multicenter studies 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 (or 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 review 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 SHP633; national or local regulatory authorities; and the IRBs/ECs 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 2-4 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 current standards. Participation as an investigator does not confer any rights to authorship of publications.

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APPENDIX 1 PROTOCOL HISTORY

Document	Date	Global/Country/Site Specific
Original Protocol	08 April 2016	Global
Amendment 1	22 Nov 2016	Global
Amendment 2	23 Mar 2017	Global
Amendment 3	16 May 2018	Global
Amendment 4	01 Oct 2019	Global

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3	**Amendment Date 16 May 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
The primary contact for EU and backup contact for NA was updated to [redacted].		Emergency Contact Information
To allow the enrollment of subjects who completed SHP633-301 where SHP633-301 was registered and approved by the local Health Authorities. The study title and eligibility criteria have been modified to accommodate younger children completing SHP633-301. SHP633-304 will evaluate long-term safety and efficacy in subjects who completed SHP633-301 and will provide a mechanism for subjects who complete SHP633-301 to receive additional teduglutide treatment if clinically indicated.		Synopsis; Table 1-1; Section 2; Section 3.1; Section 4.1; Section 4.5; Section 6.2.2; Section 7.1.1; Section 7.1.3.1; Section 7.2.1; Section 9.5; Section 9.7.1
To minimize risk to subjects, a new escape criterion was added, allowing those who had escaped during the follow-up period of a previous teduglutide treatment to omit the follow-up period during subsequent teduglutide treatment cycles. For subjects who previously escaped the follow-up period, CxW24 assessments can be combined with the next pretreatment visit assessments.		Synopsis; Table 1-3; Figure 3-1; Section 3.1; Section 4.6; Section 6.2.3; Section 7.1.3.1; Section 7.1.3.2; Section 7.1.4; Section 7.2.5
Added the recording of parenteral support prescription at screening.		Table 1-1
Clarified language that all concomitant procedures are to be captured, not just gastrointestinal procedures.		Table 1-1; Table 1-2; Table 1-3, Section 5.1; Section 7.1.1; Section 7.1.2; Section 7.1.3.1; Section 7.1.3.2; Section 7.1.5
Updated the information on the clinical studies with teduglutide in pediatric subjects to include the results of TED-C14-006 and a description of the additional core study, SHP633-301.		Section 1.3
Added new PK simulation data to further support dosing.		Section 3.1
Deleted text that was duplicated in other sentences of sections.		Section 5.1
Deleted biological therapy (eg, antitumor necrosis factor) from the table of prohibited treatments as it was included in error.		Table 5-1
Clarified that compliance with study drug is calculated from subject diaries		Section 6.5
Added direct bilirubin to the list of laboratory tests.		Table 7-1

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 3	**Amendment Date** **16 May 2018**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Specified that blood pressure should be collected in the same extremity rather than in the same arm as blood pressure is not collected using the arm in small children.		Section 7.2.3
Specified that saved serum samples should be omitted for subjects weighing less than 10 kg and whenever local blood volume limitations are exceeded.		Section 7.2.8
Clarified that if a child is under 2 years of age or unable to complete a quality of life questionnaire (due to developmental delay or other illness) it will not constitute a protocol deviation.		Section 7.2.12
Specified that an interim analysis is planned when 6 months of safety data have been collected for subjects entering from TED-C14-006. Additional interim analyses may be conducted as needed.		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 protocol

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	**Amendment Date** **23 Mar 2017**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Updated emergency contact information		Emergency Contact Information; Section 8.1.6; Section 8.2.2; Section 8.2.4
To allow for approximately 7 days for subjects to transfer from Study TED-C14-006 to Study SHP633-304 (instead of up to 7 days).		Table 1-1; Section 7.1.1
A footnote was added at the pretreatment visit in the Schedule of Events for Subjects While Receiving Teduglutide to underscore that, when the first pretreatment visit (P1) follows the screening visit, it must occur within 12 weeks of screening.		Table 1-3
Revised the language on abstinence as a contraceptive method for consistency with the Medicines and Healthcare Products Regulatory Agency (MHRA) Clinical Trial Facilitation Group's "Recommendations related to contraception and pregnancy testing in clinical trials."		Section 4.7.1
Clarification that ancillary components, in addition to sterile water for injection syringes, will also be provided and labeled in accordance with the applicable regulatory requirements.		Section 6.3.1
A footnote was added in Table 7-2 to clarify that subjects older than 18 years of age will continue to use the Child Self Report and Parent Proxy-Report for Teens (ages 13-18) when completing the Pediatric Quality of Life Generic Core Scale (PEDSQL™).		Section 7.2.12.1 (Table 7-3)

Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 2	**Amendment Date** **23 Mar 2017**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Revised the text on severity categorization to specify that a severe treatment-emergent adverse event (TEAE) that might lead to dose interruption (Section 8.4.1) or early termination of the study (Section 8.5) will also be graded according to the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE) severity grading criteria, in addition to the standard severity categorization. These events are no longer limited to only the events described in Table 8-1, entitled "CTCAE Criteria for Adverse Events that May Lead to Dose Interruption (Prospective Period of Observation Only)." Therefore, Table 8-1 has been deleted.		Section 8.1.1; Section 8.4; Section 8.4.1 Table 8-1 (deleted)
Revised the criteria for early termination of the study: stopping criteria were extended to all NCI CTCAE Grade 3 and 4 severity events reported as related to the investigational product, and no longer limited to the events described in Table 8-1, entitled "CTCAE Criteria for Adverse Events that May Lead to Dose Interruption (Prospective Period of Observation Only)."		Section 8.5

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **22 Nov 2016**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Title of the Shire medical monitor has been changed to [redacted] for clarity.		Protocol Signature Page Emergency Contact Information
Clarification has been made that during the no-teduglutide treatment period, visits will take place *approximately* every 12 weeks.		Synopsis Sections 3.1, 7.1.2 Figure 3-1
The study design flow chart has been edited for clarity.		Synopsis Figure 3-1
The collection of all actual and prescribed enteral nutrition data has been removed to reduce the burden on the subjects and investigators. Enteral nutrition data are not required as the efficacy endpoints are limited to parenteral support parameters.		Synopsis Table 1-1, Table 1-2, Table 1-3 Sections 7.1.2, 7.1.3.1, 7.1.3.2, 7.1.5, 7.2.11.2, 7.2.11.3
Exclusion criterion 11 has been revised to add Smoflipid as other experimental drugs that are allowed prior and during the study. Like glutamine and Omegaven, Smoflipid is not expected to interfere with the assessments of safety and efficacy of teduglutide and many subjects may already be receiving the treatments off-label as part of standard medical therapy.		Synopsis Section 4.5
Exclusion criterion 12 and prohibited treatment have been refined: exclusion/prohibition of treatment with growth hormone has been extended to 3 months for consistency with other teduglutide studies.		Synopsis Section 4.5 Table 5-1

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **22 Nov 2016**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
The language on escape criteria has been corrected for consistency within the protocol.		Synopsis Section 4.6
Language in efficacy and safety endpoints has been clarified.		Synopsis Sections 9.7.1, 9.8.1
Completion and review of intake and output diaries have been clarified.		Table 1-2, Table 1-3 Sections 7.1.3.2, 7.1.5
When the screening and pretreatment visits are combined, the serum pregnancy test required at the pretreatment visit should be performed at the local laboratory instead of the central laboratory. This will ensure timely results prior to starting treatment with teduglutide.		Table 1-3 Sections 7.1.3.1, 7.2.6
The requirement for urine specimen collection has been revised so that a lack of urinalysis will not constitute a protocol deviation for any pediatric subjects (not only for subjects wearing diapers).		Table 1-1, Table 1-2, Table 1-3 Section 7.2.4
Clarification has been made that the first no-teduglutide treatment visit after the screening visit will occur within 2 to 12 weeks of the screening (formerly within 12 weeks of screening).		Synopsis Table 1-2 Section 7.1.1
Windows have been clarified for visits during the no-teduglutide and teduglutide treatment periods.		Table 1-2, Table 1-3 Section 7.1.2
'Specific' has been deleted from 'positive/specific anti-teduglutide antibodies' to eliminate the redundancy. By definition, positive samples must be specific (as assessed in the confirmatory assay), or otherwise considered negative.		Table 1-2 Sections 7.2.7, 9.8.1
Parental height and gestational age at birth have been removed from medical history.		Table 1-1 (footnote b) Section 7.2.1
For consistency within the protocol, sigmoidoscopy has been added as the alternate to colonoscopy throughout the protocol.		Table 1-1, Table 1-2, Table 1-3 Sections 3.1, 7.1.2, 7.2.9.2
Removal of former footnote i on fecal occult blood test for clarity.		Table 1-3
Clarification has been made on circumstances when the CxW28 visit may be combined with the next pretreatment or EOS/ET visit.		Table 1-3 Section 7.1.4
The text on PS support requirements over time in pediatric subjects with SBS has been clarified, and text on intestinal adaptation has been refined.		Section 1.1
Status of current teduglutide approvals for use has been updated.		Section 1.2, 3.1
The term 're-challenge' has been replaced with 'additional teduglutide treatment' for clarity and consistency with other studies.		Section 3.1
Number of subjects enrolled has been corrected for consistency with protocol synopsis.		Section 3.1
Definition of a subject's completion of the study has been corrected for consistency within the protocol.		Section 3.2
Evaluations to be performed when a subject discontinues teduglutide or when withdraws from the study have been clarified.		Sections 4.8.1, 4.8.2

