STATISTICAL ANALYSIS PLAN

NCT Number: NCT02949362

Study Title: A Retrospective and Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Subjects with Short Bowel Syndrome Who Completed TED-C13-003

Study Number: SHP633-303

SAP Version and Date:

SAP – Retrospective Data: 13 Oct 2017
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INTERIM STATISTICAL ANALYSIS PLAN

(RETROSPECTIVE DATA)

SHP633-303

A Retrospective and Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Subjects with Short Bowel Syndrome Who Completed TED-C13-003

AUTHOR: [redacted]

VERSION NUMBER AND DATE: FINAL V1.0, 13OCT2017

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Retrospective Statistical Analysis Plan Final V1.0 (Dated 13OCT2017) for Protocol SHP633-303

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Draft 1.0	19May2017	[redacted]	Not Applicable – First Version
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1. LIST OF ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Events of Special Interest
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
EOS	End of Study
ICF	Informed Consent Form
IVRS	Interactive Voice Response System
MedDRA	Medical Dictionary for Regulatory Activities
PS	Parenteral Support
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBS	Short Bowel Syndrome
SOC	System Organ Class

2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of retrospective data for Protocol SHP633-303. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This interim statistical analysis plan (SAP) is based on protocol amendment 2, dated 17 March 2017.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of this interim analysis is to evaluate the retrospective safety and tolerability data of teduglutide treatment in the SHP633-303 study, which enrolled pediatric subjects with Short Bowel Syndrome (SBS) who completed TED-C13-003.

3.2. SECONDARY OBJECTIVE

The secondary objective of this interim analysis is to evaluate the efficacy data of teduglutide treatment in the SHP633-303 study, which enrolled pediatric subjects with SBS who completed TED-C13-003.

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

This is a Phase 3, retrospective and prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects who completed the TED-C13-003 study (the core study). At the time of entry into the TED-C13-003 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 the core study, pediatric subjects were entered into one of three teduglutide dosing cohorts: 0.0125 mg/kg/day, 0.025 mg/kg/day, or 0.05 mg/kg/day, based on the timing of their enrollment in the study, or a

standard of care SOC cohort. The teduglutide dosing cohorts were filled in a sequential manner.

Approximately 40 subjects who completed the core study are expected to enroll in this extension study (SHP633-303). When signing the informed consent form (ICF) for this study, subjects can choose to participate in both retrospective and prospective portions of the study or only retrospective data collection. After informed consent/assent is obtained, study eligibility will be assessed for all subjects.

To evaluate efficacy and safety from the time subjects completed the core study to the time they enter this extension study, retrospective data collection is planned for this study. The retrospective data collection will consist of specific safety and efficacy measures that were completed in the course of the subject's standard medical care between the date of the TED-C13-003 end of study (EOS), which is the final scheduled visit 4 weeks after the end of treatment, and the date the ICF (and if applicable, informed assent) is signed for this study. Retrospective PS and growth data will be captured in 12-week intervals, with the first 12-week interval beginning at the TED-C13-003 EOS. All available retrospective data should be captured in the corresponding electronic case report forms (eCRFs). The following data will be collected:

- Teduglutide use (as prescribed)
- Parenteral support (as prescribed)
- Growth (height, head circumference [up to 36 months of age], weight)
- End dates for adverse events (AEs) ongoing at the time of TED-C13-003
- All nonserious AEs related to teduglutide
- All adverse events of special interest (AESIs)
- All serious adverse events (SAEs)

In addition to this retrospective data collection, prospective study assessments of safety and efficacy will be completed as a part of this study. The prospective data analysis will be described in the prospective SAP for this study.

4.2. SCHEDULE OF EVENTS

The assessments completed as part of the retrospective data collection period can be found in Table 1-1 and Section 7.1.1 of the protocol. For subjects who only consent to retrospective data collection, these procedures are all that will be completed.

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 for Retrospective Data
- Final Analysis

The interim analyses identified in this SAP using retrospective data will be performed by Quintiles Biostatistics following sponsor authorization of this statistical analysis plan and analysis sets. The final analyses including prospective data will be performed following the sponsor-authorized SAP and analysis sets for the CSR.

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.

