STATISTICAL ANALYSIS PLAN

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SHP633-302

A 24-WEEK SAFETY, EFFICACY, PHARMACODYNAMIC, AND PHARMACOKINETIC STUDY OF TEDUGLUTIDE IN JAPANESE PEDIATRIC SUBJECTS, AGED 4 MONTHS THROUGH 15 YEARS, WITH SHORT BOWEL SYNDROME WHO ARE DEPENDENT ON PARENTERAL SUPPORT

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CTMS	Clinical Trial Management System
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EN	Enteral Nutrition
EOS	End of Study
EOT	End of Treatment
GI	Gastrointestinal
HLGT	Higher Level Group Term
ICH	International Conference on Harmonisation
ITT	Intention-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
MOS	Months
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
SE	Standard Error
SI	Standard International
SOC	Standard of Care
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
UGI/SBFT	Upper GI series with Small Bowel Follow-Through
ULN	Upper Limit of Normal
WHODD	WHO Drug Dictionary
YRS	Years

2. INTRODUCTION AND BACKGROUND INFORMATION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol SHP633-302. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. Pharmacokinetic analysis will be detailed in a separate analysis plan.

This statistical analysis plan (SAP) is based on protocol amendment 4, dated 12 June 2018.

2.1. STUDY DESIGN

This will be an open-label, 24-week study, in which subjects will receive 0.05 mg/kg/day of teduglutide. The study population will include 2 cohorts: infants 4-<12 months corrected gestational age and children 1-15 years of age.

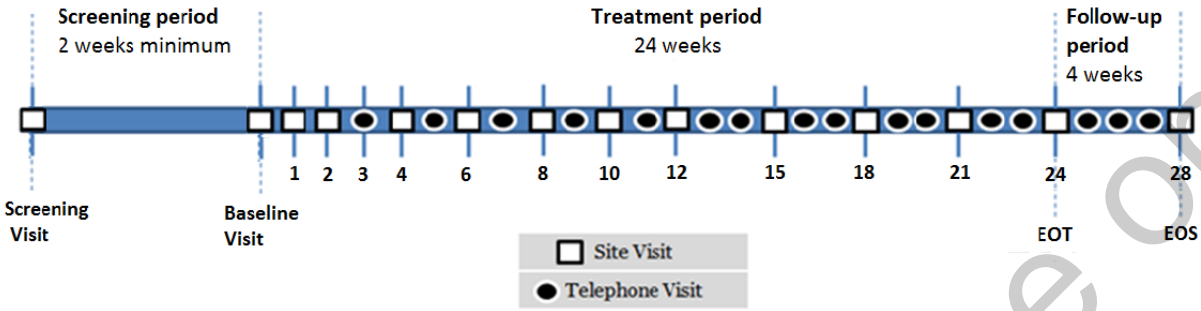
All subjects will be screened for a minimum of 2 weeks prior to start of treatment to verify the requirements for nutritional support for each subject and to ensure adherence to eligibility parameters. Attempts should be made to limit the screening period to 4 weeks.

After screening, the 24-week treatment period will consist of visits at baseline, weekly for the first 2 weeks, and then every other week through week 12. For the remainder of the treatment period, visits at the sites will be conducted every 3 weeks. Scheduled telephone contacts will be made on all other weeks during the treatment period. At all site visits and during telephone contacts, safety will be monitored and nutritional support will be reviewed and adjusted as needed. The end of study (EOS) visit will be scheduled at week 28, 4 weeks following end of treatment (EOT). Weekly telephone contact will be made during the interim weeks from EOT to EOS to monitor safety and any changes in nutritional support.

To maintain consistency across all centers, all attempts should be made to follow the nutritional support adjustment guidelines and weaning algorithms (developed with SBS expert input and provided in the protocol) for decisions regarding parenteral nutrition/intravenous fluids (PN/IV) support reduction and advances in enteral feeds based on weight gain, urine, and stool output in the setting of clinical stability. Any departure from the nutritional support adjustment guidelines and weaning algorithms will not constitute a protocol deviation.

A schematic representation of the study design is displayed in Figure 1. The study schedule of events can be found in Table 1 and Table 2 of the protocol.

Figure 1 Study Diagram



2.2. OBJECTIVE

The objective of this clinical study is to evaluate the safety, tolerability, efficacy and pharmacodynamics, and pharmacokinetics of teduglutide in pediatric subjects (4 months through 15 years of age) with short bowel syndrome (SBS) who are dependent on parenteral support.