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 1	**Amendment Date** **22 Nov 2016**	**Global**
Description of Change and Rationale		**Section(s) Affected by Change**
Withdrawal by parent/guardian has been added as reason for discontinuation.		Section 4.8.3
COUMADIN has been changed to warfarin for clarity.		Sections 5.1, 5.1.2
Clarification has been made on handling of study drug, which is for single use only and should be used within 3 hours following reconstitution.		Section 6.3.3
The investigator or designee may now dispense the unused study drug vials to the same subject if deemed appropriate to ensure sufficient supplies between visits. Also, documentation of all dispensed study medication has been clarified.		Section 6.4
Clarification has been made that local laboratory results are not required to be entered in the eCRFs.		Section 7.2.4
Collection of urine sodium and urine osmolality has been removed.		Section 7.2.4
Clarification has been made that the serum sample will not be collected at the pretreatment visit if the subject met a follow-up period escape criterion.		Section 7.2.5
Intake and output diaries (formerly in Sections 7.2.11 and 7.2.12, respectively) have been moved under a new Section 7.2.11 'Diaries' for clarity, and are now Sections 7.2.11.2 and 7.2.11.3, respectively. Information on study drug administration diary has been added in Section 7.2.11.1. Clarification has been made that only available diary data will be reviewed at each clinic and telephone visit.		Sections 7.2.11, 7.2.11.1, 7.2.11.2, 7.2.11.3
Performance of dipstick specific gravity tests by the subject at home on the first urine produced after the daily infusions of PS has been removed. It is now at the discretion of the investigator for all subjects, not just those in diapers. This change is to align with standard medical practice.		Section 7.2.11.3
Clarifications have been made to the language on dose interruption.		Sections 8.4, 8.4.1
Unscheduled safety follow up assessments (including visits conducted after EOS) are not to be recorded. However, clarification has been made that they are to be collected where requested.		Section 9.1
The protocol now refers to the data monitoring committee (DMC) Charter for the schedule of DMC reviews.		Section 9.4
Changes have been made to the Health economics and outcomes research endpoints to include the beginning of each treatment cycle (CxD1) as additional baseline. These changes are for clarity and consistency with other teduglutide studies.		Synopsis Section 9.9.1
Minor corrections have been made to the guidelines for nutritional support management during the study.		Appendix 2

APPENDIX 2 GUIDELINES FOR NUTRITIONAL SUPPORT MANAGEMENT DURING THE STUDY

Nutritional support adjustment in volume and calories should be considered at all planned visits. Please consider the following clinical parameters identified as markers for adequate management of pediatric SBS. These parameters should also be considered for managing nutritional support (PS and/or oral/enteral feeding) in terms of volume and calories during the treatment period.

- Growth trajectory, including weight, height (or length), and head circumference (for pediatric subjects up to 36 months of age)
- Other clinical evaluations
  - Serum electrolytes
  - Blood urea nitrogen /creatinine levels
  - Changes in stool frequency or volume, including mixed output
  - Stool consistency (ie, Bristol Stool Scale)
  - Urine specific gravity
- General consideration to possible clinical deterioration in SBS
  - Inability to maintain weight and growth velocity
  - Diarrhea (≥10 bowel movements per day, ≥80 mL/kg/day from an ostomy, or ≥75 mL/kg/day mixed output)
  - Colic/vomiting frequency increased
  - Electrolyte changes or imbalance
  - Skin breakdown
- 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.
- Nutritional support constituents may be adjusted at the discretion of the investigator.
- 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.
- If there is a change in EN or other food or fluid intake, the investigator should consider this when adjusting the PS/EN support in volume and calories.

