STATISTICAL ANALYSIS PLAN

TED-C14-006

A 24-week Double-blind, Safety, Efficacy, and Pharmacodynamic Study Investigating Two Doses of Teduglutide in Pediatric Subjects Through 17 Years of Age with Short Bowel Syndrome who are Dependent on Parenteral Support

AUTHOR: PPD

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Statistical Analysis Plan Signature Page

Statistical Analysis Plan Final V1.0 (Dated 14Jul2017) for Protocol TED-C14-006

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Draft 1.0	12Sep2016	PPD	Not Applicable – First Version
Draft 2.0	31Oct2016		Updated per Shire reviewers' comments.
Draft 3.0	14Dec2016		Updated per Shire reviewers' feedback.
Draft 4.0	30Jan2017		(1) Updated the Shire Bios lead contact information due to team member transition; (2) Removed the DMC analysis from the SAP; (3) Updated the MedDRA and WHO DD dictionary version to 19.0 and 01Sep2016; (4) Updated the actual PN/IV and EN volume and caloric intake derivation using average daily value normalized to weight based on the dairy data; (5) Updated the medication data imputation algorithm; (6) Updated the markedly abnormal criteria for lab data based on Shire's requirement.
Draft 5.0	10Apr2017	PPD	Updated per Shire reviewers' requests.
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	14Jul2017		Added PK concentration summaries.

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1. List of Abbreviations

ACS	Abnormal, Clinically Significant
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCS	Abnormal, Not Clinically Significant
AST	Aspartate Aminotransferase
BLQ	Below The Lower Limit of Quantification
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CTCAE	Common Terminology Criteria for Adverse Events
CTMS	Clinical Trial Management System
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EN	Enteral Nutrition
ENR	All Subjects Enrolled
EOS	End of Study
EOT	End of Treatment
GFR	Glomerular Filtration Rate
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
INR	Prothrombin Intl. Normalized Ratio
ITT	Intention-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
PD	Pharmacodynamics
PK	Pharmacokinetic
PN/IV	Parenteral Nutrition/Intravenous Fluid
PP	Per Protocol
PT	Preferred Term
SAE	Serious Adverse Event
SAF	Safety
SAP	Statistical Analysis Plan
SBS	Short Bowel Syndrome
SOC	System Organ Class
SRN	All Subjects Screened
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
ULQ	Above the Upper Limit of Quantification
WHODD	WHO Drug Dictionary

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2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol TED-C14-006. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. Pharmacokinetic (PK) concentration will be summarized but the analysis of PK parameters will be detailed in a separate analysis plan.

This statistical analysis plan (SAP) is based on protocol amendment 4, dated 15 March 2016.

3. STUDY OBJECTIVES

The objective of this clinical study is to evaluate the safety, pharmacokinetics, and efficacy/pharmacodynamics (PD) of teduglutide in pediatric subjects through 17 years of age with short bowel syndrome (SBS) and who are dependent on parenteral support.

4. STUDY DESIGN

4.1. GENERAL DESCRIPTION

This study will include 2 treatment arms: a teduglutide treatment arm and a standard of care treatment arm. Subjects in both arms will participate in a 2-week minimum screening period, a 24-week treatment period, and a 4-week follow-up period. During the screening period, subjects will choose into which arm to enroll. During the 24-week treatment period, subjects in the standard of care treatment arm will receive standard medical therapy of SBS, while those in the teduglutide treatment arm will receive daily subcutaneous injections of teduglutide (study drug) in addition to standard medical therapy. The teduglutide treatment arm subjects will be randomized 1:1 in a double-blinded manner into two parallel teduglutide dose groups: 0.025 mg/kg/day and 0.05 mg/kg/day. Randomization across dose groups will be stratified by age: <1 year, 1 to <12 years, 12 to <17 years, and 17 to <18 years.