6.1. ALL RETROSPECTIVE SUBJECTS [RETRO]

Retrospective subjects (RETRO) are all subjects who consented to the SHP633-303 study and provided data for the retrospective portion of the protocol. Subjects will be classified in treatment groups based on whether they received teduglutide in the core study TED-C13-003 and/or during the retrospective observation period in this study:

- TED/NTT – includes subjects who took teduglutide in the core study but not during the retrospective period of this study;
- TED/TED - includes subjects who took teduglutide in the core study and during the retrospective period of this study;
- ANY TED – includes subjects who took any teduglutide in the core study or during the retrospective period of this study.

No treatment-naïve patients in core study TED-C13-003 enrolled in the extension study SHP633-303, so the treatment groups associated with the NTT in the core study are removed

from the statistical analysis.

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 of retrospective period is defined as the final scheduled visit of TED-C13-003 for the safety variables, while reference start date of core study is defined as the baseline visit for the growth and efficacy variables.

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

Unless otherwise specified, baseline is defined as baseline visit in the core study TED-C13-003.

7.3. WINDOWING CONVENTIONS

Retrospective PS and growth data will be captured in 12-week intervals, with the first 12-week interval beginning at the TED-C13-003 EOS. There will be no windowing of scheduled intervals based on study day.

7.4. STATISTICAL TESTS

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

Continuous variables, including those assessed on a discrete scale, will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

7.5. 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.

7.6. 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. All available data will be included in the safety analysis.

8.4. MULTIPLE COMPARISONS/ MULTIPLICITY

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 for retrospective data.

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 based on Shire internal standards TFLs4ShireFinalV6.0. The format and content of the summary tables, figures and listings (TFLs) will be provided by Quintiles Biostatistics.

10. ENROLLMENT

All subjects who provide informed consent for retrospective data collection period will be accounted for in this interim analysis. The subjects will be encouraged to consent to participate in the prospective period of the study. However, subjects may consent to retrospective data collection only.

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-C13-003.
- Age Group – Age is categorized in pre-defined groups: < 13, 13 to <17
- Sex
- Race
- Ethnicity

- Weight Z-score at baseline of TED-C13-003
- Height Z-score at baseline of TED-C13-003
- Body Mass Index (BMI) Z-score at baseline of TED-C13-003
- Head Circumference Z-score at Baseline (only for subjects who are <= 36 months of age) of TED-C13-003

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 14.2.1.

12. EFFICACY OUTCOMES

Efficacy analyses for PS based on 12-week intervals prescribed data during the retrospective observation period will be performed. The descriptive statistics of efficacy outcomes will be summarized by treatment group as defined in Section 6.1. The listings for efficacy measures which are collected on the eCRF forms will be provided.

12.1. EFFICACY ENDPOINTS

12.1.1. EFFICACY VARIABLES & DERIVATIONS

PS investigator-prescribed data will be reported in the Parenteral Support (Retrospective Period) and Historical Teduglutide Treatment (Retrospective Period) eCRF. Data collected include weekly volume, calories, average days per week, and hours per day of prescribed PS. Prescribed data are the last representative PS prescription during each 12-week interval throughout the retrospective period, with the first 12-week interval beginning at the TED-C13-003 EOS visit, and at the beginning and end of any teduglutide treatment. Any tedgulutide was used in the 12-week interval will be indicated in the summary listing. The start date and end date of each 12-week interval will be derived based on the end of study date of TED-C13-003. The start date of the first 12-week interval will be the end of study date of TED-C13-003 + 1. The end date of the interval will be the start date of the interval + 12*7. If the teduglutide

use period (from prescription start date to prescription stop date) falls into any 12-week intervals, the 12-week intervals will be mark 'Yes' in the teduglutide used column.

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

Average daily value = (prescribed weekly PS parameter / 7) / last available weight prior to the 12-week interval.

12.1.1.1. ≥ 20% Reduction in PS volume

PS volume reduction at each 12-week interval compared to the baseline of the core study TED-C13-003 will be calculated using average daily values. The number and percentage of subjects who achieve at least a 20% reduction in PS volume (mL/kg/day) at each 12-week interval during the retrospective observation period will be summarized.

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

Changes and percent change are calculated following common calculations in Section 7.5. The baseline is defined as the PS prescribed data collected at the baseline of the core study TED-C13-003.