2.2.1. EFFICACY/PHARMACODYNAMIC ASSESSMENTS

The efficacy/pharmacodynamic endpoints include:

- Change (absolute and percent change) from baseline in PN/IV support (volume and calories), citrulline (only for the cohort of children 1-15 years of age), and enteral nutritional support (volume and calories), separately, at each visit
- Reduction in PN/IV volume of at least 20% at week 24 (or EOT) compared to baseline
- 100% reduction in PN/IV volume (complete weaning of PN/IV support) at week 24 (or EOT) compared to baseline
- ≥20% reduction in PN/IV volume at each visit
- Change (absolute and percent change) from week 24 (or EOT) in PN/IV support (volume and calories), citrulline (only for the cohort of children 1-15 years of age), and enteral nutritional support (volume and calories), separately, to week 28 (or EOS)
- Change in hours per day and days per week of PN/IV support

2.2.2. SAFETY ASSESSMENTS

Safety and tolerability will be assessed by evaluating the following:

- Adverse events, including those pertaining to GI symptoms.
- Physical examinations, including body weight, height (or length), head circumference (up to 36 months of age), and trends on growth charts
- Vital signs, including temperature, heart rate, blood pressure
- Electrocardiograms (ECGs)
- Laboratory safety data (ie, biochemistry, hematology, coagulation, urinalysis)
- Urine output
- Fecal output (by volume or number of bowel movements per day)
- Antibodies to teduglutide
- For children 1 to 15 years of age: GI-specific testing including colonoscopy or sigmoidoscopy, abdominal ultrasound, fecal occult blood testing, upper GI series with small bowel follow-through (UGI/SBFT)
- For infants 4 to <12 months corrected gestational age: UGI/SBFT

3. DETERMINATION OF SAMPLE SIZE

The sample size is determined based on enrollment feasibility of this orphan population in children in Japan, rather than power calculation.

4. UNBLINDING PROCEDURES

No unblinding procedures apply as this is an open-label study.

5. DATA MANAGEMENT

IQVIA is responsible for data management activities for this study. Details about data management, including the eCRF design, the EDC system, data validation and discrepancy management, reconciliation of data from different sources, and electronic data transfer, are included in the Data Management Plan for this study.

6. STATISTICAL/ANALYTICAL ISSUES

6.1. GENERAL METHODOLOGY

All statistical procedures will be completed using SAS version 9.4 or later.

Due to the limited size of the study population descriptive statistics will be used with a goal of summarizing the sample which discourages the use of inferential statistics. Accordingly, 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. Standard errors (SE) will be displayed for the efficacy tables, and body weight, height (or length), BMI, head circumference and weight for length. For categorical variables, descriptive statistical summaries will include number of subjects and percentages.

For summary purposes, the baseline value will be defined as the last available pre-dose value. Scheduled visits will be summarized as provided in the electronic case report forms (eCRFs). 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. Similarly, an End of Study (EOS) time point will be defined as the last determination of endpoint or last available measurement after the EOT during the 4-week follow-up period. Unscheduled measurements will not be included in by-visit summaries, but can contribute to the EOT/EOS value where applicable.

Study Day will be calculated as follows:

- If the date of the evaluation is on or after the first day of study medication then:
  Study Day = (date of the evaluation – first day of study medication) + 1.
- If the date of the evaluation is prior to the first day of study medication then:
  Study Day = (date of the evaluation – first day of study medication).

Datasets and listings will include data collected at unscheduled visits. Data collected at unscheduled visits will not be included in summaries by timepoint or visit unless specified otherwise.

Data will be analyzed and presented by subject cohorts:

- Infants: 4-<12 months corrected gestational age
- Children: 1-15 years of age

The corrected gestational age as captured on the demographics page of the eCRF will be used to determine the cohort a subject belongs to, i.e., if the corrected gestational age is <12 months, the subject will be in the infant cohort. The infant cohort will be analyzed in a manner analogous to the cohort of children 1-15 years of age unless specified otherwise.

Analyses will be done for all subjects, and subset of subjects who began treatment after protocol amendment 3.0. Main conclusions will be based on subjects who began treatment after implementation of protocol amendment 3.0.

6.2. ADJUSTMENTS FOR COVARIATES/PROGNOSTIC VARIABLES

No adjustments for covariates are planned in the statistical analyses.

6.3. HANDLING OF DROPOUTS OR MISSING DATA

All subjects in the analysis population defined in Section 7 will be included in the associated analyses.

