STATISTICAL ANALYSIS PLAN

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

SAP Version and Date:

Version 3.0: 17 Dec 2020

STATISTICAL ANALYSIS PLAN

(PROSPECTIVE DATA)

SHP633-304

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

AUTHOR: [redacted]

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Draft V3 (Dated 17Dec2020) for Protocol SHP633-304

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	[redacted]		
Position:	[redacted], GI Statistics		
Company:	Shire Pharmaceuticals, Inc. a Takeda Company		

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
Draft 1.0	11AUG2017	[redacted]	Not Applicable – First Version
Version 1.1	2FEB2018	[redacted]	To include subgroup analysis for 25%, 50%, 75% reduction in PS Volume
Version 2.0	11JUN2018	[redacted]	To incorporate Changes to Planned Statistical Analysis Plan dated 03May2018, which clarifies *extent of exposure *hours per day *change from baseline labs for certain continuous variables due to different central lab between 006 study and 304 study. Also removed, number of days on teduglutide for each cycle.
Version 3.0	17Dec2020	[redacted]	Update SAP per Protocol Amendment #4 incorporate roll over subjects from 301 study Remove mentioning of Quintiles or Shire Modification of CRO Add extension of exposure for categories for longer exposure, add overall exposure with core since exposure calculation to account for longer duration Add hours per non-zero days as sensitivity analysis Change from baseline to will not be calculated for lab parameters that have

			different normal ranges between core and extension. Clarified analysis for Quality of life stratify parents and self-reported data, handling between Ted and NT periods.

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CTMS	Clinical Trial Management System
CxDy	Cycle x Day y
eCRF	Electronic Case Report Form
EOS	End of Study
ET	Early Termination
FOBT	Fecal Occult Blood Testing
FOCBP	Females of Childbearing Potential
GFR	Glomerular Filtration Rate
GGT	Gamma Glutamyl Transferase
HRQoL	Health-Related Quality of Life
ICF	Informed Consent Form
INR	Prothrombin International Normalized Ratio
IVRS	Interactive Voice Response System
LLQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
NTT	No-Teduglutide Treatment
NTx	No-Teduglutide Period x
PedsQL	Pediatric Quality of Life
PS	Parenteral Support
PT	Preferred Term
Px	Pre-Treatment Visit x
QD	Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBS	Short Bowel Syndrome
SC	Subcutaneous
SOC	System Organ Class
SRN	All Subjects Screened
TEAE	Treatment-Emergent Adverse Event
TED	Teduglutide
TESAE	Treatment-Emergent Serious Adverse Event
TFLs	Tables, Figures and Listings
ULQ	Upper Limit of Quantification
WHODD	Who Drug Dictionary

2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of prospective data for Protocol SHP633-304. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) version 1.1 was based on protocol amendment 2, dated 23 March 2017. The updated version 2.0 was based on protocol amendment 4, dated 01 Oct 2019.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of the study is to evaluate the long-term safety and tolerability of teduglutide treatment in pediatric subjects with Short Bowel Syndrome (SBS) who completed TED-C14-006 or SHP633-301.

3.2. SECONDARY OBJECTIVE

The secondary objective of the study is to evaluate the long-term efficacy of teduglutide treatment in pediatric subjects with SBS who completed TED-C14-006 or SHP633-301.

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

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 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 parenteral support (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 SHP633-301, 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.

The TED-C14-006 and SHP633-301 studies will also be referred to as the core studies interchangeably throughout this analysis plan.

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.

Subjects not receiving teduglutide treatment (i.e., in a no-teduglutide treatment [NTT] period), will be seen approximately every 12 weeks for safety, PS requirements, and quality of life. The first NTx visit following the screening visit should occur within 2 to 12 weeks of screening. At any point after screening or during a NTT period, subjects who meet at least one 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 at least one 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 QD, followed by a 4-week follow-up period (during which no teduglutide is administered). 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.

Table A: Study Design Flow Chart

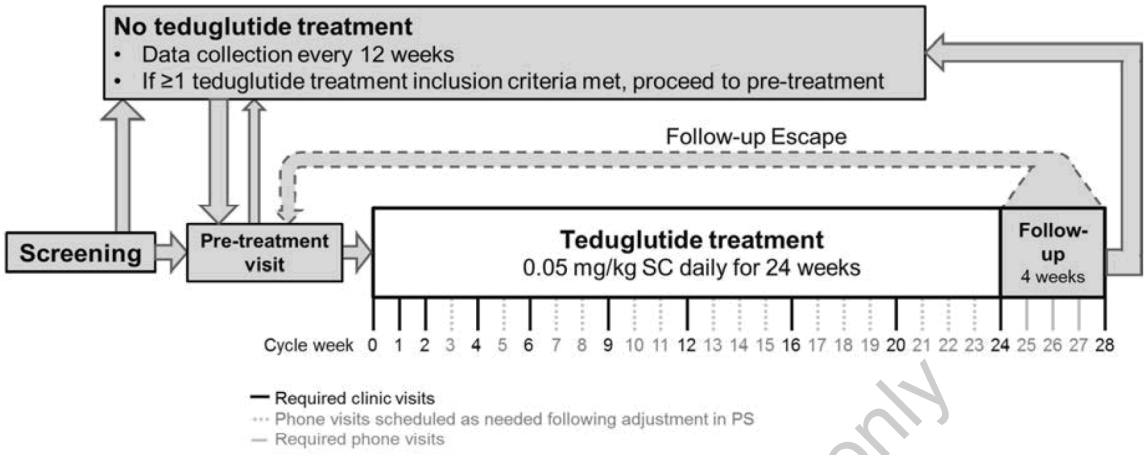

Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pre-treatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects will enter a 28-week teduglutide 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.