Figure A-1 Weaning Algorithm for Subjects Who are NOT Toilet Trained and in Diapers

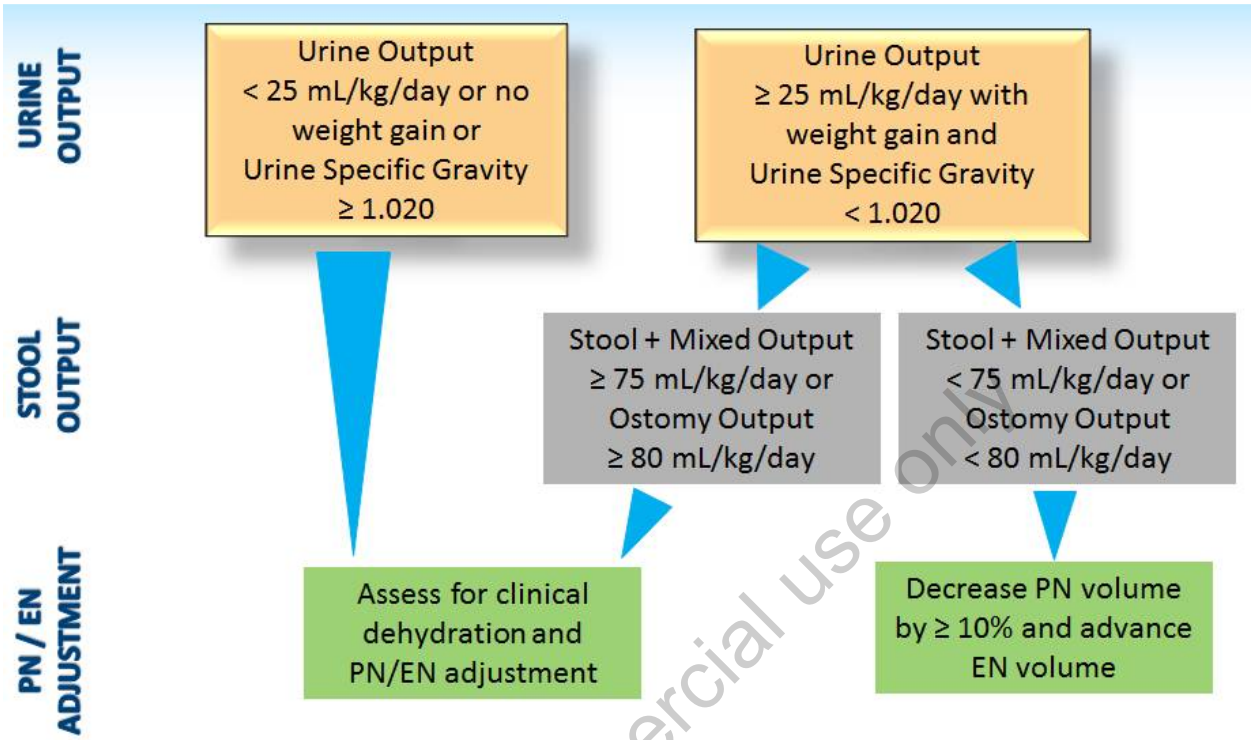


Figure A-2 Weaning Algorithm for Subjects Who are Toilet Trained and NOT in Diapers

