STATISTICAL ANALYSIS PLAN

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

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Teduglutide
PHASE 3

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

PROTOCOL IDENTIFIER: SHP633-301

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REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	11Dec2018	New Document
1.1	24Mar2020	See detailed summary of changes in Appendix 14.3

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BLQ	Below the Lower Limit of Quantification
BUN	Blood Urea Nitrogen
CTMS	Clinical Trial Management System
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EN	Enteral Nutrition
EOS	End of Study
EOT	End of Treatment
GI	Gastrointestinal
GLP-2	Glucagon-Like Peptide 2
ICF	Informed Consent Form
INR	International Normalized Ration
IP	Investigational Product
ITT	Intent-to-Treat
IWRS	Interactive Web Response System
M	Months
MedDRA	Medical Dictionary for Regulatory Activities
LLN	Lower Limit of Normal
LOCF	Last Observation Carried Forward
LOV	Last Observed Value
LVOT	Last Value on Treatment
PCS	Potentially Clinically Significant
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-Protocol
PS	Parenteral Support
Pt	Prothrombin Time
PT	Preferred Term (MedDRA)
Q1	25th Percentile
Q3	75th Percentile
RBC	Red Blood Cells
SAF	Safety
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SBS	Short Bowel Syndrome
SC	Subcutaneous
SD	Standard Deviation
SEM	Standard Error of the Mean
SI	Standard International
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SRN	Screened
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
ULN	Upper Limit of Normal
ULQ	Upper Limit of Quantification
WBC	White Blood Cells
WHO	World Health Organization
WHODD	WHO Drug Dictionary

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of safety, efficacy and pharmacokinetic data. The SAP version 1.0 was developed based on protocol amendment 2 dated 2018-Dec-04. This SAP version 1.1 was updated based on protocol amendment 4 dated 2019-Dec-17. Specifications for tables, figures, and listings are contained in separate documents and updated as needed.

2. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

2.1 Objectives

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

2.2 Estimands

There is no specified hypothesis testing. The selected estimands are described in Table 1.

Table 1: List of Selected Estimands

Estimand	Definition	Attributes			
		A: Population	**B: Variable (or endpoint)**	**C: Strategy for addressing intercurrent event**	**D: Population-level summary**
Primary	The primary estimand is the effect of teduglutide compared to standard of care on weight-normalized parenteral support (PS) volume at Week 24	ITT set, 4-12 months old infants with SBS who are dependent on parenteral support	At least 20% reduction in weight-normalized PS volume at Week 24 compared to baseline based on diary data	Evaluated regardless of treatment received or protocol violations	Number/percentage of subjects who achieved at least 20% decrease in weight-normalized PS volume at Week 24 compared to baseline, where percent reduction in PS volume is define as [(average daily value at the scheduled visit - average daily value at baseline) / average daily value at baseline] * 100 And average daily value is defined as: [(sum of non-missing daily values in the diary / number of days with non-missing values)] / last available body weight prior to the visit
Secondary	Reduction in weight-normalized parenteral calories by at least 20% from baseline to Week 24/ End of	ITT set, 4-12 months old infants with SBS who are dependent on parenteral	At least 20% reduction in weight-normalized PS calories at Week 24 compared to baseline based	Evaluated regardless of treatment received or protocol violations	Number/percentage of subjects who achieved at least 20% decrease in weight-normalized PS calories at Week 24 compared to baseline, where percent reduction in PS calories is define as [(average daily value at the scheduled visit - average daily value at baseline) / average daily value at baseline] * 100

	Treatment (EOT)	support	on diary data		And average daily value is defined as: (prescribed weekly PS volume / 7) / last available weight prior to or on the date of visit

2.3 Endpoints

2.3.1 Primary Endpoint

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

2.3.2 Secondary Endpoints

- Reduction in weight-normalized PS caloric intake by at least 20% from baseline to Week 24/EOT
- Achievement of enteral autonomy by Week 24
- Time to achieve enteral autonomy
- Change in weight-normalized PS volume from baseline to each visit
- Change in weight-normalized PS caloric intake from baseline to each visit
- Change in weight-normalized enteral nutrition (EN) volume from baseline to each visit
- Change in weight-normalized EN caloric intake from baseline to each visit
- Increase in weight-normalized EN volume by at least 20% from baseline to week 24/EOT
- Increase in weight-normalized EN caloric intake by at least 20% from baseline to week 24/EOT

2.3.3 Other Efficacy Endpoints

- Native glucagon-like peptide 2 (GLP-2)
- Change and percent change from baseline to each visit in hours per day of PS support
- Change and percent change from baseline to each visit in days per week of PS support
- Escape criteria during follow up period

2.3.4 Safety Endpoints

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

- Stool (including mixed) output
- Antibodies to teduglutide

2.3.5 Pharmacokinetic Endpoints

- Summary of plasma teduglutide concentration at nominal time point

2.3.6 Healthcare Resource Utilization Endpoint

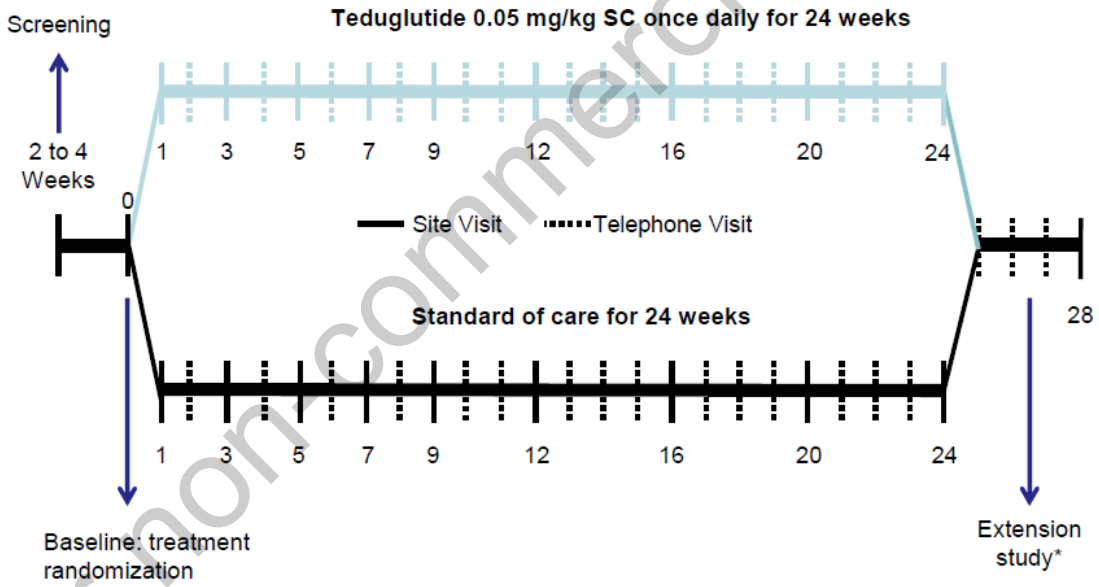
- Cumulative number of hospitalization days during the study

3. STUDY DESIGN

3.1 General Description

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

Figure 1: Study Schematic



*At EOS all subjects regardless of treatment arm may enroll in an extension study if that study is open to enrollment at the time of the SHP633-301 EOS that will capture long-term safety data and provide the opportunity for additional teduglutide treatment. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS if at least one"escape"criteria is met.

Once patients sign the informed consent they will be screened for a minimum of two and maximum of four weeks to determine their study eligibility.

At the baseline visit (Week 0), subjects will be randomized to the teduglutide or standard of care treatment arm. During the 24-week treatment period, subjects in the standard of care treatment arm will receive standard medical therapy for SBS, while those in the teduglutide arm will receive 0.05 mg/kg by subcutaneous (SC) injection once daily in addition to standard medical therapy.