All subjects will be screened for a minimum of 2 weeks prior to start of treatment to verify the requirements for nutritional support for each subject and to ensure adherence to eligibility parameters. After screening, the 24-week treatment period will consist of site visits at baseline, weekly for the first 2 weeks (week 1 and 2), and then every other week through week 12 (week 4, 6, 8, 10, and 12). For the remainder of the treatment period, visits at the sites will be conducted every 3 weeks (at week 15, 18, 21, and 24). Telephone contacts will be made on all other weeks during the treatment period. The subjects in both arms will follow the same visit schedule. At all site visits and telephone contacts, safety will be monitored and nutritional

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support will be reviewed and adjusted as needed. At the end of the treatment period (week 24/EOT), all subjects will enter a 4-week follow-up period until the end of study (week 28/EOS) during which time no study drug (ie, teduglutide) will be administered. A final visit will be scheduled at week 28, 4 weeks following week 24 or the end of treatment (EOT). Telephone contact will be made during the interim weeks from EOT to end of study (EOS) to monitor safety and any changes in nutritional support.

To maintain consistency across all centers, sites and subjects (randomized and standard of care) should be made to follow the nutritional support adjustment guidelines (developed with SBS expert input and provided in the protocol) for decisions regarding parenteral nutrition/intravenous fluid (PN/IV) support reduction and advances in enteral feeds based on weight gain, urine and stool output, and clinical stability.

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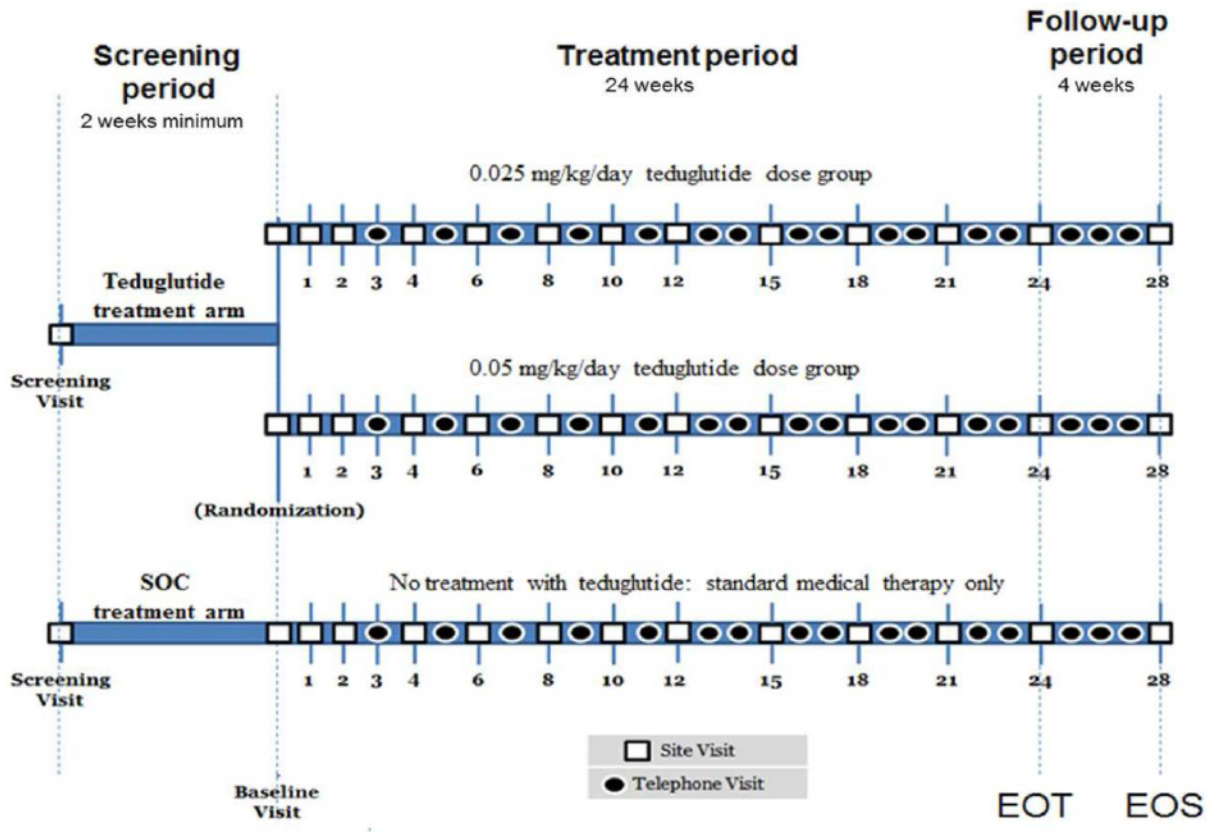
Table A Study Diagram



4.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 6 (Table 6-2, Table 6-3, Table 6-4, and Table 6-5) of the protocol.