4.2. SCHEDULE OF EVENTS

Schedule of events for prospective data collection can be found in Table 1-1, Table 1-2, Table 1-3 and Section 7.1 of the protocol.

4.3. CHANGES TO ANALYSIS FROM PROTOCOL

There is no change of analysis from the protocol.

5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Interim Analysis of Prospective Data
- Final Analysis

5.1. INTERIM ANALYSIS OF PROSPECTIVE DATA

An interim analysis is planned to complete the requirements for sNDA submission and the determination of extension of orphan drug exclusivity according to the pediatric written request.

Derivations and definitions for the interim analysis will be based on those required for the final analysis contained in this analysis plan, unless deviations are stated within the text. The list of outputs provided with the full set of output templates (planned for the final analysis) will highlight which of these outputs will also be provided for the interim analysis.

5.2. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed with sponsor authorization of this statistical analysis plan and analysis sets. The final analyses will be performed following the sponsor-authorized SAP and analysis sets for the clinical study report.

6. 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.

Subjects will be classified in treatment groups based on whether they received teduglutide in the core studies TED-C14-006 (as either 0.025 mg/kg or 0.05 mg/kg) or SHP633-301 (as 0.05 mg/kg) and/or during the prospective observation period in this study at the time of analysis:

- NTT/NTT – subjects who participated in standard of care arm in the core study and did not receive any teduglutide treatment in the extension study;
- NTT/TED – subjects who participated in the standard of care arm in the core study but who subsequently received teduglutide in the extension study;
- TED/NTT – subjects who took teduglutide in the core study but did not receive any teduglutide treatment in the extension study;
- TED/TED – subjects who received teduglutide in the core study and in the extension study;
- ANY TED – subjects who received teduglutide in either the core study or in the extension study.

For Teduglutide Treatment Period tables, only NTT/TED and TED/TED will be presented, and ANY TED will be presented for safety data.

If a treatment group defined above doesn't have any enrolled subjects at the time of analysis, that treatment group will be removed from the tables.

6.1. ALL SUBJECTS SCREENED [SRN] SET

The all subjects screened (SRN) set will contain all subjects who provide signed informed consent for the study.

Data for subjects who fail to meet study inclusion eligibility criteria will be included in the listings but will not be included in any analyses.

6.2. SAFETY POPULATION

The safety population will contain all subjects in the SRN set who meet all of the inclusion criteria. Unless specified, the safety population will be used for both safety and efficacy analyses.

7. GENERAL CONSIDERATIONS

7.1. 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 is defined as the baseline visit date of TED-C14-006 or SHP633-301 (Day 1). Study days before the reference start date 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 will be missing.

7.2. BASELINE

The baseline is defined as the last non-missing measurement on or prior to the treatment in the core studies TED-C14-006 or SHP633-301 or in the 304 study.

	NTT/NTT	NTT/TED	TED/NTT	TED/TED	Any TED
Efficacy	006 or 301 BL	Prior to treatment in 304	006 or 301 BL	006 or 301 BL	NA
Demographics	006 or 301 BL	006 or 301 BL	006 or 301 BL	006 or 301 BL	006 or 301 BL
Growth and Labs	006 or 301 BL	Prior to treatment in 304	006 or 301 BL	006 or 301 BL	Prior to treatment in 304 or 006/301
Quality of Life (collected only in extension study)	First reported	C1D1	First reported	C1D1	

7.3. RETESTS, UNSCHEDULED VISITS AND EARLY TERMINATION DATA

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 prescription adjustments carry forward until the next adjustment, and as such, may be assigned to subsequent visits.

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

7.4. STUDY VISIT CONVENTIONS

Visits will be summarized and displayed by pretreatment visit (if applicable), or, by cycle and weeks for teduglutide treatment periods, or, by no-teduglutide treatment visit NTx for NTT periods. For each teduglutide treatment period, Cycle x Day 1, Cycle x Week 1, …, Cycle x Week 24, Cycle x Week 25 Follow-up, Cycle x Week 26 Follow-up, Cycle x Week 27 Follow-up and Cycle x Week 28 data will be collected according to the schedule of events. For each NTT period, NTx data will be collected. Teduglutide treatment periods and NTT period data will be presented in separately.

7.5. WINDOWING CONVENTIONS

For teduglutide treatment period, nominal visits will occur within two days of the scheduled week 1, 2, 4 and 6 visits, within four days of the scheduled week 9, 12, 16, 20, to week 24 visits and within two days of the follow-up visits week 25 to week 28. For NTT period, nominal visits will occur within seven days of the scheduled 12-week intervals. 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 and end of treatment visits in a teduglutide treatment cycle 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.

7.6. STATISTICAL TESTS

Due to the limited sample size, descriptive statistics will be used with a goal of summarizing the sample. As such, no claims of significance will be made for any of the data.

Continuous variables, 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 efficacy continuous variables, the following will also be described standard error, quartile 1 and 3. For categorical variables, statistical summaries will include number of subjects and percentages.

7.7. 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.

7.8. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 or higher.

8. STATISTICAL CONSIDERATIONS

8.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

No adjustments for covariates are planned for the statistical analyses.

8.2. MULTICENTER STUDIES

This study will be conducted by multiple investigators at multiple centers internationally.

8.3. MISSING DATA

Missing data will in general not be imputed. However, partial dates will contribute to the analysis as described in Appendix 2. All available data will be included in the safety analysis.