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

Change and percent change from baseline in hours per day and days per week of PS during retrospective observation period will be summarized using the non-missing prescribed value using descriptive statistics.

12.1.2. ANALYSES OF EFFICACY VARIABLES

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

13. STUDY DRUG EXPOSURE

The extent of exposure is defined as the number of days on teduglutide during the core study and retrospective observation period combined. Exposure summary will be presented by treatment group (TED/NTT, TED/TED and ANY TED) as a numeric variable. It will also be categorized and presented in pre-defined groups: 0-<12, 12-<24, 24-<48, 48-<72, 72-<96, >=96 weeks.

13.1. DERIVATIONS

The extent of exposure in weeks will be calculated as:

> Extent of exposure (weeks) = [the exposure days in the core study calculated as (last dose date – first dose date + 1) + the sum of all the teduglutide prescription durations during the retrospective period where the individual duration is calculated by (prescription stop date – prescription start date +1)] / 7.

14. SAFETY OUTCOMES

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

14.1. ADVERSE EVENTS

Adverse Events collected during the retrospective observation period will be coded using ***Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, Version 19.1***. Investigator verbatim as well as preferred terms and system organ classes will be included in the listings.

An overall summary of number of subjects within each of the categories described below will be provided as specified in the templates. Adverse events that occurred during the retrospective observation period 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 AE, severity of AEs (highest category), investigator assessment of relationship of AEs to teduglutide, SAEs, and investigator assessment of relationship of SAEs to teduglutide.

Listings will include all the AEs and SAEs during the retrospective observation period. The ongoing AEs at the end of TED-C13-003 with the end dates are collected in the CRF and will be

listed only.

14.1.1. ALL AEs REPORTED DURING THE RETROSPECTIVE PERIOD

Incidence of AEs will be presented by System Organ Class (SOC) and Preferred Term (PT) for all AEs reported during the retrospective period per protocol requirement, related AEs, SAEs, and related SAEs. 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 treatment group.

14.1.1.1. Severity

Severity is categorized as mild, moderate, or severe. Adverse events with a missing severity will be classified as severe. If a subject reports an AE 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.

14.1.1.2. Relationship to Teduglutide

Relationship, as indicated by the Investigator, is categorized as *"not related"* or *"related"*. A *"related"* AE is defined as an AE with a relationship of "related" to teduglutide. AEs with a missing relationship to teduglutide will be regarded as "*related"* to teduglutide.

14.1.2. SERIOUS ADVERSE EVENTS

Serious adverse events are those events recorded as "Serious" on the Adverse Events (Retrospective Period) Form of the eCRF. Any SAE that occurs from the time of the completion of core study TED-C13-003 through the signing of the retrospective ICF for the extension study will be captured. A summary of SAEs by SOC and PT will be prepared. A listing of SAEs will be presented as well.

14.2. GROWTH DATA

The last representative value for height and weight during each 12-week interval throughout the retrospective observation period will be captured in the Growth Data (Retrospective Period) form of eCRF as well as the head circumference for subjects 36 months of age and younger at the time the data was collected.

The following growth data will be reported for retrospective observation period:

- Height (cm)
- Weight (kg)
- Head circumference (cm) for subjects ≤ 36 months of age

The following parameters will be derived during each 12-week interval:

- BMI (kg/m^2) [when both height and weight are available in the interval]
- Height Z-score
- Weight Z-score
- BMI Z-score
- Head circumference Z-score for subjects ≤ 36 months of age

Descriptive statistics will be used to summarize growth data and derived parameters in actual value and change from baseline at 12-week intervals where associated parameters are collected. A mean ± SE plot and a data listing will also be provided.

14.2.1. GROWTH DATA 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 interval

- Height, Weight, Head Circumference 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, height, and head circumference 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/.

15. DATA NOT SUMMARIZED OR PRESENTED

Any information not described will not appear in the interim analysis but may contribute to datasets that support 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

SHIRE OUTPUT STANDARDS – TFLS4SHIREFINALV6.0

Outputs will be presented according to Shire output standards document TFLs4ShireFinalV6.0.