4.3. CHANGES TO ANALYSIS FROM PROTOCOL

There is no change of analysis from protocol. The protocol defines the efficacy population as all enrolled subjects. The analysis plan refers to the efficacy population as the Intention-to-Treat (ITT) population, which is the same as the efficacy population.

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5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Final Analysis

5.1. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by Quintiles biostatistics following sponsor authorization of this statistical analysis plan, database lock, sponsor authorization of analysis sets and unblinding of treatment.

Pharmacokinetic concentration data will be summarized but the analyses of PK parameters will be performed by a Shire designated vendor in accordance with the PK SAP.

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. Inclusion/exclusion of subjects from each analysis set will be confirmed prior to the unblinding of the study based on blinded data review.

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 pass the screening period will be included in the listings but will not be included in any analyses.

6.2. ALL SUBJECTS ENROLLED [ENR] SET

The all subjects enrolled (ENR) set will contain all subjects who provide informed consent for this study, satisfy all of the inclusion criteria and none of the exclusion criteria defined in the protocol and make the choice of treatment arm (ie. teduglutide or standard of care) at the baseline visit.

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6.3. INTENTION-TO-TREAT [ITT] SET

The intention-to-treat (ITT) set will contain all subjects in the ENR set; subjects will be classified according to treatment arm (teduglutide or standard of care), and within the teduglutide treatment arm, according to dose group (0.025 or 0.05 mg/kg).

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

6.4. PER PROTOCOL [PP] SET

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

The situations that may affect inclusion in the PP set include:

- Uninterpretable PK data
- Non-compliance to study drug for the treatment group as defined in Section 15
- Clinically significant discrepancies between planned and actual treatment
- Missing baseline or week 24 efficacy data

6.5. SAFETY [SAF] ANALYSIS SET

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

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

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

6.6. PHARMACOKINETIC [PK] SET

The pharmacokinetic set will contain all enrolled subjects who receive at least one subcutaneous injection of teduglutide and have evaluable and interpretable PK data. Subjects

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will be classified according to dose group (0.025 or 0.05 mg/kg) in the teduglutide treatment arm.

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 for teduglutide arms is defined as the day of the first dose of study drug (Day 1), while for standard of care treatment arm it is defined as the day of the baseline visit date. Study days before the first dose of study drug (or baseline) will be negative.

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

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

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

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

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations will be presented based on the imputations specified in Appendix 2, Partial Date Conventions.

7.2. Baseline

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

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

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the EOS/EOT value, or best/worst case value where applicable. Unscheduled PN/IV or EN prescription adjustments carry forward until the net adjustment, and as such, may contribute to data assigned to subsequent visits.

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

7.4. WINDOWING CONVENTIONS

Nominal visits will occur within two days of the scheduled week 1 and week 2 visits, within three days of the scheduled week 3 to week 27 visits and within four days of the week 28 (EOS) visit. There will be no windowing of scheduled visits based on study day, and unscheduled visits will not be included in by-visit summaries. Early termination data will be mapped to a scheduled visit if it falls into the appropriate visit window as defined in the protocol and if that scheduled visit did not occur.

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

7.5. 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.

7.6. 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.

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7.7. 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. Randomization to treatment arms is not stratified by country/ center.

8.3. MISSING DATA

Missing data will in general not be imputed. However, partial dates will contribute to analyses 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 PN/IV support parameters (volume, calories and etc.) will be described in Section 17.1.1 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

Subgroup analyses will be conducted as stated in the exploratory analysis section. The following subgroups will be assessed and described within the section:

- Age group (years) at screening
  - <1
  - 1 to <12

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- 12 to <17
- 17 to <18

- Enteral glutamine use (Yes/No) at least once during the 24-week treatment period

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 will be accounted for in this study.

Assessment of eligibility to the inclusion and exclusion criteria will be performed at Screening and re-confirmed at the Baseline visit.

Protocol deviations (as defined in Section 6.4) 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.