Subjects in both arms will follow the same visit schedule and assessments. Subjects will be monitored weekly with phone or clinic visits. Clinic visits will occur at Weeks 1, 3, 5, 7, 9, 12, 16, 20, 24, and 28. At all site visits and telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed.
To maintain consistency across all centers, sites and subjects 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.
At the end of the treatment period (Week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (Week 28/End of Study [EOS]) during which time subjects will receive standard medical therapy, but no investigational product (IP) will be administered. At EOS, all subjects regardless of treatment arm may enroll in an extension study if that study is open to enrollment at the time of the SHP633-301 EOS. The follow-up period for subjects in the teduglutide treatment arm may be interrupted and the subjects may proceed immediately to the EOS visit if at least one of the "escape" criteria highlighted in protocol section 3.1.3.

Schedule of events can be found in Study Schedule Section (Table 1 and Table 2) of the protocol.

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

3.2 Randomization

Subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized (1:1 ratio) to either teduglutide or standard of care arm using the interactive web response system (IWRS). The randomization will be stratified per the presence of a small bowel ostomy (e.g., end jejunostomy or ileostomy).

3.3 Blinding

Not applicable for this open label study.

3.4 Sample Size and Power Considerations

Sample size is determined based on enrollment feasibility for this rare condition and the

age of the study population.

In this study, at least 10 subjects will be randomized: at least 5 subjects in a teduglutide treatment arm and at least 5 subjects in an standard of care comparator arm.

4. STATISTICAL ANALYSIS SETS

Analysis of efficacy and safety endpoints will be performed based on the analysis sets defined in this section and as specified for each endpoint throughout this SAP.

If two analysis sets are the same, then only one set of tables will be generated. Therefore, if ITT set is same as Safety Set, only ITT set of tables will be generated.

4.1 Screened Set

The Screened (SRN) set will consist of all subjects who have signed informed consent. Data for subjects who fail to pass the screening period will be included in the listings, but will not be included in any analyses.

4.2 Intent-to-Treat Set

The Intent-to-Treat (ITT) set will consist of all subjects randomized in the study. Whenever using ITT set, subjects will be presented in the treatment regimen to which they were randomized at the start of the treatment period (even if the treatment they received was different).

All efficacy analyses will be conducted on this population, unless otherwise specified.

4.3 Safety Set

The Safety (SAF) set will contain all subjects who met the following criteria:

Teduglutide treatment arm: subjects who receive at least 1 dose of teduglutide and have undergone at least 1 post-baseline safety assessment.

Standard of care treatment arm: subjects who have undergone at least 1 post-baseline safety assessment.

Subjects will be classified according to treatment they actually received. All safety analyses will be conducted on this population, unless otherwise specified.

4.4 Per-protocol Set

The Per-protocol (PP) set will contain all subjects in the ITT set who complete the study treatment period without any major protocol deviations or other situations that could potentially affect the efficacy conclusions of the study.

The situations that may affect inclusion in the PP set include, but are not limited to:

- Non-compliance to study drug for the treatment group as defined in Section 5.9.
- Clinically significant discrepancies between planned and actual treatment.
- Missing baseline or week 24 efficacy data.

4.5 Pharmacokinetic Set

All subjects who received at least one dose of teduglutide and have at least one evaluable and interpretable post-dose PK concentration value.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

All subjects who provide informed consent will be accounted for in this study. Assessment of eligibility to the inclusion and exclusion criteria will be performed at Screening and re-confirmed at the Baseline visit.

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 electronic case report form (eCRF). If a subject is withdrawn for more than one reason, each reason should be documented in the source document, and the most clinically relevant reason should be entered in the eCRF. Overall reasons for discontinuation of treatment and withdrawal from study will be summarized separately based on the following categories:

- Adverse event
- Failure to meet enrollment criteria
- Non-compliance with study drug
- Protocol deviation
- Lack of efficacy
- Physician decision
- Withdrawal by Parent/Guardian
- Lost to follow-up
- Study terminated by sponsor
- Site terminated by sponsor
- Technical Problems
- Death

- Other

The following summary tables are planned for presentation:

- Subject disposition (SRN set)
- Analysis Sets (ITT set)
- Protocol deviations (ITT set)
- Protocol deviations (SAF set)
- Enrollment duration by site (SRN set)

The presentation of planned listings will include the following:

- Subject Disposition (SRN set)
- Study inclusion and exclusion criteria violations (SRN set)
- Screen Failure Data (Screen Failures)
- Protocol deviations (SRN set)
- Subjects excluded from Per Protocol Set (SRN set)
- Subjects assignment to analysis sets (SRN set)
- Follow-up Period Escape Criteria (SAF set)

5.2 Demographic and Other Baseline Characteristics

Descriptive summaries of demographic and other baseline characteristics will be presented by treatment assignment for the ITT, Safety, and PP sets.

The following demographic and other baseline characteristics will be summarized in the following order in the tables:

- Corrected gestational age (months)
- Corrected gestational age category (months):
    - 4 - < 6 months
    - 6 - 12 months
- Chronological age (months)
- Sex
- Ethnicity

- Race
- Weight Z-scores at Baseline
- Length Z-scores at Baseline
- Weight/ length ratio Z-score at Baseline
- Head circumference Z-scores at Baseline

The demographic data collected in the eCRF will be listed by subject.

5.3 Surgical and Medical History

Medical and Surgical History conditions are defined as those conditions which began prior to informed consent. Medical and surgical history includes all relevant past medical diagnoses and surgeries other than related to the cause or diagnosis of SBS. Medical and Surgical history will be collected at the Screening Visit (Visit -1) and will be coded using Medical Dictionary for Regulatory Activities (MedDRA). A table based on ITT and Safety sets, and a listing will be provided.

Data captured on the Medical and Surgical History page of the CRF will be presented by System Organ Class (SOC) and Preferred Term (PT). SOC will be sorted alphabetically and PT within SOC will be sorted by descending frequency in the teduglutide treatment arm.

5.4 Short Bowel Syndrome History

The following SBS History will be collected at screening and will be summarized and listed using the ITT and Safety sets:

- Primary reason for the diagnosis of SBS
- Secondary reason for the diagnosis of SBS
- Presence of stoma; if Y, stoma type
- Presence of any remaining colon; if Y, estimated percent colon remaining and whether the colon is in continuity with the small bowel
- Estimated length of remaining small intestine
- Presence of Distal/Terminal Illeum and ileocecal valve

Date of first major surgical resection, date of last major surgical resection, date of diagnosis of SBS and method of determining the length of remaining anatomy will be presented in the listing only.

5.5 Upper Gastrointestinal Series with Small Bowel Follow-through

An upper gastrointestinal (GI) contrast series with small bowel follow-through collected at screening will be only listed as:

- Normal
- Abnormal, not clinically significant
- Abnormal, clinically significant

Any abnormal results or reason for positive result will be specified within the listing also.

5.6 Prior Medication and Procedure

Prior medications will be coded using the World Health Organization Drug Dictionary (WHODD). Prior therapies and procedures will be coded using MedDRA.

Prior medications (therapies/procedures) are defined as any medications (therapies/procedures) received prior to and discontinued before the reference start date (see section 11.3 for definition of reference start date).

The prior medication usage will be summarized by the number and proportion of subjects in each treatment group within each preferred term for the Safety set. The prior medication will be sorted alphabetically by preferred name. Multiple medication usage by a subject in the same category will be counted only once.

The diagnostic, surgical, or therapeutic procedures during the study that are recorded in the eCRF will be presented only in a listing.

5.7 Concomitant Medications and Procedures

Concomitant medications will be coded using the WHODD. Concomitant procedures will be coded using MedDRA.

Concomitant medication (therapy/procedure) is defined as any medication taken on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm.

The concomitant therapies and medication usage will be summarized by the number and proportion of subjects in each treatment group receiving each medication within each preferred term for the Safety set. The concomitant therapies or medication will be sorted alphabetically by preferred name. Multiple concomitant therapies or medication usage by a subject in the same category will be counted only once.

A listing of all medications, both prior and concomitant will be presented. The listing will be sorted by treatment group and subject identifier and will include reported name, dose, route of administration, dosing frequency, start date, end date, indication and period of medication (prior only, concomitant only, prior and concomitant). Investigator verbatim as well as coded terms will be included in the listings.