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

Details on how to handle partial dates for adverse events and prior/concomitant medications are described below.

Complete dates will be imputed from partial dates of adverse events and medications solely for the purpose of defining treatment emergence for adverse events and prior/concomitant status for medications (Imputed dates will not be presented in the listings). Dates will be defined using the hierarchy of derivations below.

Adverse event or medication start date (references to month and year are the month and year of the start date):

1. If year and month are known, and it is the month and year of the first dose date, use the first dose date.
2. If year and month are known, and it is not the month and year of the first dose date, use the first day of the month.
3. If only year is known, and it is the year of the first dose date, use the first dose date.
4. If only year is known, and it is not the year of the first dose date, use the first day of the year (1st January).
5. Should any of the previous start dates created be after a complete stop date provided, use the stop date as the start date, instead of the date that would otherwise be created.
6. For medication start date, if “Before Informed Consent” is ticked then use the date of informed consent.
7. Otherwise, if start date is unknown leave as missing.

Adverse event or Medication stop date (references to month and year are the month and year of the stop date):

1. If year and month are known, use the last day of the month.
2. If only year is known, use the last day of the year (31st December).
3. Otherwise, if stop date is unknown leave as missing.

6.4. INTERIM ANALYSES AND DATA MONITORING

An interim analysis of subjects 1-15 years of age will be performed at the completion of their participation.

Safety and tolerability results will be evaluated by a Data Monitoring Committee (DMC) which will convene approximately every 3 months during the active study period (date of the first subject's first dose to date of the last subject's last dose), based on subject enrollment. The DMC review will include all cumulative safety data from study assessment through the end of each review period.

6.5. MULTICENTER STUDIES

Because a small number of subjects are expected at each center, data from all centers will be pooled.

6.6. MULTIPLE COMPARISONS/MULTIPLICITY

Not Applicable.

6.7. ACTIVE-CONTROL STUDIES INTENDED TO SHOW EQUIVALENCE

Not applicable.

6.8. EXAMINATION OF SUBGROUPS

No subgroup analyses will be conducted given the small number of patients in this study.

7. ANALYSIS POPULATIONS AND VISITS

If there are two populations that consists of the same patients, the analysis planned to be conducted for the two populations will only be conducted once for the intention-to-treat population and the analysis for the latter population (per protocol, safety and/or

pharmacokinetic) in this list will not be generated since it will be the same outputs.

7.1. SCREENED POPULATION

All subjects who provided signed Informed Consent Form will be included in the Screened population.

7.2. INTENTION-TO-TREAT (ITT) POPULATION

The intention-to-treat (ITT) population will consist of all subjects who are enrolled into the study. Subjects are considered enrolled in the study when they meet all eligibility criteria at screening and eligibility criteria are confirmed at visit 2/baseline. The ITT population will be the primary analysis population analyzed for efficacy/PD endpoints.

7.3. PER PROTOCOL (PP) POPULATION

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

Major protocol deviations leading to exclusion from the PP population include:

- Subjects with no detectable teduglutide post dose in the blood as part of PK assessments, or subjects who lack all PK assessments
- Missing baseline and/or Week 24 efficacy data
- Non-compliance to study drug as defined in Section 10

Major protocol deviations will be programmatically derived.

The Per Protocol population will be the sensitivity analysis population analyzed for primary efficacy endpoints. Reasons for exclusion from the PP population will be summarized for the ITT population and presented in the data listings.

7.4. SAFETY POPULATION

The Safety population will consist of all subjects in the ITT population who receive at least 1 administration of investigational product with any safety follow-up. All safety analyses will be conducted on this population, unless otherwise specified.

All collected data will be included in the listings.

7.5. PHARMACOKINETIC (PK) POPULATION

The PK population is defined as all subjects in the Safety population for whom the primary PK data are considered sufficient and interpretable.

7.6. WINDOWING VISITS

Although there is a visit window from 2 to 4 days around the expected visit date, nominal visits will be used for the per-visit analyses. Therefore, no windowing of visits by study day will be done for data obtained at the scheduled visits. For subjects who withdraw from the study prematurely, if the early termination visit falls into the window of a scheduled visit as defined in the protocol, the early termination visit is also summarized for that scheduled visit, unless the scheduled visit already took place.

8. STUDY SUBJECTS

8.1. SUBJECTS SCREENED

The number of subjects screened will be presented.