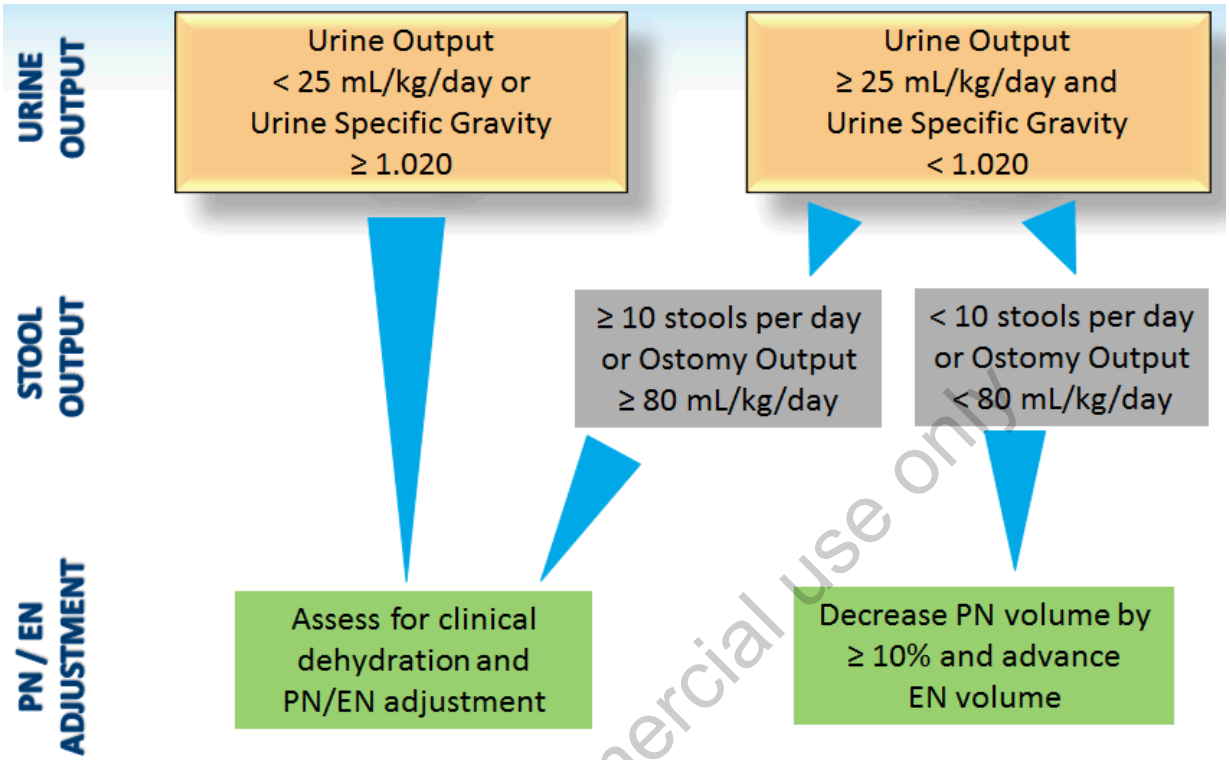
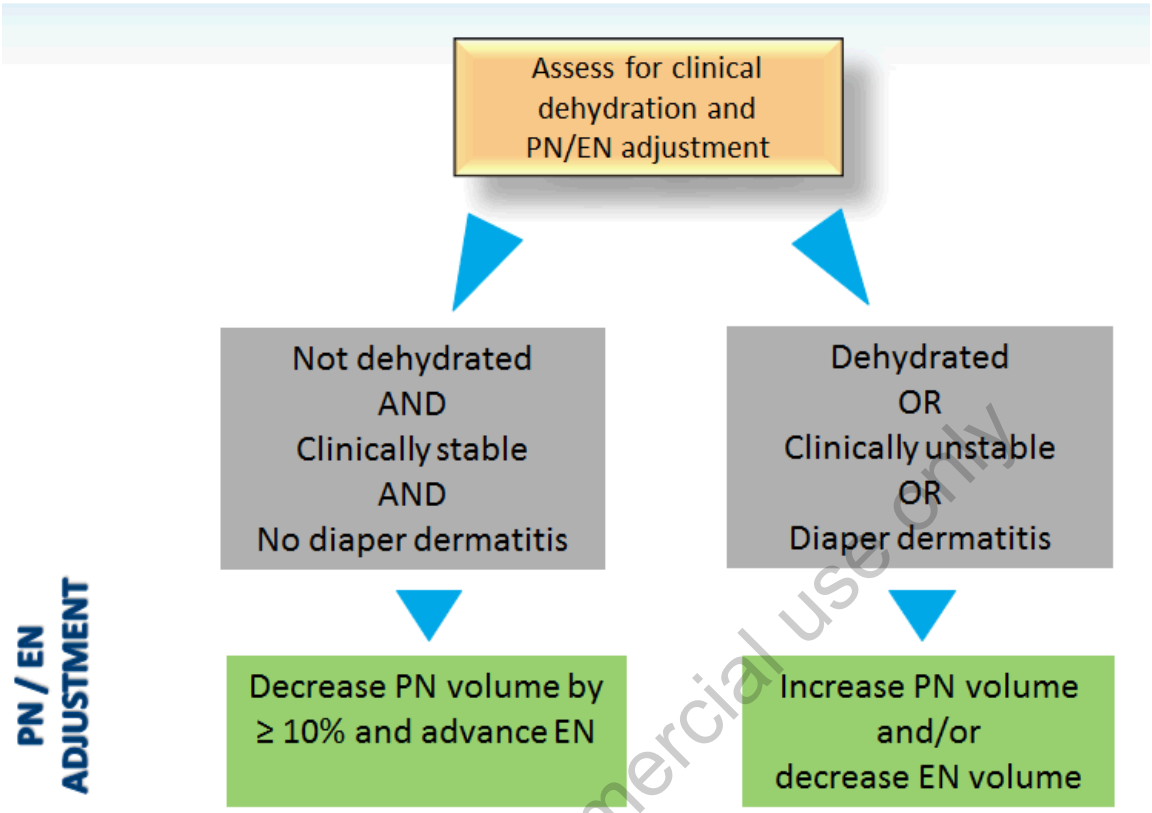