Details for the imputation algorithm for the missing endpoint values for PS parameters (volume, calories and etc.) will be described in Section 16.1.1 of this analysis plan.

8.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Given the small sample size, no hypothesis testing will be conducted. Therefore, there will be no adjustment for alpha level.

8.5. EXAMINATION OF SUBGROUPS

No subgroup analysis will be performed.

9. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs. The output templates provided together with this SAP describe the presentations for the analyses of this study. The format and content of the summary tables, figures and listings (TFLs) will be produced.

10. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent in the extension study will be accounted for in the analyses. After signed consent (and informed assent, if applicable), a subject will be

considered enrolled in the study if the subject meets all of the inclusion criteria at the screening. Teduglutide treatment eligibility does not impact study eligibility.

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 NTT period and could be evaluated for subsequent teduglutide treatment eligibility according to the study schedules. The reason for permanent treatment discontinuation will be captured.

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
- Protocol deviation
- Lack of efficacy
- Physician decision
- Withdrawal by subject
- Withdrawal by parent/guardian
- Lost to follow-up
- Pregnancy
- Death
- Other

The ongoing subjects will be counted in the table for interim analysis.

Protocol deviations as obtained from a clinical trial management system (CTMS) will be assessed throughout the study. All identified deviations will be reported in the CTMS. Protocol deviations from the CTMS will be coded to categories and provided as part of the CTMS transfer to Biostatistics. Shire will review the protocol deviation tracker.

A protocol deviation is defined as a deviation from protocol-related procedures that could affect integrity of the data or adversely affect subjects. Protocol deviation categories from CTMS include:

1. Informed Consent Criteria
2. Eligibility and Entry Criteria
3. Concomitant Medication Criteria
4. Laboratory Assessment Criteria
5. Study Procedures Criteria
6. Serious Adverse Event Criteria
7. Randomization Criteria (Not applicable to this study)
8. Visit Schedule Criteria
9. Investigational Product Compliance
10. Efficacy Criteria
11. Administrative Criteria
12. Source Document Criteria
13. Regulatory or Ethics Approvals Criteria
14. Other Criteria

The presentation of planned listings will include the following:

- Subject disposition (SRN set)
- Study Inclusion criteria violations (SRN set)
- Treatment Eligibility Criteria
- Follow-up Period Escape Criteria
- Protocol deviations

The following summary tables are planned for presentation:

- Subject disposition (SRN set)
- protocol deviations

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented.

The following demographic and other baseline characteristics will be summarized:

- Age (years) at baseline of TED-C14-006 or SHP633-301

- Age Group – Age is categorized in pre-defined groups: <1, 1 to <12, 12 to <17, 17 to 18.
- Sex (if female, the reproductive status will be reported)
- Race
- Ethnicity
- Weight Z-score at baseline of TED-C14-006 or SHP633-301
- Height Z-score at baseline of TED-C14-006 or SHP633-301
- Body Mass Index (BMI) Z-score at baseline of TED-C14-006 or SHP633-301
- Head Circumference Z-score at Baseline (only for subjects who are <= 36 months of age) of TED-C14-006 or SHP633-301

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

11.1. DERIVATIONS

- BMI (kg/ m^2) = 10000*weight (kg)/ height $(cm)^2$
- Z-score of weight, height, BMI and head circumference will be calculated based on the method described in Section 18.7.1.

12. MEDICAL HISTORY

Medical history will be presented for the safety population.

12.1. MEDICAL AND SURGICAL HISTORY

Medical and Surgical History will supplement the medical history information collected at the start of the TED-C14-006 or SHP633-301 core studies and 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
- Updates to previously reported medical history

Medical and Surgical History will be coded using ***Medical Dictionary for Regulatory Activities (MedDRA)***. 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 incidence in the any teduglutide (ANY TED) treatment group.

12.2. SHORT BOWEL SYNDROME HISTORY

If the subject has any changes to the SBS history collected at the baseline visit of the TED-C14-006 or SHP633-301 study, that information (updated SBS history) will be collected. The data at the baseline visit of the TED-C14-006 or SHP633-301 will be used if there is no update for the enrolled subjects in the extension study.

The following SBS History will be summarized:

- Primary reason for the diagnosis of SBS
- Presence of stoma; if Y, stoma type
- Presence any remaining colon; if Y, estimated percent colon remaining and whether the colon is in continuity
- Total estimated remaining small intestinal length
- Presence of distal/terminal ileum and ileocecal valve

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

13. CONCOMITANT TREATMENTS

Medications and procedures will be presented for the safety population.

Concomitant treatments are defined as all treatments taken between the dates of informed consent for the SHP633-304 extension study and end of study (EOS), inclusive. Concomitant treatments include all non-study treatments (medications, herbal treatments, vitamins, invasive and diagnostic procedures). Concomitant treatment information will be recorded on the Prior and Concomitant Medications and Diagnostic/Surgical/Therapeutic Procedures eCRF pages.

13.1. CONCOMITANT MEDICATIONS

Medications will be coded to preferred name using ***WHO Drug Dictionary (WHODD)***. Concomitant medication use will be summarized by preferred name using the number and percentage of subjects by treatment group. Medications will be sorted alphabetically by

preferred name. Subjects with multiple occurrences of a medication in preferred name will only be counted once within each preferred name. Medication summaries will be presented by treatment group for the safety population.

Listings of all medications will be presented.