The diagnostic, surgical, or therapeutic procedures recorded during the study will be presented only in a listing.

5.8 Exposure to Investigational Product

Exposure to investigational product for the Safety, ITT and PP sets will be summarized in terms of treatment duration, which is calculated as the number of days from the date of first dose of investigational product taken to the date of the last dose of investigational product taken, inclusively:

> Extent of exposure (days) = (date of last study drug administration – date of first study drug administration) + 1.

The date of first study drug administration is collected on the eCRF "First SC Injection" form. The date of last study drug is collected on the eCRF "End of Treatment" form.
The number and percentages of subjects will be tabulated for extent of exposure categorized into weeks (<4, 4-<12, 12-<24, >=24). Descriptive statistics (n, mean, standard deviation (SD), median, 25th Percentile (Q1), 75th Percentile (Q3), minimum, and maximum) will be presented to describe the exposure to investigational product for teduglutide treatment group (excluding the standard of care treatment arm).

Compliance and dose interruptions are not considered when determining the extent of exposure.

Information about interruptions of study drug by investigator decision (start date of interruption, date study drug resumed, and reason for interruption) will be included in data listing. Separate listings summarizing the study drug accountability and its administration will be produced.

5.9 Measurements of Treatment Compliance

Study drug administration diary data will be used to measure study drug compliance. The first SC Injection page and the diary entries with "Yes" in response to the question: "Was the study drug administered per instructions today?" will be counted towards compliance.

Subjects will be considered compliant overall for study drug administration if the calculated compliance is >=80%.

Compliance with investigational drug will be calculated as the number of doses administered divided by the planned number of doses expressed as a percentage. This can be summarized as:

> Overall percent compliance = (Total number of diary days marked "Yes" for study drug administration and the first injection page/ Number of days on treatment) * 100

where number of days on treatment will be calculated as (Date of last study drug – Date of first study drug + 1) and dose interruption days will be excluded, the sum of (Date of study drug resumed – start date of interruption +1).

Overall treatment compliance will be presented for percent compliance calculations using descriptive statistics and the number and percentage of subjects who are >=80% compliant by treatment group for the ITT and PP sets.

5.10 Protocol Deviations

Protocol deviations from the CTMS will be coded to categories and provided as part of the CTMS transfer to Biostatistics. Protocol deviation categories from CTMS include:

- Informed Consent
- Eligibility and Entry
- Concomitant Medication
- Laboratory Assessment
- Study Procedures
- Serious Adverse Event
- Randomization
- Visit Schedule
- Investigational Product Compliance
- Efficacy
- Administrative
- Source Document
- Regulatory or Ethics Approvals
- Other

Confirmed protocol deviations will be summarized by category for each treatment group (Teduglutide and standard of care) and overall, for the ITT and Safety sets. All protocol deviations will be listed including the site of origin, type, class and description.

6. EFFICACY ANALYSES

All efficacy analyses will be based on the ITT set. Baseline for all efficacy analyses is defined as the last observed value for the efficacy assessment prior to taking the first dose of investigational product (based on dates or date/times) or baseline visit for standard of care arm. All efficacy analyses will be conducted as per the treatment assigned. Given the small sample size, no hypothesis testing will be conducted. Endpoints will be evaluated descriptively. Therefore, there will be no adjustment for alpha level.

Efficacy endpoints will be evaluated separately based on:

- Subject diary data (also referred to as "diary")
- Investigator-prescribed data (referred to as "prescribed")

PS/EN support will be reported in both subject diary data and the investigator-prescribed data in the eCRF. Investigator-prescribed data are the most recent PS/EN prescription (from either baseline or prescription adjustments) prior to or on the date of visit, captured in the PS/EN history and PS/EN adjustments eCRF pages.

PS/EN diary data are collected over 24-hour periods that start on the assigned date. Depending on the time of day at which the 24-hour period begins, which can vary by subject, overnight PS infusion volumes after midnight may be associated with prior the date. Baseline diary PS/EN parameters will be calculated using all the diary data collected within 14 days prior to the first dose or baseline visit. Calculation of post-baseline diary PS/EN parameters will be based on the daily support recorded in subjects' diaries within 7 days prior to the date of each scheduled post-baseline visit.

For the definitions and derivations of average daily values, refer to section 11.6.

6.1 Analyses of Primary Efficacy Endpoint

The primary efficacy endpoint is the reduction in weight-normalized PS volume of at least 20% at Week 24/EOT compared to baseline. Subjects who achieve at least 20% reduction in weight normalized PS support are considered responders.

The number and percentage of subjects who achieve ≥ 20%, ≥ 50%, ≥ 75%, and 100% reduction in weight-normalized average daily diary PS volume at EOT will be summarized by treatment arm. The denominator will be the number of subjects for the ITT set in each treatment arm.

The same descriptive statistics will also be summarized based on investigator

prescribed data.

For the definition and derivation of percent reduction and weight-normalized average daily value, refer to section 11.6.

6.1.1 Sensitivity Analyses of Primary Efficacy Endpoint

A sensitivity analysis will also be performed using the PP set for both the subject diary data and the investigator prescribed data.

6.2 Analyses of Secondary Efficacy Endpoints

6.2.1 Reduction in PS Caloric Intake from Baseline to Week 24/EOT

Similar to the primary analysis, PS caloric intake reduction at week 24/EOT compared to baseline will be calculated. The number and percentage of subjects who achieve ≥ 20%, ≥ 50%, ≥ 75%, and 100% reduction in weight-normalized PS caloric intake at week 24/EOT visit will be summarized by treatment group for diary data as well as prescribed data.

6.2.2 Complete Weaning Off PS Support

During the treatment period:

A subject will be considered to have achieved enteral autonomy (completely weaned off PS support) at a given visit if the investigator prescribes no PS at that visit and for the remainder of the treatment period and there is no use of PS recorded in the subject diary during the week prior to that visit and for the remainder of the treatment period.

During the follow-up period:

A subject will be considered to have achieved enteral autonomy (completely weaned off PS support) at a given visit if the investigator prescribes no PS at that visit and for the remainder of the follow-up period and there is no use of PS recorded in the subject diary during the week prior to that visit and for the remainder of the follow-up period.

During the overall study period:

A subject will be considered to have achieved enteral autonomy (completely weaned off PS support) at a given visit if the investigator prescribes no PS at that visit and for the remainder of the overall study period and there is no use of PS recorded in the subject diary during the week prior to that visit and for the remainder of the overall study period.

The number and percentage of subjects, who achieve enteral autonomy at each scheduled visit, including EOT, follow up visits and EOS, will be summarized by treatment arm.

A supporting listing summarizing PS support status at week 28, escape criteria and last

visit date will be produced.

6.2.3 Time to Achieve Enteral Autonomy

Descriptive statistics will be used to summarize time to achievement of enteral autonomy (complete weaning off PS support) during treatment period, where the time to achievement of enteral autonomy is defined as the time from the reference start date until the date a subject is considered to have achieved enteral autonomy during a specific period:

> Time to achievement of enteral autonomy (weeks) = (date subject meets all enteral autonomy criteria – reference start date +1) / 7

Data permitting, time to achievement of enteral autonomy during the treatment period will be analyzed using Kaplan Meier method including Kaplan Meier plot. Log-rank test p-value will be provided as a supportive analysis. Subjects who will not achieve the enteral autonomy at the end of a specific period (treatment period, overall study period) or subjects who discontinue the treatment during the treatment period or the study during the overall study period will be censored.

A supporting listing of subjects achieving enteral autonomy and its durations during treatment period and overall study period will be produced.

6.2.4 Change and Percent Change from Baseline in PS Support at Each Visit

Changes in average daily weight-normalized diary and prescribed PS volume at each post-baseline visit during the 24-week treatment period and 4-week follow-up period will be derived using the same formulas as for primary efficacy calculations.