Figure A-3 Clinical Dehydration Assessment and PS/EN Adjustment



APPENDIX 3 CAREGIVER INTERVIEW GUIDE

Exit Interviews With Caregivers Following Participation in a Short Bowel Syndrome Clinical Trial

1. Introduction (5 Minutes)

Introduce interviewers

Confirm caregiver's first name and study ID

Review consent form and obtain consent

Remind participants of the purpose and format of the interview

We are interested in learning more about your child's symptoms and impacts due to short bowel syndrome and parenteral support. We would also like to understand your experiences caring for your child as well as you and your child's experiences with regard to treatment during the clinical trial.

The information you share with us will help the study sponsors learn more about potential treatment benefits of the clinical trial drug.

As we go along, please feel comfortable to speak openly and share your opinions freely. There are no wrong answers. You are the expert.

Unless you report a side effect potentially related to a medication that our study sponsors produce during today's call, your name will never be associated with anything you share with us.

- If you *do* report a side effect during today's call, I have to let the study sponsors know. I may ask you some follow-up questions to fully understand the nature of the experience so I can fully communicate information to the study sponsor.

REMEMBER TO TURN ON THE AUDIO RECORDER ONCE CONSENT IS PROVIDED. INTERVIEWER WILL VERBALLY NOTE STUDY ID AND INTERVIEW DATE

2. History and Symptoms (10 minutes)

Just briefly, please tell us about your child's history with SBS.

- How old is your child?
- How long has your child had SBS?
- How long has your child received parenteral support?

- What symptoms of SBS does your child experience? What symptoms due to parenteral support does your child experience? Are there other symptoms your child experienced in the past but doesn't experience currently? What are those? [Probe for complete list and write down each symptom provided by the participant; for each symptom, probe to understand whether due to SBS, parenteral support, or both]

  - Symptom 1: _____
  - Symptom 2: _____
  - Symptom 3: _____
  - Symptom 4: _____
  - Symptom 5: _____

[If not provided spontaneously by the participant, specific symptoms will be probed.]

Now we would like to discuss other symptoms that some patients or caregivers have described to see whether or not they are things your child has experienced as well.

- As I read each symptom, please let me know if your child has experienced this symptom in relation to his or her SBS or parenteral support. [Only read those symptoms not already provided by the participant; probe to understand whether due to SBS, parenteral support, or both]

  - Pain/discomfort
  - Fatigue
  - Frequent need to empty bowels/bag
  - Diarrhea

- Of the symptoms you have described which would you say is the most bothersome for your child? Why?

3. Impacts (10 minutes)

- How does your child's SBS and parenteral support affect his or her life? [Probe for complete list and write down each impact provided by the caregiver; probe to understand whether impact of SBS, parenteral support, or both]

  - Impact 1: _____
  - Impact 2: _____
  - Impact 3: _____
  - Impact 4: _____
  - Impact 5: _____

[If not provided spontaneously by the participant, specific impacts will be probed.]

Now we would like to now discuss other impacts that some patients and caregivers have described to see whether or not they are things your child has experienced as well.