13.2. DIAGNOSTIC, SURGICAL, OR THERAPEUTIC PROCEDURES

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

14. STUDY DRUG EXPOSURE

The total extent of exposure is defined as the number of days on teduglutide during the core study and prospective observation period combined. Exposure summary will be presented by treatment group (TED/TED, NTT/TED and ANY TED only) as a numeric variable. It will also be categorized and presented in pre-defined groups by 6 weeks intervals: 0 – < 6, 6 - <12, etc.. . The overall number of cycles on teduglutide will also be summarized as a numeric variable. Finally, the number of days on teduglutide for each cycle will be summarized.

14.1. DERIVATIONS

The extent of exposure in days will be calculated as:

Extent of exposure in Extension study (weeks)

= [the sum of the durations of all the teduglutide treatment periods where the individual duration is calculated by (the last dose date of the treatment cycle X – Cycle X Day 1 + 1)] / 7.

Total exposure (Core+Extension) (weeks)

= [the sum of the durations of all the teduglutide treatment periods in weeks] and Core extent of exposure in weeks.

The extent of observation will be calculated as:

Extent of observation = (end of study visit – informed consent date of 304)/7.

15. STUDY DRUG COMPLIANCE

Study drug administration diary data will be used to measure study drug compliance. Only diary entries with "Yes" in response to the question "Was the study drug administered per instructions today?" will be deemed compliant days.

Subjects will be considered compliant overall for study drug administration if the calculated overall compliance is >= 80%. Overall and by-cycle treatment compliance will be presented for percent compliance calculations using descriptive statistics and the number and percentage of subjects entering the timeframe who are >= 80% compliant by treatment group for the safety population.

15.1. DERIVATIONS

For each treatment cycle, compliance 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:

> Percent compliance = (Total number of diary days marked "Yes" for study drug administration / Number of days on treatment) * 100

where number of days on treatment within each cycle will be calculated as (the last dose date in the treatment cycle X - the visit date of Cycle X Day 1 +1) and dose interruption days will not be excluded.

16. EFFICACY OUTCOMES

Efficacy endpoints for PS 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 last period of the last cycle for each patient will also be summarized.

The efficacy analyses will be performed on PS diary data and PS prescribed data for safety population. The descriptive statistics of efficacy outcomes will be summarized by treatment group as defined in Section 6. The listings for efficacy measures which are collected on the CRF forms will be provided.

16.1. EFFICACY ENDPOINTS

16.1.1. EFFICACY VARIABLES & DERIVATIONS

The efficacy endpoints will be analyzed in two ways: 1) based on the subject diary data (also referred to as "actual"), and 2) based on the investigator-prescribed data (referred to as "prescribed"). PS will be reported in both subject diary data and the investigator-prescribed data in the eCRF. Investigator-prescribed data are the most recent PS prescription (prescription adjustments) prior to or on the date of visit, captured in the PS adjustments eCRFs. Data collected include prescribed weekly total kilocalories, volume, number of days per week, and average hours per day. PS diary data are collected 2 weeks prior to all scheduled site visits (except at pre-treatment visit) in the Intake Diary eCRFs 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 volumes after midnight may be associated with the prior date. Data collected include actual PS total infusion duration, total volume and total kilocalories on the assigned date.

For subject who received teduglutide treatment in core studies, the baseline from core values will be used, otherwise efficacy baseline will be derived from 304 data.

Data will also be presented separately for teduglutide treatment cycles and no treatment periods.

The calculation of average daily prescribed PS volume/caloric intake normalized to weight will follow the formula below:

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

The calculation of average daily actual PS will be based on the daily support recorded in subjects' diaries within 7 days prior to the date of each scheduled visit. If more than 2 days' values in a week are missing, the average daily value will not be calculated and will be assigned as missing. The same strategy will be used to calculate all other average diary parameters. The calculation of actual PS volume normalized to weight will follow the formula below:

> Average daily value = [(sum of non-missing daily values in the diary / number of days with non-missing values)] / last available body weight prior to the visit

Baseline actual PS will be calculated using all the diary data collected within 14 days prior to the first dose or baseline visit of the core study. If more than 5 days' values in two weeks before the baseline visit the core study are missing, the baseline value will not be calculated.

16.1.1.1. ≥ 20%, 50%, and 75% Reduction in PS volume

PS volume reduction at the end of each teduglutide treatment period (Week 24 or EOT) and at all other study scheduled visits compared to the baseline [See Section 7.2 for baseline description]will be calculated using average daily values. The number and percentage of subjects who achieve at least a 20%, 50%, and 75% reduction in PS volume (mg/kg/day) at the end of each teduglutide treatment period and each NT visit will be summarized. This parameter will be summarized for both actual and prescribed data.

16.1.1.2. Change and percent change from baseline in PS volume and intake calories

Changes and percent change in prescribed and actual PS volume and calories from baseline to all the study visits will be calculated following common calculations in Section 7.7 [See Section 7.2 for baseline description]. These parameters will be summarized for both actual and prescribed data.

16.1.1.3. Complete weaning off PS

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

The analysis will summarize how many subjects achieve complete weaning off PS at the end of each teduglutide treatment period (Week 24 or EOT).

16.1.1.4. Change and percent change from baseline in hours per day and days per week of PS

Change and percent change in hours per day and days per week of PS from baseline to each study visit will be summarized.