8.2. STUDY ANALYSIS POPULATIONS

The number and percent of subjects in each study analysis population (i.e., ITT, PP, Safety and PK) will be presented for the Screened population.

8.3. PROTOCOL DEVIATIONS

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 severity categories (“minor”, “important” and “priority”) and provided as part of the CTMS transfer to Biostatistics. Protocol deviations will be summarized for the ITT population. A listing of protocol deviations by subject will be presented in the data listings.

8.4. DISPOSITION OF SUBJECTS

For the ITT, PP, PK and Safety populations, study enrollment as well as treatment and study completion status will be summarized. The reason for discontinuing treatment and/or study early will also be presented.

9. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

9.1. ANALYSIS OF DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

The baseline and demographic characteristics will be summarized with descriptive statistics defined in Section 6.1 for the ITT and Safety populations. Demographic and baseline characteristics to be presented include:

- Age at informed consent date in years for the cohort of children 1-15 years of age. Age in years will be rounded to 1 decimal place for reporting.
- Chronological (actual) age at informed consent date in months for the infant cohort. Chronological age in months will be rounded to 1 decimal place for reporting.
- Corrected gestational age at informed consent date in months for the infant cohort. Corrected gestational age in months will be rounded to 1 decimal place for reporting.
- Sex
- Race
- Ethnicity
- Height or length for age Z-score at Baseline
- Weight for age Z-score at Baseline
- Head Circumference for age Z-score at Baseline (only for subjects who are <= 36 months of age)
- BMI for age Z-score at Baseline only for children 2-15 years of age
- Weight for length Z-score at Baseline only for the infant cohort

BMI, Z-score of weight, height or length, BMI and head circumference for age as well as weight for length Z-score will be calculated based on the method described in Section 13.4. Z-scores will be rounded and presented to 2 decimal places.

The following Short Bowel Syndrome History information collected at the Screening visit will be summarized with descriptive statistics defined in Section 6.1 for the ITT and Safety populations:

- Duration of SBS
- Primary reason for the diagnosis of SBS (necrotizing enterocolitis, midgut volvulus, intestinal atresia, gastroschisis, trauma, cancer, crohn's disease, long-segment hirschprung disease, other)
- Secondary reason for the diagnosis of SBS (Y/N), secondary reason (necrotizing enterocolitis, midgut volvulus, intestinal atresia, gastroschisis, trauma, cancer, crohn's disease, long-segment hirschprung disease, other)
- stoma (Y/N), stoma type (jejunostomy, ileostromy, colostomy, other)
- Remaining colon (Y/N), estimated percent of colon remaining, and colon in continuity (Y/N)
- Colonoscopy in the last 12 months (Y/N/NA)
- Total estimated remaining small intestinal length (cm)
- Presence of the distal/terminal ileum (Y/N) and ileocecal valve (Y/N)
- Method to determine remaining anatomy length (surgery, radiology, other)

For children 1-15 years of age, duration of SBS in years will be calculated as (Date of informed consent form signed – Date of diagnosis of SBS +1) / 365.25 and rounded to 1 decimal place for reporting.

For infants, duration of SBS in months will be calculated as (Date of informed consent form signed – Date of diagnosis of SBS +1) / (365.25/12) and rounded to 1 decimal place for reporting.

The following Parenteral Nutrition/Intravenous History and Enteral Nutrition (EN) History information collected at the Baseline visit will be summarized with descriptive statistics defined in Section 6.1 for the ITT and Safety populations:

- Years or months since start of PN/IV dependency
- Current use of EN (Y/N), reason not taking EN (following a regular diet, other)
- Years or months since start of EN dependency

For children 1-15 years of age, years since start of PN/IV dependency will be calculated as (Date of informed consent form signed – Start date of PN/IV dependency +1)/365.25.

For infants 4-12 months corrected gestational age, months since start of PN/IV dependency will be calculated as (Date of informed consent form signed – Start date of PN/IV dependency +1)/ (365.25/12).

Years and months since start of EN dependency will be calculated in a similar manner but using the start date of EN dependency. Both these durations will be rounded to 1 decimal place for reporting.

The following Parenteral Nutrition/Intravenous History information collected at baseline will be summarized in the by-visit efficacy tables and listed:

- Prescribed weekly PN/IV volume
- Prescribed weekly PN/IV calories
- Prescribed number of days per week of PN/IV
- Prescribed average number of hours per day of PN/IV
- Prescribed weekly EN volume
- Prescribed weekly EN calories

The following Gastrointestinal Symptoms History collected at the Baseline visit will be summarized for the ITT and Safety populations 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

Partial dates for the date of diagnosis of SBS and start of PN/EN dependency will use the first day of the month if only the day is missing. If both the day and month are missing, the first day of January will be used.