- As I read each impact, please let me know if you have experienced this in relation to your child's SBS and parenteral support. [Only read those impacts not already provided by the participant. For endorsed impacts, ask the participant to describe their experiences with the impact and whether they feel it is due to SBS or parenteral therapy or both]
  - Daily activities, including school if applicable
    - Need to know/plan for bathroom facilities when leaving home
  - Physical functioning
  - Social functioning
  - Emotional functioning
  - Sleep
- Of the impacts you have described, which would you say is the most bothersome to your child? Why?

4. Clinical Trial Experiences (10 minutes)

Now we would like to talk about your experience during the clinical trial.

- What were your expectations of treatment prior to entering the clinical trial?
- Thinking back to before you started the clinical trial, what were some of the reasons you decided to enroll your child in the trial?
- Were there specific symptoms/issues which you most wanted treatment to help? Which ones? Why?
- How frequently was your child receiving parenteral therapy at the beginning of the trial? [Probe on how many times a week, for how many hours, and when administered].
- What improvements, if any, have you noticed in your child since starting the study? [Have caregivers describe each improvement reported]
  - Improvement 1: _____
  - Improvement 2: _____
  - Improvement 3: _____
  - Improvement 4: _____
  - Improvement 5: _____

- What were the biggest improvements you noticed? How important, if at all, were these improvements to you?
- Were there smaller or other improvements that you noticed that were also meaningful to you? If so, please describe these improvements. [Add these improvements to the list above]
- I would like to review each of the improvements that you noticed. Thinking about [a symptom from the list], how would you describe them before the study? [Probe *mild*, *moderate*, or *severe*, as applicable]
- How would you describe them after the study? [Probe *none*, *mild*, *moderate*, or *severe*, as applicable]
- [If not reported] Were there any improvements in your child's parenteral therapy during the study? How important, if at all, was this change to you? [Probe to capture current parenteral frequency]
- Of all of the improvements we have talked about, which do you think was the most important to your child? Why? Which was the most important to you? Why?
- How would you describe the change in your child's SBS overall after participating in the study? [Probe: *very much better*, *much better*, *a little better, no change*, *a little worse*, *much worse*, or *very much worse*]

5. Caregiver Experiences (10 minutes)

Now we would like to talk about your experience as a caregiver of a child with SBS.

- How has having a child with SBS impacted your life? [Probe for complete list and write down each impact provided by the caregiver; probe to understand whether impact of SBS, parenteral support, or both]
  - Impact 1: _____
  - Impact 2: _____
  - Impact 3: _____
  - Impact 4: _____
  - Impact 5: _____

[If not provided spontaneously by the participant, specific impacts will be probed.]

Now we would like to now discuss other impacts that some caregivers have described to see whether or not they are things you have experienced as well.

- As I read each impact, please let me know if you have experienced this in relation to caring for your child with SBS [Only read those impacts not already provided by the participant. For endorsed impacts, ask participants to describe their experiences with the impact and whether they feel it is due to their child's SBS, parenteral therapy for the SBS, or both.]

  - Caregiver's daily activities
    - Need to know/plan for bathroom facilities when leaving home with child
  - Caregiver's physical functioning
  - Caregiver's emotional functioning
  - Caregiver's social functioning
  - Caregiver's sleep
  - Financial impact

- Of the impacts you have described which would you say is the most bothersome for you? Why?

- Which, if any, of the above do you feel was improved during your child's participation in the clinical trial? How important, if at all, was this improvement?

6. Closing

Is there anything else you would like to add about your child's SBS?

Thank you for taking the time to meet with us today. Your input has been very helpful and will also be helpful for the patients that will participate in further research on SBS. Thank you again.

APPENDIX 4 PEDIATRIC SUBJECT INTERVIEW GUIDE

Exit Interviews With Pediatric Subjects Following Participation in a Short Bowel Syndrome Clinical Trial

7. Introduction (5 Minutes)

Introduce interviewers

Confirm subject's first name and study ID with caregiver

Review parental consent form and confirm consent

Confirm pediatric subject assent

Remind participants of the purpose and format of the interview

We are interested in learning more about your symptoms and impacts due to short bowel syndrome and parenteral support (the nutrition and fluids you get because of your short bowel). We would also like to understand your experiences during the study you were in.

The information you share with us will help the study sponsors learn more about potential treatment benefits of the clinical trial drug.

As we go along, please feel free to speak openly and share your opinions freely. There are no wrong answers. You are the expert.

Unless you report a side effect that might be related to a medication that our study sponsors produce during today's call, your name will never be associated with anything you share with us.