Hours per day of actual PS for all visits except the baseline visit will be calculated as follows:

Hours per day of actual PS

= (sum of hours per day for each day that PS intake data is recorded within the 7 days prior to the visit / number of days that PS hours per day data is recorded as non-zero within the 7 days prior to the visit)

Hours per non-zero day of actual PS for all visits will be calculated as sensitivity analysis:

Hours per Non-zero day of actual PS

= (sum of hours per day for each day that PS intake data is recorded as non-zero within the 7 days prior to the visit / number of days that PS hours per day data is recorded as non-zero within the 7 days prior to the visit)

Days per week of actual PS for all visits except the baseline visit will be calculated as follows:

> Days per week of actual PS = (number of days with non-zero values for PS volume within the 7 days prior to the visit / number of days for which any PS intake data is recorded within the 7 days prior to the visit) * 7

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

The change and percent change in hours per day and days per week of PS will be summarized by ≥ 20%, ≥ 50%, and ≥ 75% reduction in PS volume.

16.1.2. ANALYSES OF EFFICACY VARIABLES

For the variables of pre-specified percent reduction in PS volume, the number and percentage of subjects will be presented by treatment group for treatment cycles and NTT periods. Baseline values, post-baseline values, change from baseline and percent change from the baseline in PS will be summarized by study visit and treatment group using descriptive statistics including number of subjects, mean, standard deviation, median, minimum and maximum.

17. HEALTH-RELATED QUALITY OF LIFE ANALYSIS

Throughout the study, health-related quality of life (HRQoL) assessments will be performed using the Pediatric Quality of Life (PedsQL) Generic Core Scales at the time points CxD1, CxD12 and CxD24 for treatment period, at 12-week intervals for NTx and at EOS.

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.

Subscale scores and summary scores will be computed separately based on subject self-report and parent report.

The baseline is defined as the assessment collected during the subject's first study period, either at the visit of Cycle 1 Day 1 for the treatment period or the assessment at the visit of first 12-week interval for the no-treatment period, as appropriate.

The HRQoL will not be included in the interim analysis.

17.1. 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 at the time points.

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).

17.1.1. VARIABLES & DERIVATIONS

Items are collected as either a 5-point Likert scale [from 0 (Never) to 4 (Almost always)] or 3-point scale [0 (Not at all), 2 (Sometimes) and 4 (A lot)] are transformed on a scale from 0 to 100. Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, and 4=0. If more than 50% of the items in the defined subscale are missing, the corresponding subscale score should not be computed. If 50% or more items are completed, impute the mean of the completed items in a defined subscale, where mean is calculated as the sum of the items over the number of items answered. If any subscale score is missing in the summary score calculation, the summary score will be missing.

- Subscale Scores
  - Physical Functioning
  - Emotional Functioning
  - Social Functioning
  - School Functioning
- Summary Scores
  - Psychosocial Health Summary Score - Sum of the items over the number of items answered in the Emotional, Social, and School Functioning Subscales
  - Physical Health Summary Score - Physical Functioning Subscale Score
  - Total Scores - Sum of all the items over the number of items answered on all the

subscales

17.2. 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. 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. 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).

17.2.1. VARIABLES & DERIVATIONS

Items are collected as a 5-point Likert scale from 0 (Never) to 4 (Almost always) which are transformed on a scale from 0 to 100. Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, and 4=0. If more than 50% of the items in the defined subscale are missing, the corresponding subscale score should not be computed. If 50% or more items are completed, impute the mean of the completed items in a defined subscale, where mean is calculated as the sum of the items over the number of items answered. If any subscale score is missing in the summary score calculation, the summary score will be missing.

- Subscale Scores
  - Physical Functioning
  - Emotional Functioning
  - Social Functioning
  - Cognitive Functioning
  - Communication
  - Worry
  - Daily Activities
  - Family Relationships
- Summary Scores

- Parent HRQL Summary Score - Sum of the items divided by the number of items answered in the Physical, Emotional, Social, and Cognitive Functioning subscales
- Family Functioning Summary Score - Sum of the items divided by the number of items answered in the Daily Activities and Family Relationships subscales
- Total Scores - Sum of all the items over the number of items answered on all the subscales

17.3. 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. Only the scales of Food and Drink Limits (6 items) and Diarrhea (7 items) will be collected in this study. The scales will be completed by either the parent or legal guardian and subject.

17.3.1. VARIABLES & DERIVATIONS

Items are collected as a 5-point Likert scale from 0 (Never) to 4 (Almost always) that are transformed to a 0 to 100 scale. Items are reversed scored and linearly transformed to a 0-100 scale as follows: 0=100, 1=75, 2=50, 3=25, and 4=0. If more than 50% of the items in the scale are missing, the corresponding scale score should not be computed. If 50% or more items are completed, impute the mean of the completed items in a scale, where mean is calculated as the sum of the items over the number of items answered.

- Symptoms Total Scales Score
  - Food and Drink Limits Scale Score
  - Diarrhea Scale Score

17.4. MISSING DATA METHODS

Missing item scales will not be imputed. The subscale scores and the total scores will be set to missing if more than 50% of the items in the scale are missing in the scale.

17.5. ANALYSIS OF HRQOL VARIABLES

Total scores, subscale scores and summary scores will be summarized by study visit and treatment group using descriptive statistics including number of subjects, mean, standard

deviation, median, minimum and maximum. Change from baseline by visit will be summarized, with subjects excluded from change from baseline summaries at the visit associated with the subject's baseline measurement.

18. SAFETY OUTCOMES

There will be no statistical comparisons between the treatment groups for safety data.

18.1. ADVERSE EVENTS

Adverse Events collected during the prospective observation period will be coded using ***Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary***. Investigator verbatim as well as preferred terms and system organ classes will be included in the listings.