Analogous calculations will be used to calculate changes in weight-normalized diary and prescribed PS calories. Mean ± SE plots of percent change from baseline in PS volume (mL/kg/day) and caloric intake (kcal/kg/day) based on prescribed and diary data will be generated.

Baseline values, post-baseline values, change from baseline and percent change from the baseline in PS support and PS calories will be summarized by visit and treatment arm for diary data and prescribed data using descriptive statistics including number of subjects, mean, SD, median, Q1, Q3, minimum and maximum.

There will be subject level figures for PS support and PS calories based on diary data.

6.2.5 Change and Percent Change from Baseline in Enteral Nutritional Support at Each Visit

The change and percent change from baseline in average daily weight-normalized diary and prescribed EN volume and EN calories at each post-baseline visit during the 24-week treatment period and 4-week follow-up period will be calculated and summarized

using analogous methods used for PS parameters.

Baseline values, post-baseline values, change from baseline and percent change from the baseline in EN support and EN calories will be summarized by visit and treatment arm for diary data and prescribed data using descriptive statistics including number of subjects, mean, SD, median, Q1, Q3, minimum and maximum.

There will be subject level figures for EN support and EN calories based on diary data.

6.2.6 Increase in Enteral Nutritional Support from Baseline to Week 24/EOT

EN volume and caloric intake increase at week 24/EOT compared to baseline will be calculated. The number and percentage of subjects who achieve ≥ 20%, ≥ 50%, ≥ 75%, and 100% increase in weight-normalized EN volume or EN caloric intake at week 24/EOT visit will be summarized by treatment group for diary data and prescribed data using analogous methods used for PS parameters.

6.2.7 Supplementary Analyses of Secondary Efficacy Endpoints

There are no supplementary analyses of secondary efficacy endpoints planned.

6.3 Analysis of Other Efficacy endpoints

Since diary and prescribed PS and EN data will be analyzed separately, visit-level listing for average daily weight-normalized PS/EN volume, caloric intake, days per week and hours per day of PS support, will present diary and prescribed data side-by-side.

6.3.1 Native GLP-2

Native GLP-2 at baseline will be graphically summarized using scatter plots by percent change in PS Volume at Week 24/EOT for the ITT analysis set with a regression line and r-value by responder and non-responder.

Native GLP-2 at baseline will be summarized by percent change in PS Volume (responder/non-responder) at Week 24/EOT for the ITT analysis set.

A listing of collected GLP-2 will be produced.

6.3.2 Change and Percent Change from Baseline in Hours per Day and Days per Week of PS Support

Change and percent change of diary and prescribed PS hours per day and PS days per week from baseline to each visit during 24-week treatment period and the 4-week follow-up period will be summarized. These summaries will be presented by treatment arm using descriptive statistics.

Prescribed PS hours per day for each visit (including baseline) will be taken from the most recent prescription data prior to or at that visit.

For the derivations of hours per day and days per week parameters, refer to section 11.6.

6.3.3 Escape Criteria During Follow up Period

A table summarizing the number and percentages of subjects who escaped during follow up period as well as the escape reasons will be produced. This table will also display descriptive statistics (n, mean, SD, median, Q1, Q3, minimum and maximum) of the escape duration, where the time to escape is defined as the time from the last teduglutide dose to the date subject meets escape criteria:

> Time to escape (days)= (date subject meets escape criteria – date of last teduglutide dose) +1

6.4 Multiplicity Adjustment

There is no statistical testing due to the small sample size. Therefore, no adjustment to the p-value to control Type I error is necessary.

6.5 Subgroup Analysis

There are no subgroup analyses for efficacy endpoints.

7. SAFETY ANALYSIS

The safety analysis will be performed using the Safety set. Safety variables include AEs, clinical laboratory variables, and vital signs. For each safety variable where applicable, the last value collected before the first dose of investigational product for teduglutide treatment arm or the last value collected at baseline visit for standard of care treatment arm will be used as baseline for all analyses of that safety variable. Last Value on Treatment (LVOT) will be defined as the last valid assessment obtained after Baseline and whilst on investigational product (until Week 24/EOT visit for standard of care treatment arm). Last Observed Value (LOV) will be defined as the last valid assessment obtained after Baseline for both: standard of care treatment arm and teduglutide treatment arm.

All safety analyses will be conducted according to the treatment the subject actually received.

7.1 Adverse Events

Adverse events will be coded using MedDRA.

7.1.1 All TEAEs

Treatment-emergent adverse event (TEAE) is defined as any adverse event on or after the first dose for the subjects teduglutide treatment arm, and on or after the randomization date for the subjects in standard of care treatment arm.

If more than 1 AE with the same preferred term is reported before the date of the first dose of investigational product (date of baseline visit for standard of care treatment arm), then the AE with the greatest severity will be used as the benchmark for comparison to the AEs occurring during the treatment period under the preferred term. In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified by the worst case; i.e. treatment-emergent.

An overall summary of the number of subjects with TEAEs as well as the number of events will be presented, including the number and percentage of subjects with any TEAEs and serious TEAEs (TESAEs), TEAEs and serious TEAEs related to investigational product, TEAE highest severity and TEAEs leading to discontinuation of investigational product or death.

Incidence of TEAEs will be also presented by SOC and PT as well as analyzed by relationship to study drug and maximum severity, respectively. Summaries by SOC and PT will present SOC in alphabetical order and PT within the SOC in descending order of incidence in the teduglutide treatment arm.

If more than 1 AE occurs with the same preferred term for the same subject, then the subject will be counted only once for that preferred term using the most severe and most related occurrence for the summarization by severity and by relationship to investigational product. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending incidence in the teduglutide treatment arm.

Listings will include both TEAEs and Non-TEAEs (unless specified otherwise) and will also list serious adverse events, adverse events leading to death, and adverse events leading to discontinuation of study drug. Listings will indicate whether an AE is treatment emergent or not and whether it is related to study drug or not.

7.1.2 Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as “Serious” on the Adverse Events Form of the eCRF. Any SAE that occurs from the time of the signing of the informed consent form (ICF) through last study visit (week 28 or EOS) will be captured. A summary of TESAEs by SOC and PT will be prepared, as well as

summaries by event and causal relationship to study drug. A listing of SAEs will be presented.

7.1.3 AEs Leading to Discontinuation of Study Drug

AEs leading to permanent discontinuation of study drug will be identified by the "Study drug discontinued" response for action taken with study treatment in the Adverse Events Form of the eCRF.

Separate listings will be provided for AEs leading to permanent discontinuation of study drug.

7.1.4 Adverse Events Leading to Death

AEs leading to Death are those events which are recorded as "Fatal" on the Adverse Events Form of the eCRF. A listing of AEs leading to death will be presented.

7.1.5 Adverse Events of Special Interest

Separate summary table will be provided for the selected adverse events of special interest (AESI) that will be determined in accordance with Table 2.

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

Table 2 AESI Categories

AESI Categories	System Organ Class (SOC)	Preferred Terms (PT)	Higher Level Group Terms (HLGTs)
Tumor-promoting ability	Neoplasms benign, malignant and unspecified		
Growth of pre-existing polyps of the colon		Duodenal polyp	
		Intestinal polyp	
		Rectal Polyp	
		Large intestine polyp	
		Gastrointestinal polyp	
Benign neoplasia of the GI tract			Gastrointestinal neoplasms benign
			Hepatic and biliary neoplasms benign

Note: MedDRA terms are based on MedDRA version 21.0.

A supporting listing will be provided.

7.2 Clinical Laboratory Data

Laboratory evaluations that are done at study site visits will be collected and processed via a central laboratory, including panels for Hematology, Clinical Chemistry, Coagulation and Urinalysis.

The central laboratory data will be transferred to IQVIA for analyses. Laboratory evaluations that are required at intervals that do not coincide with study site visits may be obtained by a local laboratory. The local laboratory data will be collected on the local laboratory tests form of eCRF. The summaries will be based on central laboratory results only, while all reported data will be listed including local laboratory data.

Descriptive statistics for clinical laboratory values in standard international (SI) units from central lab and changes from baseline at each assessment time point will be presented by treatment group.