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Investigator verbatim as well as preferred terms and system organ class will be included in the listings. The medical and surgical history will be summarized by system organ class (SOC) and preferred term (PT) within system organ class for the Safety population, with SOC sorted alphabetically and PT within SOC by descending incidence.

10. MEASUREMENTS OF TREATMENT COMPLIANCE

Percent compliance will be calculated as 100 times the number of days the study treatment was administered per instructions by the number of days on treatment. Number of days on treatment is calculated as (last dose date – first dose date +1). The information whether the study treatment was administered per instructions is captured on the study drug administration daily diary. Administration of the study treatment by the investigator will be considered per instructions. Subjects will be considered compliant overall for study medication if the calculated compliance is ≥ 80%. Overall treatment compliance will be presented for both percent compliance calculations using descriptive statistics and the number and percentage of

subjects who are ≥ 80% compliant for the ITT and Safety populations. Treatment compliance by visit will not be calculated.

11. EFFICACY/PHARMACODYNAMIC EVALUATION

11.1. ANALYSIS OF EFFICACY AND PHARMACODYNAMIC VARIABLES

Primary efficacy/pharmacodynamic analyses will be conducted on the ITT population. The PP population will be used for sensitivity analysis purpose.

PN/IV and EN support will be reported in both subject diary data and the investigator-prescribed data in the eCRF. Diary and prescribed PN/IV and EN volume/calories will be normalized to weight in order to facilitate comparability of results across patients in this pediatric population. Data will be summarized at all scheduled visits during the 24-week treatment period and the follow-up period (Week 25, 26, 27, 28). An End of Treatment (EOT) time point will also be added. Data collected at unscheduled time points will be included in the listings but will not be summarized at those unscheduled time points.

Prescribed data are the most recent PN/IV or EN prescription (from either baseline or prescription adjustments) prior to or on the date of visit, captured in the PN/IV or EN history and PN/IV or EN adjustments eCRFs.

Average daily values normalized to weight will be calculated for PN/IV volume, PN/IV calories, EN volume and EN calories as follows:

Average Prescribed daily value = (prescribed weekly value / 7) / last available body weight prior to or on the date of visit

Calculation of post-baseline diary PN/IV and EN parameters (including hours per day and days per week of PN/IV support) will be based on the daily support recorded in subjects' diaries within 7 days prior to the date of each scheduled post-baseline visit. Baseline diary PN/IV and EN parameters will be calculated using the most recent 14 days of diary data collected prior to the first dose, and week 1 calculations will not use any pre-baseline diary data.

Average daily values normalized to weight will be calculated for PN/IV volume, PN/IV calories, EN volume and EN calories as follows:

Average diary 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. If more than 5 days' values in two weeks before baseline visit, the baseline values are missing. These missing data handling rules will be used to calculate all other diary average diary parameters, including PN/IV calories, PN/IV hours per day, PN/IV days per week, EN volume, and EN calories.

Percent reduction in weight-normalized diary 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

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

Change and percent change from baseline in PN/IV and EN support

The absolute and percent change from baseline in average daily values for PN/IV and EN support (volume and calories) to each scheduled visit during the 24-week treatment period, as well as at EOT and the follow-up period (Week 25, 26, 27, 28), will be presented using descriptive statistics defined in Section 6.1. For EN summary, change from baseline will only be calculated for subjects who took any EN at baseline.

Mean ± SE plots of percent change in PN/IV and EN support (volume and caloric intake) will be generated.

Plots of PN/IV and EN support (volume and caloric intake) by visit will be presented for each individual subject in the ITT population.

95% confidence intervals of the mean will be generated for Week 20 and Week 24/EOT.

Change and percent change from baseline in citrulline

The absolute and percent change in citrulline from baseline to each scheduled visit during the 24-week treatment period, as well as at EOT and the follow-up period (Week 28), will be presented using descriptive statistics defined in Section 6.1 for the cohort of children 1-15 years of age.

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

PN/IV volume reduction at each study visit compared to baseline will be calculated using average daily values. The number and percentage of subjects who achieve at least a 20% reduction in PN/IV volume will be presented at each scheduled visit during the 24-week treatment period, as well as at EOT and the follow-up period (Week 25, 26, 27, 28).