General considerations which are applicable to the study are summarized as following:

- **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 TFLs4Shire table shells for continuous variables include n, mean, standard deviation, median, minimum, and maximum. 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 TED/NTT, TED/TED, and ANY TED. The subjects will be grouped based on the treatment they received in the core study TED-C13-003 (teduglutide exposed) and retrospective period (teduglutide exposed and non-exposed). 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 presenting subgroups, Shire 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. TABLE, FIGURE AND DATA LISTING SHELLS

TABLE AND FIGURE SHELLS

See separate file.

DATA LISTING SHELLS

See separate file.

STATISTICAL ANALYSIS PLAN

(PROSPECTIVE DATA)

SHP633-303

A Retrospective and Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Pediatric Subjects with Short Bowel Syndrome Who Completed TED-C13-003

AUTHOR: [redacted]

VERSION NUMBER AND DATE: DRAFT V1.2, 16JAN2018

STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Draft V1.2 (Dated 16JAN2018) for Protocol SHP633-303

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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.

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Draft 1.2	16Jan2018	[redacted]	General Edits

TABLE OF CONTENTS

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
CSR	Clinical Statistical Report
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
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 SHP633-303. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol amendment 2, dated 17 March 2017.

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-C13-003.

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-C13-003.

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

This is a Phase 3, retrospective and prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in pediatric subjects who completed the TED-C13-003 study (the core study). At the time of entry into the TED-C13-003 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 the core study, pediatric subjects were entered into one of three teduglutide dosing cohorts: 0.0125 mg/kg/day, 0.025 mg/kg/day, or 0.05 mg/kg/day, based on the timing of their enrollment in the study, or a standard of care SOC cohort. The teduglutide dosing cohorts were filled in a sequential manner.

Approximately 40 subjects who completed the core study are expected to enroll in this extension study (SHP633-303). When signing the informed consent form (ICF) for this study, subjects can choose to participate in both retrospective and prospective portions of the study or only retrospective data collection. After informed consent/assent is obtained, study eligibility will be assessed for all subjects.

Subjects who previously received teduglutide during TED-C13-003, as well as subjects who were in the standard of care treatment group, may be eligible to receive repeat doses of teduglutide 0.05 mg/kg subcutaneous (SC) once daily injection in this extension study. 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 once daily, 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

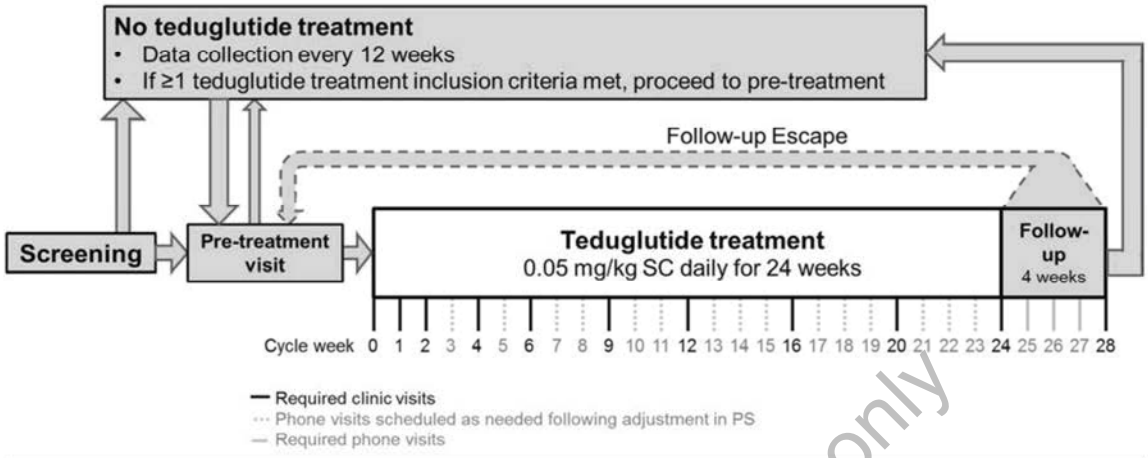

Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pre-treatment visit at any time in order to assess eligibility for teduglutide therapy. Eligible subjects will enter a 28-week teduglutide 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 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 of prospective data is conducted to support the sNDA submission, the results of which will be based on the defined treatment groups (See Section 6).