Hematology Hemoglobin, hematocrit, red blood cells (RBC), platelet count, white blood cell count (WBC), neutrophils, lymphocytes, monocytes,

eosinophils, basophils, neutrophils/leukocytes, lymphocytes/leukocytes, monocytes/leukocytes, eosinophils/leukocytes, basophils/leukocytes

Biochemistry Albumin, alkaline phosphatase, aspartate transaminase, alanine aminotransferase, amylase, aspartate aminotransferase, bicarbonate, indirect bilirubin, total bilirubin, blood urea nitrogen, calcium (total), chloride, cholesterol, C-creative protein, creatinine, estimated glomerular filtration rate (Schwartz formula), gamma glutamyl transferase, glucose, lipase, magnesium, phosphorus, potassium, sodium, triglycerides

Urinalysis Specific gravity, urine sodium

Coagulation Prothrombin time (Pt), international normalized ration (INR)

Liver enzyme parameters, namely alkaline phosphatase, aspartate transaminase, alanine aminotransferase, aspartate aminotransferase, total and direct bilirubin and gamma glutamyl transferase will be presented graphically by visit.

7.2.1 Reference Ranges

Quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit inclusive).
- High: Above the upper limit of the laboratory reference range.

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be categorized as per above instruction, taking into account the direction sign. That is if the reported value is <3 and the lower limit of the laboratory reference range equals 3 then the reported value will be categorized as low.

7.2.2 Markedly Abnormal Laboratory Criteria

Markedly abnormal laboratory tests will be identified in accordance with the predefined potentially clinically significant criteria (PSC) presented in Table 3.

The number and percentage of subjects with post-baseline PCS values will be tabulated by treatment group. The percentages will be calculated relative to the number of

subjects in the Safety Population. A listing of subjects will be provided for a parameter if there was a markedly abnormal laboratory value at any timepoint during the study.

Table 3: PSC Criteria for Markedly Abnormal Laboratory Tests

Parameter	SI Unit	Lower Limit	Higher Limit
Biochemistry			
Albumin	g/L	<20	>68
Alkaline Phosphatase (ALP)	U/L		>5*ULN
Alanine Aminotransferase (ALT)	U/L		>8*ULN
Aspartate Aminotransferase (AST)	U/L		>8*ULN
Amylase	U/L		>3*ULN
Bilirubin Total	umol/L		>5*ULN
Direct Bilirubin	umol/L		>68.4147
Blood Urea Nitrogen (BUN)	mmol/L		> 12.495
Calcium	mmol/L	< 1.5	> 3
Creatinine	µmol/L		>132.6
C Reactive Protein	mg/L		>=100
Glucose	mmol/L	< 2.22	> 13.875
Lipase	U/L		>3*ULN
Magnesium	mmol/L	< 0.4114	> 1.2342
Phosphorus	mmol/L	<0.644	> 2.254
Potassium	mmol/L	< 2.5	> 6.5
Sodium	mmol/L	< 120	> 160
Triglycerides	mmol/L		>5.65
Hematology			
Hemoglobin	g/L	< 70	>200
Hematocrit	fraction of 1	<0.21	>0.60
Platelets	10^9/L	< 75	>700
Leukocytes	10^9/L	< 2	>30
Neutrophils, absolute	10^9/L	<0.5	
Coagulation			
International normalized ration (INR)	NA		> 1.5

LLN: Lower limit of normal value provided by the laboratory

ULN: Upper limit of normal value provided by the laboratory

7.3 Antibodies to Teduglutide

The number and percentage of subjects with an antibody finding (Antibodies to Teduglutide Negative/Positive, Neutralizing Antibodies Present/ No Neutralizing Antibodies Present) will be summarized at baseline, Week 12 and Week 28/EOS. Non-specific antibodies will be categorized as Negative.

If at a specific visit a screening value as well as a confirmation value is present for a subject, the confirmed antibody value will be used in the table summary.

The follow-up antibody assessments after study completion will not be transferred from the lab vendor for any statistical analysis.

7.4 Vital Signs

The following vital signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Temperature (°C)
- Weight (kg)
- Length (cm)
- Head circumference (cm)

The following vital signs parameters will be derived for this study:

- Weight Z-score
- Length Z-score
- Head circumference Z-score
- Weight/length ratio Z-score

Descriptive statistics will be used to summarize vital signs measurements and derived parameters in actual value and change from baseline for each treatment group, only vital signs (not derived parameters) by age group (4-< 6 months and 6-12 months) at study site visits where associated parameters are collected. The Weight, Length, Weight/Length ratio and Head Circumference Z-scores will be graphed. A listing will also be provided.

For Weight, Length, Weight/Length ratio and Head Circumference Z-scores

Official and validated SAS programs created by WHO will be used to calculate z-

scores:

http://www.who.int/childgrowth/software/en/

7.5 Physical Examination

Physical examination dates and reason that an examination was not done will be presented in data listings. Any clinically significant findings for physical examination are recorded as adverse events.

7.6 Fecal and Urine Output

Urine and stool output data is recorded over a 48-hour period of PS and EN stability before every scheduled site visit and within 1 week of implementing any PS prescription adjustment.

The average daily urine output (mL/kg/day) at the scheduled site visit will be calculated as follows:

(Total urine output over 48 hours / 2) / body weight (kg) at the scheduled visit

where total urine output is calculated as the sum of the urine output in mL and the urine-only diaper weights in g (1g = 1mL) for the subject collected on the output diary form of eCRF.

If there are two or more days reported (Monday, Wednesday, Friday) the most recent two days will be summed up (Wednesday, Friday) and divided by 2 and then divided by body weight. The days do not have to be consecutive, so if (Tuesday, Wednesday, Friday) is available, then Wednesday and Friday would be selected as the two most recent days. Values will not be calculated if at least two urine outputs are not available at the visit. If the body weight at the scheduled visit is missing, the last available weight assessment will be used.

The average daily fecal output will be summarized separately by the average number of stools per day, the average total daily stool/mixed stool diaper weight (g/kg/day) and the average ostomy output per day (mL/kg/day) for each visit. The average number of stools per day will be calculated as (sum of the daily data in a 48-hour period / 2). The body weight will be used to calculate the daily stool/mixed stool diaper weight (g/kg/day) and the total ostomy output per day (mL/kg/day) using the same formula as we use to calculate the average daily urine output.

The change in average daily output for stool and urine from baseline to each scheduled visit, as well as at EOT, will be presented by treatment group using descriptive statistics. The change and the percent change in average daily output for fecal and urine output from baseline to each scheduled visit, as well as at EOT, will be presented by treatment group using descriptive statistics. A listing will also be provided.

8. PHARMACOKINETIC ANALYSIS

8.1 Drug Concentration

Descriptive statistics (mean, SD, CV%, median, Q1, Q3, minimum and maximum values, Geometric mean and Geometric mean CV%) of plasma teduglutide concentration will be calculated to summarize the observed values at each nominal timepoint. When analysis at one timepoint will occur, only the observed values will be summarized at the nominal timepoint.

Mean teduglutide plasma concentrations will be visually presented over time.

Pharmacokinetic concentration data will be summarized based on the Pharmacokinetic set defined in section 4.5.

8.2 Handling Below Limit of Quantitation (BLQ) Values

In the calculation of summary statistics of concentrations at individual time point the BLQ concentration will be considered to be zero for pre-dose time point and set to missing for any other time point.

8.3 Pharmacokinetic Parameters

Pharmacokinetic parameters will be analyzed separately and reported separately.

8.4 Statistical Analysis of Pharmacokinetic Data

Statistical analysis of PK data will be documented separately.

9. OTHER ANALYSES

9.1 Health-related Quality of Life Analyses

Cumulative number of hospitalization days during the treatment period and during the follow up period will be summarized separately using descriptive statistics (number, mean, median, SD, Q1, Q3, minimum and maximum).

A supporting listing presenting the date of admission, date of discharge, primary reason for hospitalization, discharge diagnosis and discharge status will be produced.