Treatment-emergent adverse events (TEAEs) are defined as adverse events that started or worsened on or after the date of first dose of teduglutide in either the core study or the extension study for treatment groups TED/TED, TED/NTT, NTT/TED and ANY TED and adverse events that started or worsened on or after the baseline visit of the core study for NTT/NTT.

Adverse Events will be summarized in 3 categories: Overall, Prior Teduglutide, and After Teduglutide.

For events that start or worsen on the date of first dose, any available start time will be compared to the time of first dose for the treated subjects.

See APPENDIX 2 for handling of partial dates for AEs. 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 number of subjects within each of the categories described below will be provided as specified in the templates. Adverse events will be summarized using descriptive statistics (e.g., number and percentage of subjects). The number of events will also be presented except for summaries by highest category. The summary will include any TEAE, severity of TEAEs (highest category), investigator assessment of relationship of TEAEs to study drug, treatment-emergent serious AEs (TESAEs), investigator assessment of relationship of TESAEs to study drug, TEAEs leading to study drug discontinuations, TEAEs leading to study discontinuations and TEAEs leading to death. Adverse events will be tabled separately for teduglutide treatment cycles and no treatment periods according to AE start date. In addition, no treatment periods will be further subset as prior to any teduglutide exposure and following teduglutide exposure.

Listings will include both TEAEs and Non-TEAEs. And, Listings will be provided for serious

adverse events, adverse events leading to death, adverse events leading to discontinuation of study drug, adverse events leading to discontinuation of study and adverse events of special interest. Listings will indicate whether an AE is treatment emergent or not. Information for severe adverse events that are graded according to CTCAE criteria will only be presented in the listings.

18.1.1. ALL TEAEs

Incidence of TEAEs will be presented by System Organ Class (SOC) and Preferred Term (PT) for all TEAEs, related TEAEs, TESAEs, and related TESAEs. Incidence will also be presented by SOC and PT for severity and maximum severity. Summaries by SOC and PT will present SOC in alphabetical order and PT within the SOC in descending order of incidence in the any teduglutide (ANY TED) treatment group.

18.1.1.1. Severity

Severity is categorized as mild, moderate, or severe. Adverse events with a missing severity will be classified as severe. If a subject reports a TEAE more than once within that SOC/PT, summaries by severity will only provide the highest severity classification of the subject for the corresponding incidence summaries by SOC/PT.

18.1.1.2. Relationship to Teduglutide

Relationship, as indicated by the Investigator, is classed as *"not related"* or *"related"*. TEAEs with a missing relationship to teduglutide will be regarded as "related" to teduglutide. TEAE summaries by relationship will exclude the NTT/NTT treatment group.

18.1.2. 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) for the SHP633-304 extension study through last study visit (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 drugs. A listing of SAEs will be presented as well.

18.1.3. AEs LEADING TO DISCONTINUATION OF STUDY DRUG

AEs leading to temporary or permanent discontinuation of study drug will be identified by the

"Drug Withdrawn" response for action taken with study treatment in the Adverse Events Form of the eCRF.

A listing will be provided for AEs leading to discontinuation of study drug.

18.1.4. AEs Leading to Discontinuation of Study

AEs leading to permanent discontinuation of study will be identified by the "Yes" response for the question "Did this adverse event cause the subject to be discontinued from the study?" in the Adverse Events Form of the eCRF.

A listing will be provided for AEs leading to permanent discontinuation of study.

18.1.5. 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.

18.1.6. Adverse Events of Special Interest

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

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

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

A review of preferred terms will be performed by a medical reviewer prior to interim and final analysis, with the identified events of special interest being documented prior to the analysis data transfer. The AEs of special interest will be presented in a listing.

18.2. Laboratory Evaluations

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. During the teduglutide treatment period, subjects will also have safety labs within approximately 5-7 days after a PS adjustment. 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. Laboratory evaluations to be included in the tables or listings are presented in the lab test table (Table B) below.

Table B: Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis
Hemoglobin	Albumin	Prothrombin Time	Ur Blood*
Hematocrit	Alkaline Phosphatase	Prothrombin International Normalized Ratio (INR)	Ur Glucose*
Platelets	Alanine Aminotransferase (ALT)		Ur Microscopic*
Erythrocytes	Aspartate Aminotransferase (AST)		Ur pH
RBC Morphology*	Amylase		
Leukocytes	Lipase		Ur Protein
Neutrophils	Bicarbonate		
Lymphocytes	Bilirubin		Ur Specific Gravity
Monocytes	Direct Bilirubin		Ur Leukocytes
Eosinophils	Indirect Bilirubin		
Basophils	Blood Urea Nitrogen		
Neutrophils/Leukocytes	Calcium		
Lymphocytes/Leukocytes	Chloride		
Monocytes/Leukocytes	Cholesterol		
Eosinophils/Leukocytes	Creatinine		
Basophils/Leukocytes	C Reactive Protein		
	Glomerular Filtration Rate (GFR) Schwartz formula		
	Glucose		
	Gamma Glutamyl Transferase (GGT)		
	Lipase		
	Magnesium		
	Phosphorus		
	Potassium		
	Sodium		
	Triglycerides		
	Uric Acid		

Note: * lab tests with categorical results.

Lab data will be presented in SI units. The summaries will be based on central lab results only.