Subjects who discontinue the study prior to completion (through week 28 or EOS) will have their reason for discontinuation documented in the eCRF. Regardless of the reason for early discontinuation, all data available for the subject at the time of completion/discontinuation will be recorded on the eCRF and included in the analyses.

The presentation of planned listings will include the following:

- Subject Disposition (SRN set)
- Inclusion and exclusion criteria violations (SRN set)
- Protocol deviations (ENR set).
- Subjects excluded from Per Protocol Set (ENR set)
- Assignment to analysis sets (ENR set)

The following summary tables are planned for presentation:

- Subject disposition (SRN set) by region and overall

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- Analysis sets (ENR set)
- Summary of site visits (ENR set)
- Major protocol deviations (ENR set)

11. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the ITT and PP Analysis Sets.

The following demographic and other baseline characteristics will be summarized for this study:

- Age (years) - calculated as a continuous parameter relative to date of screening. If partial date of birth date is entered with missing day and/or month due to regulatory constraints, age information will be obtained from Interactive Voice Response System (IVRS); if it is not available in IVRS, birth date will be imputed as the first day of the month if day is missing or first day of the year if both day and month are missing.
- Age Group – Age is categorized in pre-defined groups: <1, 1 to <12, 12 to <17, 17 to <18
- Sex (with reproductive status for females)
- Race
- Ethnicity
- Height Z-score at Baseline
- Weight Z-score at Baseline
- Head Circumference Z-score at Baseline (only for subjects who are <= 36 months of age)
- BMI Z-score at Baseline

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

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 19.6.1.

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12. MEDICAL HISTORY

Medical history will be presented for the ITT Analysis Set.

12.1. SHORT BOWEL SYNDROME HISTORY

The following Short Bowel Syndrome (SBS) History will be collected at screening and will be summarized and listed:

- 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 with the small bowel
- Presence of distal/terminal ileum and ileocecal valve

12.2. GASTROINTESTINAL SYMPTOMS HISTORY

The following Gastrointestinal Symptoms History collected at Baseline will be summarized based on categories of not present, mild, moderate, and severe, with clinical significance also summarized where the event is present:

- Abdominal/belly pain
- Nausea/feeling queasy
- Vomiting/throw up
- Heartburn/reflux/spit up
- Gas/bloating
- Diarrhea/loose stool
- Constipation/very hard stool

A listing will also be presented by treatment group and subject identifier.

12.3. SURGICAL AND MEDICAL HISTORY

Medical and Surgical History will be coded using ***Medical Dictionary for Regulatory Activities (MedDRA) version 19.1***. Medical and Surgical History conditions are defined as those

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conditions which began prior to informed consent. Medical and surgical history includes all relevant past medical diagnoses and surgeries other than related to the cause or diagnosis of SBS. Data captured on the Medical and Surgical History page of the CRF will be presented by System Organ Class (SOC) and Preferred Term (PT). SOC will be sorted alphabetically and PT within SOC will be sorted by descending incidence in the Total Teduglutide treatment group.

13. PRIOR AND CONCOMITANT MEDICATIONS

Medications will be presented for the SAF analysis set.

'Prior' medications are those taken by the subject within 14 days before screening and discontinued prior to the first dose of study drug (or the baseline visit for the standard of care treatment arm).

'Concomitant' medications are defined as:

- medications with onset dates on or after the first dose of study drug (or baseline visit for standard of care treatment arm); or
- medications with onset dates prior to first dose of study drug (or baseline visit for standard of care treatment arm) without a stop date or stop date after the first dose of study drug

The subject's usage of prior medication will be assessed at screening and baseline and the subject's usage of concomitant medication will be assessed at the baseline visit and visit thereafter. The changes in medication or dosage of medications will be recorded on the eCRF. Concomitant medications include IV medications mixed into the PN/IV fluids, like heparin or H2 blockers. Medications used for line maintenance, such as TPA, and ethanol and taurolidine locks, are also included as concomitant medications. However, IV fluid and nutritional components of parenteral nutrition, including electrolytes, vitamins and minerals, other micronutrients, amino acids, glucose, and lipids, are part of PN/IV will not be included as a prior or concomitant medications.