10. DATA MONITORING COMMITTEE/INTERIM ANALYSIS

A Data Monitoring Committee (DMC) was set up to review the safety during the course of the trial. For further details of the DMC can be found in the separate DMC SAP.

Interim analysis will be conducted for regulatory submissions, as needed. The interim analysis will focus on the ITT set and Safety set. The Per-Protocol Analysis Set will not be in the scope.

Analyses will be descriptive in nature. No formal comparisons are planned, and no hypotheses will be formally tested.

11. DATA HANDLING CONVENTIONS

11.1 General Data Reporting Conventions

Continuous variables will be summarized using the following descriptive statistics: n, mean, median, standard deviation, interquartile ranges (Q1, Q3), minimum, maximum. Categorical and count variables will be summarized by the number of subjects (n) and the percentage of subjects in each category and treatment arm.

See Appendix 14.1 for rules on the number of decimal places to present data.

11.2 Common calculations

For quantitative measurements, change from baseline will be calculated as:

Test Value at Visit X – Baseline Value

Percent change from baseline will be calculated as:

((Test Value at Visit X – Baseline Value) / Baseline Value) *100

Change (or percent change) from baseline tables will be calculated based on the number of subjects in the treatment group with a non-missing value at baseline and at the time point being analyzed unless otherwise specified.

11.3 Reference Start Date and Study Day

Study Day will be calculated from the reference start date, and will be used to show start/stop day of assessments and events.

Reference start date for teduglutide arm is defined as the day of the first dose of study drug, while for standard of care treatment arm it is defined as the day of the baseline visit date. Study days before the first dose of study drug (or baseline) will be negative.

If the date of the event is on or after the reference start date then:

Study Day = (date of event – reference start date) + 1.

If the date of the event is prior to the reference start date then:

Study Day = (date of event – reference start date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day.

11.4 Definition of Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to or on the reference start date (including unscheduled assessments). For AEs or concomitant medications that start on the reference start date, the time of onset will be compared to the time of the first dose of study drug to determine if the AE or medication was pre-baseline or post-baseline. If the timing relative to the first dose of study drug is unknown, AEs and medications commencing on the reference start date will be considered post-baseline. Actual PS and EN administration on the day of the reference start will be considered post-baseline.

11.5 Definition of Visit Windows

Nominal visits will occur within two days of the scheduled week 1 and week 2 visits, within three days of the scheduled week 3 to week 15 visits and within four days of the scheduled week 16 to week 28 (EOS) visit. There will be no windowing of scheduled visits based on study day, and unscheduled visits will not be included in by-visit summaries. Early termination data will be mapped to a scheduled visit if it falls into the appropriate visit window as defined in the protocol and if that scheduled visit did not occur.

An EOT time point, defined as the last determination of endpoint or last available measurement after the date of first dose during the 24-week treatment period, will be analyzed in addition to the scheduled visits.

11.6 Derived Efficacy Endpoints

The calculation of diary PS/EN parameter normalized to weight will follow the formula below unless otherwise specified:

Baseline values:

Baseline average daily value = [(sum of non-missing daily values in the diary within 14 days prior to the first dose or baseline visit / number of days with non-missing values within 14 days prior to the first dose or baseline visit)] / last available weight prior to the first dose or baseline visit

Days per week of diary PS support at baseline = (number of days with non-zero values for PS intake within the 14 days prior to the first dose or baseline visit / number of days for which any PS intake data is recorded within the 14 days prior to the first dose or baseline visit) *7

Hours per day of diary PS support at baseline = (sum of hours per day for each day that PS intake data is recorded within the 14 days prior to the first dose or baseline visit / number of days that PS hours per day data is recorded within the 14 days prior to the

first dose or baseline visit)

A Sensitivity Analysis will be added for Hours per day of diary PS:

Hours per non-zero day of diary PS support at baseline = (sum of non-zero hours per day for each day that PS intake data is recorded within the 14 days prior to the first dose or baseline visit / number of days with non-zero that PS hours per day data is recorded within the 14 days prior to the first dose or baseline visit)

If more than 7 days' values in two weeks prior to the first dose or baseline visit are missing, the baseline average daily value will be set to missing.

Post-baseline values:

Post-baseline average daily value = [(sum of non-missing daily values in the diary within 7 days prior the date of each scheduled post-baseline visit / number of days with non-missing values within 7 days prior the date of each scheduled post-baseline visit)] / last available weight prior to the visit

Days per week of diary PS support post-baseline = (number of days with non-zero values for PS intake within the 7 days prior the date of each scheduled post-baseline visit / number of days for which any PS intake data is recorded within the 7 days prior the date of each scheduled post-baseline visit) *7

Hours per day of diary PS support post-baseline = (sum of hours per day for each day that PS intake data is recorded within the 7 days prior the date of each scheduled post-baseline visit / number of days that PS hours per day data is recorded within the 7 days prior the date of each scheduled post-baseline visit

A Sensitivity Analysis will be added for Hours per day of diary PS:

Hours per non-zero day of diary PS support post-baseline = (sum of non-zero hours per day for each day that PS intake data is recorded within the 7 days prior the date of each scheduled post-baseline visit / number of days that PS hours per day with non-zero data is recorded within the 7 days prior the date of each scheduled post-baseline visit

If more than 2 days' values in a week are missing, the post-baseline average daily value will not be calculated and will be assigned as missing. Week 1 visit calculations will exclude any pre-baseline diary data.

The calculation of prescribed PS/EN parameter normalized to weight for baseline and post-baseline average daily values will follow the formula below unless otherwise specified:

Average daily value = (most recent prescribed weekly PS/EN parameter prior to or on the date of visit / 7) / last available weight prior to or on the date of visit

Prescribed PS hours per day and PS days per week for each visit (including baseline) will be taken from the most recent prescription data prior to or at that visit.

Percent reduction in weight-normalized diary and prescribed PS/EN parameter from baseline at the scheduled visit will be calculated using the formula below:

% reduction in PS/EN value at the visit = [(average daily value at the scheduled visit - average daily value at baseline) / average daily value at baseline] * 100

11.7 Repeated or Unscheduled Assessments

In general, for by-visit summaries, data recorded at the nominal visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but can contribute to the best/worst case value where applicable. Unscheduled PS or EN prescription adjustments carry forward until the next adjustment, and hence may contribute to data assigned to subsequent visits.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

11.8 Handling of Missing, Unused, and Spurious Data

No imputation for missing data (e.g., last observation carried forward [LOCF]) will be applied except for the partial dates for adverse events and prior/concomitant medications.

Imputation will be performed for partial dates of AEs and medications solely for the purpose of defining treatment emergence for AEs, determining whether an AE started in the treatment period and prior/concomitant status for medications. Details on how to handle partial dates for adverse events and prior/concomitant medications are described below.

Details for the imputation algorithm for the missing endpoint values for PS support parameters (volume, calories and etc.) are described in Section 6 of this analysis plan.

11.8.1 Missing Date of Investigational Product

No imputations will be done for the investigational product.

11.8.2 Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)

Imputation of Partial Medication Dates

START DATE	STOP DATE	ACTION

START DATE	STOP DATE	ACTION
Known	Partial	If medication stop year and month are known and the reference end date during that month and year: Impute stop date as the reference end date if medication start date <= the reference end date; Else if medication stop year and month are known and are not the month and year of the reference start date: Impute stop date as the last day of the month; Else if only medication stop year is known and is the year of the reference end date: Impute stop date as the reference end date if medication start date <= the reference end date; Else if only medication stop year is known and is prior to the year of the reference end date: Impute stop date as the last day of the year (31st December).
	Missing	If medication stop date is unknown leave as missing.
Partial	Known	If medication start year and month are known and it is the month and year of the reference start date: Impute start date as the reference start date if medication stop date > the reference start date; Else if medication start year and month are known and it is the month and year of the informed consent: Impute start date as the informed consent date if medication start year and month < the year and month of the reference start date; Else if medication start year and month are known and are not the month and year of the reference start date or informed consent: Impute start date as the first day of the month; Else if only medication start year is known and is the year of the reference start date: Impute start date as the reference start date if medication stop date > the reference start date; Else if only medication start year is known and is the year of the informed consent date: Impute start date as the informed consent date if medication start year < the year of the reference start date; Else if only medication start year is known and is after year of the reference start date: Impute start date as the first day of the year (1st January).