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 by Quintiles Biostatistics following 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 (CSR).

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 study TED-C13-003 (as 0.0125 mg/kg/day, 0.025 mg/kg or 0.05 mg/kg) and/or during the prospective observation period in this study:

- TED/NTT – includes subjects who took teduglutide in the core study but not in the extension study;
- TED/TED – includes subjects who took teduglutide in the core study and in the extension study;
- ANY TED – includes subjects who took teduglutide in either the core study or in extension study.

No treatment-naïve patients in core study TED-C13-003 enrolled in the extension study SHP633-303, so the treatment groups associated with the NTT in the core study are removed from the statistical analysis.

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 enrolled subjects who provided informed consent for the prospective portion and met all 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. In addition, Day of Teduglutide Treatment will be calculated from the date of first dose of Teduglutide following signing of informed consent for the core study.

Reference start date of prospective period is defined as the start of the first cycle within the study, either treatment on Cycle 1 Day 1 for the teduglutide treatment period or the first date of the NTT period of SHP633-303. Note that the reference start date of core study TED-C13-003 is defined as the baseline visit of the extension study SHP633-303 for the efficacy variables. 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

Unless otherwise specified, baseline is defined as the last non-missing measurement on or prior to baseline visit in the core study TED-C13-003.

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 contribute to data assigned to subsequent visits.

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

7.4. STUDY CYCLE CONVENTIONS

Visits will be summarized within the associated pretreatment period or treatment cycle or no treatment period. For teduglutide treatment cycles, 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 NTT periods, NTx data will be collected approximately every 12 weeks. Data for teduglutide treatment periods and NTT periods will be presented in separate tables.

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 to week 24 visits and within two days of the follow-up visits week 25 to week 28 (EOS). 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 (EOT) visits with 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. EOT visits, if occurring differently from week 24 will be tabled as a separate visit.

7.6. STATISTICAL TESTS

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

Continuous variables, including those assessed on a discrete scale, will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

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. MULTI-CENTER 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 for prospective data.

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 based on Shire internal standards TFLs4ShireFinalV6.0. The format and content of the summary tables, figures and listings (TFLs) will be provided by Quintiles Biostatistics.

10. DISPOSITION AND WITHDRAWALS

All subjects who provide informed consent for prospective data collection 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. 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-C13-003
- 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-C13-003
- Height Z-score at baseline of TED-C13-003
- Body Mass Index (BMI) Z-score at baseline of TED-C13-003

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

11.1. DERIVATIONS

- BMI (kg/ m^2) = 10000*weight (kg)/ height $(cm)^2$
- Z-score of weight, height, and BMI 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-C13-003 core study and will consist of the following:

- ongoing adverse events at the time of core study completion
- new medical conditions not related to SBS since core study participation
- Updates to a 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 frequency 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-C13-003 study, that information (updated SBS history) will be collected. The value at the baseline visit of the TED-C13-003 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 and 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 overall 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, TED/NTT and ANY TED only) as a numeric variable. It will also be categorized and presented in pre-defined groups: 0-<12, 12-<24, 24-<48, 48-<72, 72-<96, 96-<120, 120-<144, 144-<168, >=168 weeks. The overall number of cycles on teduglutide will also be summarized as a numeric variable. Finally, the number of days on teduglutide for each prospective period cycle will be summarized.

14.1. DERIVATIONS

The overall extent of exposure in weeks will be calculated as:

> Extent of exposure (weeks) = [the exposure days in the core study calculated as (last dose date – first dose date + 1) + the sum of the durations of all the teduglutide treatment periods where the individual duration is calculated by (the last treatment visit of the treatment cycle X – Cycle X Day 1 + 1)] / 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 compliance is >= 80% for each treatment period. 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 and overall, 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 visit 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 cycle (Week 24 or EOT), and at each study visit, relative to the baseline of the core study (TED-C13-003). 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 prior the date. Data collected include actual PS total infusion duration, total volume and total kilocalories on the assigned date.

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 actual 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 are missing in two weeks before the baseline visit the core study, the baseline values are missing.