Medications will be coded to preferred name using ***WHO Drug Dictionary (WHODD), 01SEP2016***. Prior and 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 SAF analysis set.

A listing of all medications, both prior and concomitant will be presented. The listing will be sorted by treatment group and subject identifier and will include reported name, dose, route of administration, dosing frequency, start date, end date, indication and period of medication

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(prior only, concomitant only, prior and concomitant). Investigator verbatim as well as coded terms will be included in the listings.

See Appendix 2 for handling of partial dates for medications.

14. DIAGNOSTIC, SURGICAL, OR THERAPEUTIC PROCEDURES DURING THE STUDY

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

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.

Subjects will be considered compliant overall for study drug administration if the calculated compliance is > 80%. Overall treatment compliance will be presented for percent compliance calculations using descriptive statistics and the number and percentage of subjects who are > 80% compliant by treatment group for the ITT and PP and SAF Analysis Sets.

15.1. DERIVATIONS

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

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

where number of days on treatment will be calculated as (Date of last study drug – Date of first study drug + 1) and dose interruption days will not be excluded.

Drug administration diary data, first dose date, and last dose data are reported in the eCRF.

16. PHARMACOKINETICS

The pharmacokinetic (PK) concentration data will be summarized on the PK set for the subjects in the teduglutide treatment arm only. The descriptive statistics of PK concentration will be

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summarized by treatment arm and dose group for each timepoint. The listings for PK concentration data will also be provided.

For the PK evaluation, blood will be collected at the clinic on day 0 when the subject receives the first dose of teduglutide. Blood sampling will occur at the following timepoints: predose and 1, 2, and 4 hours postdose.

- 0-hour (predose) draw: any time prior to the daily dose, on the day of dosing, but at least 14 hours after the previous dose (if the PK blood draw does not occur at day 0)
- 1-hour postdose draw: ±10 minutes
- 2-hour postdose draw: ±10 minutes
- 4-hour postdose draw: ±30 minutes

If a subject is unable to provide blood samples at baseline (day 0) on the first day of treatment, then blood may be collected for PK analysis during any other future clinic visit while the subject is still receiving treatment with teduglutide.

The actual date and time of teduglutide administration and blood draw will be documented on the PK blood sampling eCRF.

Descriptive statistics (mean, median, standard deviation, minimum and maximum values) of PK concentration will be calculated to summarize the absolute values and change from predose at each timepoint. The PK parameters will be derived and estimated based on measured teduglutide plasma concentrations using a population PK modeling approach and will be described within a separate SAP.

17. EFFICACY OUTCOMES

Efficacy analyses for the primary efficacy endpoint, ≥20% reduction in weight-normalized PN/IV volume between the baseline and week 24/EOT visit, will be performed using both diary and prescribed data on the ITT and PP analysis sets. All other efficacy analyses will be performed on the ITT analysis set only. Analyses based on diary data and prescribed data will be presented separately. The descriptive statistics of efficacy outcomes will be summarized by treatment arm and dose group. The listings for efficacy measures which are collected on the CRF forms will be provided.

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17.1. PRIMARY EFFICACY

17.1.1. PRIMARY EFFICACY VARIABLE & DERIVATION

The primary efficacy variable is weight-normalized reduction in PN/IV volume of at least 20% at EOT compared to baseline. This 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"). PN/IV support will be reported in both subject diary data and the investigator-prescribed data in the eCRF. Investigator-prescribed data are the most recent PN/IV prescription (from either baseline or prescription adjustments) prior to or on the date of visit, captured in the PN/IV history and PN/IV adjustments eCRFs. PN/IV diary data are collected over 24-hour periods that start on the assigned date. Depending on the time of day at which the 24 hour period begins, which can vary by subject, overnight PN/IV infusion volumes after midnight may be associated with prior the date. Baseline actual PN/IV parameters will be calculated using all the diary data collected within 14 days prior to the first dose or baseline visit. Calculation of post-baseline actual PN/IV parameters will be based on the daily support recorded in subjects' diaries within 7 days prior to the date of each scheduled post-baseline visit. Week 1 calculations will exclude any pre-baseline diary data. The calculation of actual PN/IV volume normalized to weight will follow the formula below:

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

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, including PN/IV calories, PN/IV hours per day, EN volume, and EN calories. If more than 5 days' values in two weeks before baseline visit, the baseline values are missing.