START DATE	STOP DATE	ACTION
	Partial	If medication start year and month are known and it is the month and year of the reference start date: Impute start date as the reference start date if medication stop year and month are known and >= the year and month of the reference start date Or If only AE stop year is known and >= year of the reference start date; Else if medication start year and month are known and it is the month and year of the informed consent: Impute start date as the informed consent date if medication start year and month < the year and month of the reference start date; Else if medication start year and month are known and are not the month and year of the reference start date or informed consent: Impute start date as the first day of the month; Else if only medication start year is known and is the year of the reference start date: Impute start date as the reference start date if medication stop year and month are known and >= the year and month of reference start date Or If only AE stop year is known and >= year of reference start date; Else if only medication start year is known and is after year of the reference start date: Impute start date as the first day of the year (1st January). If medication stop year and month are known and study drug stopped during that month and year: Impute stop date as the stop date of study drug if medication start date <= the stop date of study drug; Else if medication stop year and month are known and are not the month and year of the reference start date: Impute stop date as the last day of the month; Else if only medication stop year is known and is the year of the reference end date: Impute stop date as the reference end date if medication start date <= the reference end date; Else if only medication stop year is known and is prior to the year of the reference end date: Impute stop date as the last day of the year (31st December).

START DATE	STOP DATE	ACTION
	Missing	If medication start year and month are known and it is the month and year of the reference start date: Impute start date as the reference start date; Else if medication start year and month are known and it is the month and year of the informed consent: Impute start date as the informed consent date if medication start year and month < the year and month of the reference start date; Else if medication start year and month are known and are not the month and year of the reference start date or informed consent: Impute start date as the first day of the month; Else if only medication start year is known and is the year of the reference start date: Impute start date as the reference start date; Else if only medication start year is known and is after year of the reference start date: Impute start date as the first day of the year (1st January). If medication stop date is unknown leave as missing.
Missing	Known	If medication stop date is unknown leave as missing.
	Partial	If medication stop date is unknown leave as missing.
	Missing	If medication stop date is unknown leave as missing.

11.8.3 Missing Date Information for Adverse Events

Imputation of Partial AE Dates

START DATE	STOP DATE	ACTION
Known	Partial	If AE start year and month are known, impute stop date as latest possible date (that is the last day of the month if day is unknown or 31st December if day and month are unknown).
	Missing	If AE stop date is unknown leave as missing.
Partial	Known	If AE start year and month are known and it is the month and year of the reference start date: Impute start date as the reference start date if AE stop date > the reference start date; Else if AE start year and month are known and it is the month and year of the informed consent: Impute start date as the informed

START DATE	STOP DATE	ACTION
		consent date if AE start year and month < the year and month of the reference start date; Else if AE start year and month are known and are not the month and year of the reference start date or informed consent: Impute start date as the first day of the month; Else if only AE start year is known and is the year of the reference start date: Impute start date as the reference start date if AE stop date > the reference start date; Else if only AE start year is known and is after year of the reference start date: Impute start date as the first day of the year (1st January).
	Partial	If AE start year and month are known and it is the month and year of the reference start date: Impute start date as the reference start date if AE stop year and month are known and >= the year and month of the reference start date Or If only AE stop year is known and >= year of the reference start date; Else if AE start year and month are known and it is the month and year of the informed consent: Impute start date as the informed consent date if AE start year and month < the year and month of the reference start date; Else if AE start year and month are known and are not the month and year of the reference start date or informed consent: Impute start date as the first day of the month; Else if only AE start year is known and is the year of the reference start date: Impute start date as the reference start date if AE stop year and month are known and >= the year and month of the reference start date Or If only AE stop year is known and >= year of the reference start date; Else if only AE start year is known and is after year of the reference start date: Impute start date as the first day of the year (1st January). Impute stop date as latest possible date (that is the last day of the month if day is unknown or 31st December if day and month are unknown).
	Missing	If AE start year and month are known and it is the month and year of the reference start date: Impute start date as the reference start date; Else if AE start year and month are known and it is the month and year of the informed consent: Impute start date as the informed

START DATE	STOP DATE	ACTION
		consent date if AE start year and month < the year and month of the reference start date; Else if AE start year and month are known and are not the month and year of the reference start date or informed consent: Impute start date as the first day of the month; Else if only AE start year is known and is the year of the reference start date: Impute start date as the reference start date; Else if only AE start year is known and is after year of the reference start date: Impute start date as the first day of the year (1st January). If AE stop date is unknown leave as missing.
Missing	Known	If AE start date is unknown leave as missing; event will be considered treatment-emergent if stop date >= the reference start date.
	Partial	If AE start date is unknown leave as missing; event will be considered treatment-emergent if stop date partial stop date >= same partial portions of the reference start date
	Missing	If AE start or stop date is unknown leave as missing; event will be considered treatment-emergent.

11.8.4 Missing Severity Assessment for Adverse Events

If the severity is missing for a TEAE, a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries, while both the actual and imputed values will be presented in data listings.

11.8.5 Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for a TEAE, a causality of "Related" will be assigned. The imputed values for relationship to investigational product will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

For subjects in standard of care treatment arm, missing causality will not be imputed as subjects in this arm did not receive any investigational product. AE summaries by relationship will exclude the standard of care treatment arm.

11.8.6 Character Values of Clinical Laboratory Variables

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of

quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

11.8.7 Unused data

Other than select fields that capture reason an assessment is not done, all comments and specified text fields captured in the eCRF will be displayed in appendix listings only. These variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

Other data collected in eCRF, IRT system or any other clinical trial data collection system which is not described above will be presented in the appendix listings, such as randomization information, IE criteria not met and procedures.

12. ANALYSIS SOFTWARE

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® on a suitably qualified environment.

13. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

The protocol specifies that the stool consistency will be scored. However, this information is not captured on the eCRF hence its evaluation is not included in this SAP.

14. APPENDICES

14.1 Decimal Places and Rounding Rules

1. For measures of median and mean, use 1 decimal place beyond those used for the measurement.
2. For measures of standard deviation and standard error of the mean, use 2 decimal places beyond those used for the measurement.
3. For measures of minimum and maximum values, use the same number of decimal places as those used for the measurement.
4. >=5 is rounded up away from zero, whereas <5 is rounded down toward zero to account for rounding of negative numbers.
5. Derived questionnaire scores, and other similar efficacy parameters recorded as integers, should be rounded to 1 decimal place for reporting.
6. For PK Related shells, display as reported.

14.2 Identified Tables/Figures/Listings for Interim Analysis

All Listings except Listing 16.2.3.1 for Subjects Excluded from the Per Protocol Set would be generated for the interim analysis.