16.1.1.1. 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 of the core study TED-C13-003 will be calculated using average daily values. The number and percentage of subjects who achieve at least a 20% reduction in PS volume (mg/kg/day) at the end of each teduglutide treatment period during the prospective observation period will be summarized. Similar analysis will be done for 50% and 75% reduction in PS volume. 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 intake calories from baseline to all the study visits are calculated following common calculations in Section 7.7. The baseline is defined as the PS data collected at the baseline of the core study TED-C13-003. These parameters will be summarized for both actual and prescribed data.

16.1.1.3. Complete weaning off PS at EOT

A subject will be considered to have achieved independence from PS (completely weaned off PS) at the end of each teduglutide treatment period (Week 24 or EOT) 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 of 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 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.

16.1.1.5. Change in hours per day and days per Week PN/IV Support from Baseline to End of Treatment within a cycle by Percent Reduction in PN/IV Volume

For ≥ 20%, ≥ 50%, and ≥ 75% reduction in PS volume from Baseline to End of Treatment within a cycle, Change and percent change in hours per day and days per week of PS will be summarized.

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

Health-Related Qualify of Life Analysis is not applicable for the Interim 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. 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. These analyses will not be presented for the Interim Analysis.

17.1. PEDIATRIC QUALITY OF LIFE (PEDSQL™) GENERIC CORE SCALE, 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 (PEDSQL™) FAMILY IMPACT MODULE , 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) 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 (PEDSQL™) GASTROINTESTINAL SYMPTOMS MODULE, 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 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 first dose of teduglutide treatment in the core study TED-C13-003.

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 for both TED and NNT cycles. Adverse events will be summarized for treatment cycles and no treatment periods, and for the entire on study time interval as well.

Listings will include both TEAEs and Non-TEAEs (unless specified otherwise and excluding adverse events which began during the core study that did not worsen after the start of this study) and 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 adverse events that satisfy the dose interruption criteria of CTCAE Grade 3 and 4 will only be presented in the listings.

18.1.1. ALL TEAEs

Incidence of TEAEs will be presented by SOC and PT for all TEAEs, related TEAEs, TESAEs, and related TESAEs. Incidence will also be presented by SOC and PT for highest 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.

18.1.1.3. 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 (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.

18.1.2. 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.

18.1.3. 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.

18.1.4. 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.

18.1.5. 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		Ur Osmolality
Leukocytes	Lipase		Ur Protein
Neutrophils	Bicarbonate		Ur Sodium
Lymphocytes	Bilirubin		Ur Specific Gravity
Monocytes	Direct Bilirubin		Ur Leukocytes
Eosinophils	Indirect Bilirubin		
Basophils	Blood Urea Nitrogen		
Neutrophils/Leukocytes	Calcium		

Lymphocytes/Leukocytes Monocytes/Leukocytes Eosinophils/Leukocytes Basophils/Leukocytes	Chloride Cholesterol Creatinine 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, every 12 weeks in the NTTx 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, every 12 week in the NTTx and End of Study
- Incidence of markedly abnormal values according to criteria defined in section APPENDIX 3
- Listing of subjects meeting markedly abnormal criteria

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, 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. Subjects who test positive for antibodies to teduglutide will also be tested for neutralizing antibody. Subjects who have been previously treated with teduglutide, and who test positive for antibodies to teduglutide, will have follow-up blood draws for antibodies to teduglutide every 12 weeks while on study until a negative result is

obtained.

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 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)

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

- BMI (kg/m2)
- Height Z-score
- Weight Z-score
- BMI 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 (<1, 1-<12, 12-<17, 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 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.

For outcomes where baseline values are available, 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

SHIRE OUTPUT STANDARDS – TFLS4SHIREFINALV6.0

Outputs will be presented according to Shire output standards document TFLs4ShireFinalV6.0.

General considerations which are applicable to the study are summarized as following:

- **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 TFLs4Shire table shells for continuous variables include n, mean, standard deviation, median, minimum, and maximum. 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 TED/NTT group first, followed by TED/TED. When required, a column for all subjects who exposed to teduglutide in core study or retrospective period 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 study TED-C13-003 (teduglutide exposed and non-exposed) and prospective period (teduglutide exposed and non-exposed). For teduglutide treatment period tables, only 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 events 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; 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	STOP DATE	ACTION
		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

START DATE	STOP DATE	ACTION
		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.