- If you *do* report a side effect during today's call, I have to let the study sponsors know. I may ask you some follow-up questions to fully understand what happened so I can fully share this with the study sponsor.

REMEMBER TO TURN ON THE AUDIO RECORDER ONCE CONSENT IS PROVIDED. INTERVIEWER WILL VERBALLY NOTE STUDY ID AND INTERVIEW DATE

8. History and Symptoms (15 minutes)

Just briefly, please tell us about history with SBS.

- How old are you?
- How long have you had SBS?
- How long have you been getting parenteral support? [Confirm participant understanding of term and use term if understood/used or use the participant preferred term throughout the interview]

- What symptoms of SBS do you experience? What symptoms due to parenteral support do you experience? Are there other symptoms you have had in the past but do not experience today? What are those? [Probe for complete list and write down each symptom provided by the participant; for each symptom, probe to understand whether due to SBS, parenteral support, or both]

  - Symptom 1: _____
  - Symptom 2: _____
  - Symptom 3: _____
  - Symptom 4: _____
  - Symptom 5: _____

[If not provided spontaneously by the participant, specific symptoms will be probed.]

Now we would like to discuss other symptoms that some patients have described to see whether or not they are things you have experienced as well.

- As I read each symptom, please let me know if you have experienced this symptom in relation to your SBS or parenteral support. [Only read those symptoms not already provided by the participant; probe to understand whether due to SBS, parenteral support, or both]

  - Pain/discomfort
  - Fatigue
  - Frequent need to empty bowels/bag
  - Diarrhea

- Of the symptoms you have described which would you say is the most bothersome for you? Why?

9. Impacts (15 minutes)

- How does your SBS and parenteral support affect your life? [Probe for complete list and write down each impact provided by the participant; probe to understand whether impact of SBS, parenteral support, or both]

  - Impact 1: _____
  - Impact 2: _____
  - Impact 3: _____
  - Impact 4: _____
  - Impact 5: _____

[If not provided spontaneously by the participant, specific impacts will be probed.]

Now we would like to now discuss other impacts that some patients have described to see whether or not they are things you have experienced as well.

- As I read each impact, please let me know if you have experienced this in relation to your SBS and parenteral support. [Only read those impacts not already provided by the participant. For endorsed impacts, ask the participant to describe their experiences with the impact and whether they feel it is due to SBS or parenteral therapy or both]

  - Daily activities, including school if applicable
    - Need to know/plan for bathroom facilities when leaving home
  - Physical functioning
  - Social functioning
  - Emotional functioning
  - Sleep

- Of the impacts you have described, which would you say is the most bothersome to? Why?

10. Clinical Trial Experiences (10 minutes)

Now we would like to talk about your experience during the clinical trial.

- What did you think the study would be like before you started it?

- Thinking back to before you started the study, what were some of the reasons you decided to be a part of the study?

- Were there specific symptoms/issues which you most wanted treatment to help? Which ones? Why?

- How frequently were you child receiving parenteral therapy at the beginning of the trial? [Probe on how many times a week, for how many hours, and when administered].

- What improvements, if any, have you noticed since you started the study? [Have participants describe each improvement reported]

  - Improvement 1: _____

  - Improvement 2: _____

  - Improvement 3: _____

  - Improvement 4: _____

  - Improvement 5: _____

- What were the biggest improvements you noticed? How important, if at all, were these improvements to you?
- Were there smaller or other improvements that you noticed that were also meaningful to you? If so, please describe these improvements. [Add these improvements to the list above]
- I would like to review each of the improvements that you noticed. Thinking about [a symptom from the list], how would you describe them before the study? [Probe *mild*, *moderate*, or *severe*, as applicable]
- How would you describe them after the study? [Probe *none*, *mild*, *moderate*, or *severe*, as applicable]
- [If not reported] Were there any improvements in your parenteral therapy during the study? How important, if at all, was this change to you? [Probe to capture current parenteral frequency]
- Of all of the improvements we have talked about, which do you think was the most important to you? Why?
- How would you describe the change in your SBS overall after being in the study? [Probe: *very much better*, *much better*, *a little better, no change*, *a little worse*, *much worse*, or *very much worse*]

11. Closing

Is there anything else you would like to add about your SBS?

Thank you for taking the time to meet with us today. Your input has been very helpful and will also be helpful for the patients that will participate in further research on SBS. Thank you again.