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

The following summaries will be provided for hematology, clinical chemistry and selected urinalysis laboratory data with quantitative results:

- Actual and change from baseline at Cycle x Day 1, Cycle x Week 12, Cycle x Week 24, each NTx visit and End of Study
- Shift from baseline according to normal range criteria at Cycle x Day 1, Cycle x Week 12, Cycle x Week 24, each NTx visit, and End of Study
- Incidence of markedly abnormal values according to criteria defined in section APPENDIX 3
- Listing of subjects meeting markedly abnormal criteria
- Change from baseline will not be calculated for lab values with drastically different normal ranges between core and extension.

18.2.1. LABORATORY REFERENCE RANGES AND MARKEDLY ABNORMAL CRITERIA

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.

In addition to the high and low quantitative laboratory assignments (as identified by means of the laboratory reference ranges), markedly abnormal quantitative safety (and other) laboratory assessments will also be identified in accordance with the predefined markedly abnormal criteria as presented in APPENDIX 3.

The number and percentage of subjects whose post-baseline results qualify as markedly abnormal will be summarized by treatment group and the parameter. A listing will present all values for a subject and laboratory parameter if at least one post-baseline value for that subject and parameter is markedly abnormal.

Laboratory results will also be included in appendix data listings for each lab panel (chemistry, hematology, coagulation and urinalysis) by treatment, subject, visit and parameter. Values outside the normal range will be flagged. Local lab test results will only be presented in

appendix data listings. Categorical test results, coagulation and pregnancy results (B-hCG, Qualitative and B-hCG, Quantitative) also will only be included in data listings.

18.3. PREGNANCY TESTING

A serum pregnancy test is performed on all females of childbearing potential (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 administrated at all other visits according to the study schedules. The pregnancy test result (Positive, Negative) will be presented in a listing.

18.4. ANTIBODIES TO TEDUGLUTIDE

Blood samples for antibodies will be drawn for all the teduglutide-exposed subjects. The sample drawn on CxD1 must be drawn prior to administration of the first dose of teduglutide. Once the subject has started teduglutide treatment (CxW12 and CxW24), samples must be drawn at least 14 hours after dosing.

At each visit, all subjects will be assessed for a screening anti-drug antibodies test. For those subjects who test positive for screening anti-drug antibodies, a confirming anti-drug antibodies test will be given. Either screening or confirmed anti-drug antibodies test shows negative result, antibodies to teduglutide is considered negative. If both tests show positive result, antibodies to teduglutide is consider positive. Subjects who test positive for antibodies to teduglutide will also be tested for titer of anti-drug antibodies and neutralizing anti-drug antibodies. 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.

The number and percent of subjects with an antibody finding (Antibodies to Teduglutide Negative/Positive, Neutralizing Antibodies Present/ No Neutralizing Antibodies Present) will be summarized at CxD1, CxW12, CxW24, CxW28, each NTx, and EOS. Non-specific antibodies will be categorized as Negative.

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

18.5. GASTROINTESTINAL-SPECIFIC TESTING

Fecal occult blood testing (FOBT) must be performed on all subjects at the pre-treatment visit (Px), CxW12, and CxW24 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). The colonoscopy or sigmoidoscopy will be performed in response to positive FOBTs.

GI-specific testing will be summarized for the teduglutide treatment cycles only. The clinically significant abnormal results will be presented in a data listing. Fecal occult blood testing will be summarized as 'Negative', 'Positive, not clinically significant', 'Positive, clinically significant'. The results of colonoscopy or sigmoidoscopy will be reported as 'Normal', 'Abnormal, not clinically significant', or 'Abnormal, clinically significant'. All FOBT, along with subsequent colonoscopy or sigmoidoscopy testing, will be presented in an appendix listing.

18.6. 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.

18.7. 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)
- Height or length (cm)
- Head circumference (cm) for subjects $\leqslant$ 36 months of age

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

- BMI (kg/m2)
- Height Z-score
- Weight Z-score
- BMI Z-score
- Head Circumference Z-score

Descriptive statistics will be used to summarize vital signs measurements and derived BMI in

actual value and change from baseline for each treatment group by age group (age stratification used for randomization in the core studies TED-C14-006 or SHP633-301: <1 year, 1-<12 years, 12-<17 years and 17-<18 years and overall) at study site visits where associated parameters are collected. Z-scores of vital signs by site visits will also be summarized and presented in Mean ± SE Plot. A listing will also be provided.

18.7.1. VITAL SIGNS SPECIFIC DERIVATIONS

- BMI

BMI = 10000* Body weight (kg)/body height $(cm)^2$, where both body weight and body height data are available at the same scheduled visit

- Height, Weight and BMI Z-scores

Official and validated SAS programs created by Centers for Disease Control and Prevention (CDC) will be used to calculate the Z-scores (standard deviations) for a child's sex and age (up to 20 years of age) for BMI, weight, and height based on the CDC growth charts for children age 2 years and older and the WHO growth charts for infants and children < 2 years of age. For more information on the CDC SAS programs, see http://www.cdc.gov/growthcharts/computer_programs.htm.

Z-scores are calculated as the formula below:

Z-score= [((observed value / M) ^ L) – 1] / (S * L)

In which 'observed value' is the child's height, weight, head circumference or derived BMI. The L, M, and S values vary according to the child's sex and age. For more information on the LMS method, see http://www.ncbi.nlm.nih.gov/pmc/articles/PMC27365/.

18.8. FECAL AND URINE OUTPUT

Urine and stool output data is recorded over a 48 hour period of PS stability before every scheduled site visit and within 1 week of implementing any PS 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. Values will not be calculated if the urine output is 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 typical stool form score using Bristol Stool Form Scale, 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 and the average typical stool form score 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 for the average daily urine output.