The calculation of prescribed PN/IV volume normalized to weight will follow the formula below:

> Average daily value = (prescribed weekly PN/IV volume / 7) / last available weight prior to or on the date of visit

An analogous strategy will be used to calculate other prescribed parameters, including PN/IV calories, PN/IV hours per day, EN volume, and EN calories.

Percent reduction in weight-normalized actual and prescribed PN/IV volume from baseline at the scheduled visit will be calculated using the formula below:

> % reduction in PN/IV volume at the visit = [(average daily value at the scheduled visit - average daily value at baseline) / average daily value at baseline] * 100

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Percent reduction calculation will be performed on both actual and prescribed PN/IV volume data.

17.1.2. Primary Analysis of Primary Efficacy Variable

Efficacy analyses will be conducted on the ITT and PP set.

The number and percentage of subjects who achieve at least a 20% reduction in weight-normalized average daily actual and prescribed PN/IV volume at EOT will be summarized by treatment arm and dose group. The denominator will be the number of subjects for the population in each treatment arm and dose group.

17.1.3. Sensitivity Analysis of Primary Efficacy Variable

The same descriptive statistics will also be summarized on investigator prescribed data.

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

17.2. Other Efficacy

17.2.1. Other Efficacy Variables & Derivations

17.2.1.1. ≥ 20% Reduction in PN/IV volume at each study visit

Similar to the primary analysis, PN/IV volume reduction at each study visit compared to baseline will be calculated. The number and percentage of subjects who achieve at least a 20% reduction in weight-normalized PN/IV volume at each visit during the 24-week treatment period will be summarized by treatment group.

Subgroup analysis by age group and by oral glutamine use will be performed on subject diary data as an exploratory analysis for the ITT analysis set only.

17.2.1.2. Complete weaning off PN/IV support at EOT

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

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The analysis will summarize how many subjects achieve complete weaning of PN/IV support at EOT.

17.2.1.3. Change and percent change from baseline in PN/IV support

Changes in average daily weight-normalized actual and prescribed PN/IV volume at all post-baseline visits during the 24-week treatment period and 4-week follow-up period will be derived using the same formulas as for primary efficacy calculations. Analogous calculations will be used to calculate changes in weight-normalized actual and prescribed PN/IV calories. Mean ± SE plots of percent change in PN/IV volume (mL/kg/day) and caloric intake (kcal/kg/day) will be generated.

17.2.1.4. Change and percent change from baseline in citrulline

Plasma citrulline levels are measured, collected and transferred by Covance central lab with other lab data. Change and percent change from baseline in plasma citrulline at week 12, week 24 and EOT will be presented by treatment arm and dose group using descriptive statistics.

17.2.1.5. Change and percent change from baseline in enteral nutritional support

The change and percent change from baseline in average daily weight-normalized actual and prescribed EN volume and calories at each post-baseline visit during the 24-week treatment period and 4-week follow-up period will be calculated and summarized using analogous methods as for PN/IV parameters. However, percent change will not be calculated if subject did not take any EN at baseline.

17.2.1.6. Change and percent change from EOT in PN/IV support, citrulline, EN support at EOS

The change from EOT in each parameter or measurement at EOS will be calculated using the formula below:

> Change from EOT in parameter (or measurement) at EOS = Value at EOS – Value at EOT

The percent change from EOT in each parameter or measurement at EOS will be calculated using the formula below:

> Percent change from EOT in parameter (or measurement) at EOS = [(Value at EOS – Value at EOT) / Value at EOT] * 100

If the EOS value is not available, the last non-missing assessment after the EOT will be used as EOS for calculation. If subject has weaned-off PN/IV or EN at EOT, percent change for those parameters will not be calculated.

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17.2.1.7. Change and percent change from baseline in hours per day and days per week of PN/IV support

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

Hours per day of actual PN/IV support for all visits except the baseline visit will be calculated as follows:

> Hours per day of actual PN/IV support = (sum of hours per day for each day that PN/IV intake data is recorded within the 7 days prior to the visit / number of days that PN/IV hours per day data is recorded within the 7 days prior to the visit)

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

Days per week of actual PN/IV support for all visits except the baseline visit will be calculated as follows:

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

For the week 1 visit, data prior to the baseline visit will not be used for the calculation.