The following Figures would be generated for the interim analysis
Figure 14.2.3.4.1 – Individual Percent Change in PS Volume (mL/kg/day) by Visit Based on Diary Data – Intent-to-treat Set
Figure 14.2.3.6.1 – Individual Percent Change in PS Caloric Intake (kcal/kg/day) by Visit Based on Diary Data – Intent-to-treat Set
Figure 14.2.3.12.1 – Individual PS Volume (mL/kg/day) Based on Diary Data Over Time – Intent-to-treat Set
Figure 14.2.3.13.1 – Individual PS Calories (kcal/kg/day) Based on Diary Data Over Time – Intent-to-treat Set
Figure 14.3.5.3.1 – Individual Weight, Length, Weight/Length Ratio and Head Circumference Z-score by Visit – Safety Set

The following Tables would be generated for the interim analysis:
Table 14.1.1.1: Subject Disposition (Screened Set)
Table 14.1.1.2: Analysis Sets (Enrolled Set)
Table 14.1.2.2: Protocol Deviations (Safety Set)
Table 14.1.4.1.3: Demographic Characteristics (Safety Set)
Table 14.1.4.2.3: Baseline Characteristics (Safety Set)

Table 14.1.4.3.2: Medical and Surgical History by System Organ Class and Preferred Term (Safety Set)
Table 14.1.4.4.2: Short Bowel Syndrome History (Safety Set)
Table 14.1.4.5: Prior Medications (Safety Set)
Table 14.1.4.6: Concomitant Medications (Safety Set)
Table 14.1.5.1: Study Drug Compliance (Intent-to-treat Set)
Table 14.2.2.2.1: Summary of Complete Weaning off PS Support by Visits (Intent-to-treat Set)
Table 14.2.2.3: Change from Baseline in PS Volume (mL/kg/day) by Visit (Intent-to-treat Set)
Table 14.2.2.4: Change from Baseline in PS Caloric Intake (kcal/kg/day) by Visit (Intent-to-treat Set)
Table 14.2.2.5: Change from Baseline in EN Volume (mL/kg/day) by Visit (Intent-to-treat Set)
Table 14.2.2.6: Change from Baseline in EN Caloric Intake (kcal/kg/day) by Visit (Intent-to-treat Set)
Table 14.2.2.9: Summary of ≥ 20% Reduction in PS Volume (mL/kg/day) by Visit (Intent-to-treat Set)
Table 14.2.2.10: Summary of ≥ 20% Reduction in PS Caloric Intake (kcal/kg/day) by Visit (Intent-to-treat Set)
Table 14.2.2.11: Change from Baseline in Days per Week of PS Support (days/week) by Visit (Intent-to-treat Set)
Table 14.2.2.12: Change from Baseline in Hours per Day of PS Support (hours/day) by Visit (Intent-to-treat Set)
Table 14.2.2.14: Summary of Escape Criteria During Follow-up Period (Safety Set)
Table 14.2.2.15: Summary of Teduglutide Plasma Concentrations by Timepoints (Pharmacokinetic Set)
Table 14.3.1.1: Overall Treatment-Emergent Adverse Events (TEAEs) by Treatment Group (Safety Set)
Table 14.3.1.2: Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Treatment Group (Safety Set)
Table 14.3.1.3: Treatment-Emergent Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and Treatment Group (Safety Set)
Table 14.3.1.4: Treatment-emergent Serious Adverse Events by System Organ Class, Preferred Term and Treatment Group (Safety Set)
Table 14.3.1.5: Treatment-emergent Serious Adverse Events Considered Related to Investigational Product by System Organ Class, Preferred Term and Treatment Group (Safety Set)

Table 14.3.1.6: Adverse Events of Special Interest by System Organ Class, Preferred Term and Treatment Group (Safety Set)
Table 14.3.1.7: Treatment-Emergent Adverse Events by Maximum Severity, System Organ Class, Preferred Term and Treatment Group (Safety Set)
Table 14.3.2.1: Listing of Serious Adverse Events (Safety Set)
Table 14.3.2.2: Listing of Adverse Events Leading to Treatment Discontinuation (Safety Set)
Table 14.3.2.3: Listing of Adverse Events Leading to Death (Safety Set)
Table 14.3.3.1: Listing of Adverse Events of Special Interest (Safety Set)
Table 14.3.4.1: Quantitative Clinical Laboratory Results by visit and Treatment Group: Chemistry (Safety Set)
Table 14.3.4.2: Quantitative Clinical Laboratory Results by visit and Treatment Group: Hematology (Safety Set)
Table 14.3.4.3: Quantitative Clinical Laboratory Results by visit and Treatment Group: Urinalysis (Safety Set)
Table 14.3.4.4: Markedly abnormal Laboratory Results by Treatment Group: Chemistry (Safety Set)
Table 14.3.4.5: Markedly abnormal Laboratory Results by Treatment Group: Hematology (Safety Set)
Table 14.3.4.6: Markedly abnormal Laboratory Results by Treatment Group: Coagulation (Safety Set)
Table 14.3.4.7: Listing of Subjects who met Markedly Abnormal Criteria: Chemistry (Safety Set)
Table 14.3.4.8: Listing of Subjects who met Markedly Abnormal Criteria: Hematology (Safety Set)
Table 14.3.4.9: Listing of Subjects who met Markedly Abnormal Criteria: Coagulation (Safety Set)
Table 14.3.5.1: Actual Values and Change from Baseline in Vital Signs by visit, age and Treatment Group (Safety Set)
Table 14.3.5.2: Summary of Body Weight, Length, Weight/Length Ratio and Head Circumference Z-Score by Visit (Safety Set)
Table 14.3.6.1: Summary of Antibody Results by Visit (Safety Set)
Table 14.3.7.1: Summary of Fecal Output by Visit (Safety Set)
Table 14.3.7.2: Summary of Urine Output by Visit (Safety Set)
Table 14.3.8.3: Investigational Product Exposure by Treatment Group (Safety Set)

14.3 Changes in the Statistical Analysis Plan

Changes from the SAP v1.0 dated 11Dec2018 to this current version 1.1 is summarized below.

Section	Change	Rationale
1.0 Introduction	Addition and mention of Protocol Amendment 4 dated 2019 Dec 17	To be consistent with amendments to the protocol made in Protocol version 4.0, dated 2019 Dec 17
3.4 Sample Size	Added details from the Protocol	Added details from Study Population Section of Protocol.
4 Statistical Analysis Set	Added details for when ITT Set equals Safety Set, only one set of outputs will be generated for tables that are repeated	To narrow down programming work, when there are repeat tables but Analysis Sets are equal.
4.2 Intent-to-Treat Set	Updated ITT Set to The Intent-to-Treat (ITT) set will consist of all subjects randomized in the study.	To be consistent with amendments to the protocol made in Protocol version 4.0, dated 2019 Dec 17
5.6 Prior Medication	Added clarification for reference date	To add hyperlink to location of details
5.7 Concomitant Medications	Updated con med definition to include all medications after reference date	To be consistent with other Gattex SAPs – i.e. TED-C14-006 Study.
6.2.7 Supplementary Analyses of Secondary Efficacy Endpoints	Added sentence to clarify blank section.	Clarified nothing applicable for this section.

6.3.1 Native GLP-2	Added details around analysis timepoint, and percentage change	To add details in analysis.
7.1.1 All TEAEs	Updated TEAE definition to include all AEs after reference date	To be consistent with other Gattex SAPs – i.e. TED-C14-006 Study.
7.1.5 Adverse Events of Special Interest	Added Specific AESI terms	To add clarity to analysis with the confirmed MedDRA version 21.0
10. DATA MONITORING COMMITTEE/INTERIM ANALYSIS	Updated Interim Analysis Section	To be consistent with amendments to the protocol made in Protocol version 4.0, dated 2019 Dec 17
11.6 Derived Efficacy Endpoints	Added analysis for Hours per non-zero day of diary PS	To be sensitivity analysis
11.6 Derived Efficacy Endpoints	Updated allowance of missing days for diary inputs	Because seven days value within a two-week period would provide a good estimate for baseline and would not introduce bias from previous method.
11.8.2 Missing Date Information for Prior or Concomitant Medications (Therapies/Procedures)	Added more details to imputation algorithm and changed to tabular format	To complete the algorithm rules
11.8.4 Missing Severity Assessment for Adverse Events	Clarified Missing TEAE will be classified as Severe	To be consistent with other Gattex SAPs – i.e. TED-C14-006 Study.
11.8.5 Missing Relationship to Investigational Product	Clarified Missing TEAE relationship will be classified as 'related' and SoC relationship analysis will be	To be consistent with other Gattex SAPs – i.e. TED-C14-006 Study.

for Adverse Events	excluded	
Section Titles	Editorial changes made to this section, e.g, Upper Case and Lower case, ITT Population vs ITT Set	Text revised for purposes of improved clarity, completeness, and transparency.

STATISTICAL ANALYSIS PLAN Signature Page

Statistical Analysis Plan V1.1 (Dated: March 24, 2020) for Protocol SHP633-301

	Name	Signature	Date
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