The change in average daily output for fecal and urine output from baseline to each scheduled visit of treatment periods, as well as at 12-week intervals of NTx, will be presented by treatment group using descriptive statistics. A listing will also be provided.

19. DATA NOT SUMMARIZED OR PRESENTED

Any information not described will not appear in the interim analysis but may contribute to datasets that support listings for the final study report.

Other data collected in eCRF, Interactive Voice Response System (IVRS) or any other clinical trial data collection system which is not described above will be presented in the appendix listings.

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

- **Statistics Presentation**

For the by-time-point tables, the number of subjects at each timepoint (n) represents the number that had a valid result for a given parameter at that timepoint.

The default summary statistics presented in the table shells for continuous variables include n, mean, standard deviation, median, minimum, and maximum. For efficacy continuous variables, SE, Q1, Q3 will be added. For categorical variables, the count (n) and percent (%) are the default statistics; unless otherwise stated or the associated number of subjects for the corresponding time point is provided, the denominator for percentages is N (the number of subjects in the treatment group/analysis set). Note that for any summary by subgroups (e.g., by sex), the denominator is the number of subjects in that subgroup/treatment group/analysis set. For most safety tables the study teams should use the default statistics; the study team should carefully consider and give sufficient justification prior to requesting the use of other summary statistics. Percentages will be reported to 1 decimal place, except when the

percentage equals exactly 100 where it will be displayed as an integer (100). For zero, only count and no percentage will be displayed.

- **Alignment**

Output should be aligned so that in the body of the table, where applicable, text is left-justified within a cell, stats output is aligned centrally within a cell and lined up by decimal point.

Handling of missing values: In listings, missing values for numerical data will be reported as a period "." and missing values for character data as a blank " ". In the summary tables for categorical data, "Missing" will always be displayed as a category to represent missing data, where applicable. The default denominator will be all subjects in the analysis set unless otherwise specified in the SAP. For both tables and listings where there are no observations (and hence there would be no output), the table/listing should be produced with all titles and footnotes as per its shell, but with the text showing no observations in the body of the output.

- **Decimal Places and Rounding Rules**
  - For measures of median and mean, use 1 decimal place beyond those used for the measurement.
  - For measures of standard deviation and standard error, use 2 decimal places beyond those used for the measurement.
  - For measures of minimum and maximum values, use the same number of decimal places as those used for the measurement.
  - >=5 is rounded up away from zero, whereas <5 is rounded down toward zero to account for rounding of negative numbers.
  - BMI should be rounded to 1 decimal place for reporting.
  - Derived questionnaire scores, and other similar efficacy parameters recorded as integers, should be rounded to 1 decimal place for reporting.
- **Presentation of Treatment Groups**

Tables will present NTT/NTT group first, followed by NTT/TED, TED/NTT and TED/TED. When required, a column for all subjects who exposed to teduglutide in core study in the extension study will be included and it will be labeled "ANY TED". The subjects will be grouped based on the treatment they received in the core studies TED-C14-006 or SHP633-301 (teduglutide exposed and non-exposed) and prospective period (teduglutide exposed and non-exposed). For teduglutide treatment period tables, only NTT/TED and TED/TED will be presented. If the number of treatment groups dictates that not all can fit on 1 page, then, unless specified in the corresponding "General considerations", it will be left to the discretion of the shell author, following discussions with study team, as to how these will be presented. For example, some

of the treatment groups may be presented in a separate table. If the study is to be summarized by dose group rather than treatment group, then the nomenclature "Actual Dose" will be used in place of "Treatment Group" throughout. If presenting subgroups, TFL4Shire recommends that sub-headers are added so that a tabulation is repeated by subgroup (rather than adding extra columns in the table to show the subgroups). These should be ordered per the CRF decode e.g. 1=Male, 2=Female.

APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings. The reference start date for adverse events (excluding those event entered as part of the medical history) will be the first tedugludtide dose date, if the subject entered a teduglutide treatment period during the study, otherwise the start date of the first non-teduglutide period. The reference start date for medications will be the informed consent date. The reference end date will be the EOS date.

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 consent date if AE start year and month < the year and month of the reference start date;

START DATE	STOP DATE	ACTION
		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

START DATE	STOP DATE	ACTION
		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 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.

IMPUTATION OF PARTIAL MEDICATION DATA

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.

START DATE	STOP DATE	ACTION
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.

APPENDIX 3. MARKEDLY ABNORMAL LABORATORY CRITERIA

Lab Parameter	Unit	Lower Limit Criteria	Upper Limit Criteria
Chemistry			
Albumin	g/L	<20	>68
Alkaline Phosphatase	U/L		>5 x ULN
Alanine Aminotransferase (ALT)	U/L		>8 x ULN
Aspartate Aminotransferase (AST)	U/L		>8 x ULN
Amylase	U/L		>3 x ULN
Lipase	U/L		>3 x ULN
Bilirubin Total	umol/L		>3 x ULN
Direct Bilirubin	umol/L		>34.208
Blood Urea Nitrogen	mmol/L		>12.495
Calcium	mmol/L	<1.5	>3
Creatinine	umol/L		>132.6 if age < 10 y; >150.28 if age 10-<13 y; >176.8 if age 13-<16 y; >221 if age 16+
C Reactive Protein	mg/L		>=100
Glucose	mmol/L	<2.22	>13.875
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	

APPENDIX 4. TABLE, FIGURE AND DATA LISTING SHELLS

TABLE AND FIGURE SHELLS

See separate file.

DATA LISTING SHELLS

See separate file.