17.2.2. ANALYSIS OF OTHER EFFICACY VARIABLES

17.2.2.1. Analysis of All Other Efficacy Variables

Actual and prescribed PN/IV and EN data will be analyzed and summarized separately. However, visit-level listings for average daily weight-normalized PN/IV volume, caloric intake, days per week and hours per day of PN/IV support, will present actual and prescribed data side-by-side.

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

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18. STUDY DRUG EXPOSURE

The extent of exposure is defined as the number of days on treatment. The number and percentages of subject will be tabulated for extent of exposure categorized into weeks (<4, 4-<12, 12-<24, >=24). Exposure summaries will be presented by teduglutide dose group (excluding the standard of care treatment arm) for the ITT, PP and SAF Analysis Sets. The study drug administration and study drug accountability data which are collected on the CRF will be listed.

Compliance and dose interruptions are not taken into account for the extent of exposure.

Information about interruptions of study drug by investigator decision (start date of interruption, date study drug resumed, and reason for interruption) will be included in data listings.

18.1. DERIVATIONS

The extent of exposure in days will be calculated as:

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

The date of first study drug administration is collected on the eCRF "First SC Injection" form. The date of last study drug is collected on the eCRF "End of Treatment" form.

19. SAFETY OUTCOMES

All outputs for safety outcomes will be based on the Safety Analysis Set.

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

19.1. ADVERSE EVENTS

Adverse Events (AEs) 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.

Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsened on or after the date of first dose for treatment arms and adverse events that started or worsened on or after the baseline visit for standard of care group. For events that start or worsen on the date of

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first dose, any available start time will be compared to the time of first dose for the treatment arms.

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) for each treatment arm and dose group. 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 discontinuation and TEAEs leading to death.

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

19.1.1. ALL TEAEs

Incidence of TEAEs will be presented by System Organ Class and Preferred Term and also analyzed by relationship to study drug, seriousness, 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 total teduglutide treatment arm.

19.1.1.1. Severity

Severity is classified as mild/moderate/severe. TEAEs 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.

The events that are graded according to CTCAE criteria will be indicated in the listings.

19.1.1.2. Relationship to Study Drug

Relationship, as indicated by the Investigator, is classed as *"not related"* or *"related"*. A *"related"* TEAE is defined as a TEAE with a relationship of "related" to study drug. TEAEs with a missing relationship to study drug will be regarded as "*related*" to study drug. AE

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summaries by relationship will exclude the standard of care treatment arm.

19.1.2. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as "Serious" on the Adverse Events Form of the eCRF. Any SAE that occurs from the time of the signing of the ICF through last study visit (week 28 or EOS) will be captured. A summary of TESAEs by SOC and PT will be prepared, as well as summaries by event and causal relationship to study drugs. A listing of SAEs will be presented.

19.1.3. AEs Leading to Discontinuation of Study Drug

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

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

19.1.4. 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.

19.2. Laboratory Evaluations

Laboratory evaluations that are done at study site visits will be collected and processed via a central laboratory (Covance), including panels for Hematology, Clinical Chemistry, Coagulation and Urinalysis. The central laboratory data will be transferred to Quintiles for analyses. Laboratory evaluations that are required at intervals that do not coincide with study site visits may be obtained by a local laboratory. The local laboratory data will be collected on the local laboratory tests form of eCRF. Laboratory evaluations to be included in the tables or listings are presented in the lab test table (Table B) below.

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Table B Laboratory Tests

Hematology	Chemistry	Coagulation	Urinalysis
Hemoglobin	Albumin	Prothrombin Time	Ur Blood*
Hematocrit	Alkaline Phosphatase	Prothrombin Intl. 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		
Eosinophils	Indirect Bilirubin		
Basophils	Blood Urea Nitrogen		
Neutrophils/Leukocytes	Calcium		
Lymphocytes/Leukocytes	Chloride		
Monocytes/Leukocytes	Cholesterol		
Eosinophils/Leukocytes	Creatinine		
Basophils/Leukocytes	C Reactive Protein		
	Glomerular Filtration Rate (GFR)		
	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 (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

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

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- Actual and change from baseline by scheduled site visit
- Shift from baseline according to normal range criteria at each scheduled post-baseline site visit
- Incidence of markedly abnormal values according to criteria defined in section Appendix 3
- Listing of subjects meeting markedly abnormal criteria

19.2.1. 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 qualifying as markedly abnormal will be summarized by treatment group and the parameter. A listing will present all values for a subject and laboratory parameter if at least one post-baseline value for that subject and parameter is markedly abnormal.

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

19.3. ANTIBODIES TO TEDUGLUTIDE

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 baseline, EOT and EOS. Non-specific antibodies will be categorized as Negative.

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

19.4. GASTROINTESTINAL-SPECIFIC TESTING

GI-specific testing will be reported for the teduglutide treatment arm only. The clinically significant abnormal results will be presented in a data listing. The results of upper gastrointestinal (GI) series with small bowel follow through, abdominal ultrasound, and colonoscopy or sigmoidoscopy will be reported as 'Normal', 'Abnormal, not clinically significant', or 'Abnormal, clinically significant'. Fecal occult blood testing will be reported as 'Negative', 'Positive, not clinically significant', 'Positive, clinically significant'.

19.5. PHYSICAL EXAMINATION

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

19.6. VITAL SIGNS

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

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Temperature (°C)
- Weight (kg)
- Height or length (cm)
- Head circumference (cm) for subjects ≤ 36 months of age

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

- BMI (kg/m^2)
- Height Z-score
- Weight Z-score
- BMI Z-score

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- Head circumference Z-score for subjects ≤ 36 months of age

Descriptive statistics will be used to summarize vital signs measurements and derived parameters in actual value and change from baseline for each treatment group by age group (age stratification used for randomization: <1 year, 1-<12 years, 12-<17 years and 17-<18 years and overall) at study site visits (including EOT) where associated parameters are collected. Z-scores of vital signs by site visits will be presented in box plots. A listing will also be provided.

19.6.1. 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, 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/.

19.7. ECG EVALUATIONS

Electrocardiogram (ECG) results with description of any findings will be recorded in the eCRF. The following ECG parameters will be reported for this study:

- Overall assessment of ECG (Investigator's judgment):
  - Normal
  - Abnormal, Not Clinically Significant (ANCS)

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- Abnormal, Clinically Significant (ACS)

The following summaries will be provided for ECG data by treatment group at baseline, week 12, week 24 and EOT:

- Incidence of Normal, ANCS and ACS
- Listing of all ECG descriptions for subjects meeting ACS criteria

19.8. FECAL AND URINE OUTPUT

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

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

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

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

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

20. DATA NOT SUMMARIZED OR PRESENTED

Other than select fields that capture reason an assessment is not done, all comments and

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specified text fields captured in the eCRF will be displayed in appendix listings only. These variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets.

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

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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.

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- **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.
  - Averaged lab results e.g. Diastolic/Systolic Blood Pressure and Pulse (when taken in triplicate) should be rounded to 1 decimal place for reporting.

- **PRESENTATION OF TREATMENT GROUPS**

Tables will be organized by ascending order of Shire drug treatment dose levels, followed by all doses of Shire drug, then followed by the standard of care at the end e.g., 0.025 mg/kg/day Teduglutide, 0.05 mg/kg/day Teduglutide, Total Teduglutide, Standard of Care. 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.

When required, a column for combined active and comparator statistics will be included and it will be labeled "Total". By default, this column has only been included in the disposition, demographics, and important protocol deviations TFL shells. Use in any other domains should be carefully discussed with the study team.

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APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings. The first dose date for teduglutide groups and the date of baseline visit for standard of care treatment group will be treated as the reference start date, and the last dosing date or the date of last visit for standard of care group during the 24-week treatment period will be treated as the reference end 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 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).

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

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START DATE	STOP DATE	ACTION
		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

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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.

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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).

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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).

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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.

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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

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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	

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APPENDIX 4. TABLE, FIGURE AND DATA LISTING SHELLS

TABLE AND FIGURE SHELLS

See separate file.

DATA LISTING SHELLS

See separate file.

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