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) if the investigator prescribes no PN/IV (volume and calories) and there is no use of PN/IV (volume and calories) recorded in the subject diary during the 7 days prior to EOT. The number and percentage of subjects who completely wean off PN/IV support up to EOT will be presented. A listing will present the study week when complete wean off was first achieved for these subjects who completely wean off PN/IV support at EOT.

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

The absolute and percent change from EOT to EOS in average daily values for PN/IV and EN support (volume and calories) as well as citrulline (only for the cohort of children 1-15 years age) will be presented using descriptive statistics defined in Section 6.1. If subject has weaned-off PN/IV or EN at EOT, change from EOT for those parameters will not be calculated.

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

Change and percent change from baseline in hours per day and days per week of PN/IV support to each visit during 24-week treatment period, as well as at EOT and the follow-up period (Week 25, 26, 27, 28), will be presented using descriptive statistics defined in Section 6.1.

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

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

Days per week of diary 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.

12. PHARMACOKINETIC EVALUATION

The pharmacokinetic (PK) concentration data will be summarized on the PK population for the protocol scheduled sampling time points:

- Baseline: 0-hour (pre-dose), 1-hour post-dose and 6-hour post-dose
- Week 4: 0-hour (pre-dose), 2-hour post-dose and 4-hour post-dose

Descriptive statistics of PK concentration (mean, standard deviation, coefficient of variation (CV) % mean, geometric mean, CV (%) geometric mean, median, minimum and maximum values) will be calculated at each time point. A listing for PK concentration data will also be provided.

The PK parameters will be derived and estimated based on measured teduglutide plasma concentrations using a population PK modeling approach by a Takeda designated vendor in accordance with the PK SAP.

13. SAFETY EVALUATION

All safety evaluations will be conducted on the Safety population. By-visit summaries will include all protocol scheduled visits during the 24-week treatment period, EOT and Week 28 visit.

13.1. EXTENT OF EXPOSURE

The extent of exposure is defined as the number of days on treatment, calculated as:

(date of last dose - date of first dose) + 1.

The first dose date and last dose date will be based on the eCRF. The extent of exposure, the number of days that the dose was administered will be summarized. The number and percentages of subject will be tabulated for extent of exposure categorized into weeks (<4, 4-<12, 12-<24 and ≥24). Exposure summaries will be presented for the ITT and Safety populations.

The information related to the study drug training provided by the study physician will be listed for all subjects in the Safety population.

13.2. ADVERSE EVENTS

Adverse Events (AEs) will be coded using MedDRA. Investigator verbatim as well as preferred term and system organ class will be included in the listings.

Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases during or after receiving the study medication. AEs with an unknown date of onset and a stop date after the start of the study period or unknown will be included as treatment emergent AEs. Any AE with a start date equal to the date of first dose, where the time of the AE cannot definitively place the start of the AE prior to the first dose, will be considered treatment emergent. If any AE records contain only partial dates, these will be handled by imputation, as described in Section 6.3. AEs which are not treatment emergent will be flagged in listings.

AEs will be summarized overall using descriptive statistics (e.g., number and percent of subjects). The number of events will also be presented. Categories summarized will include any TEAE (Y/N), severity of TEAEs (any and highest category), investigator assessment of relationship of TEAEs to study treatment, treatment emergent serious AEs (TESAEs), severity of TESAEs, investigator assessment of relationship of TESAEs to study treatment, TEAEs leading to death, TEAEs leading to discontinuation, and TEAEs of special interest.

Treatment emergent AEs will be summarized using number and percentage of subjects. Subject incidence for AEs within each SOC and PT will be presented, unless otherwise

specified. The number of events will also be summarized. Categories summarized will be the same as those summarized in the overview tabulations, except that no summary table will be provided for TEAEs leading to death. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending incidence.

Summaries of TEAEs, TEAEs by relationship, TESAEs and TESAEs by relationship will also be presented by PT. These presentations will be sorted by descending incidence.

For the summaries described above, TEAEs with a missing severity will be classified as severe and TEAEs with a missing relationship to study drug will be regarded as related to study drug.

In addition, AEs of special interest will be considered. An AE of special interest is an AE (serious or nonserious) of scientific and medical concern specific to the sponsor's product or program. The AEs of special interest will include the following groupings:

- 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)

The MedDRA terms corresponding to each grouping of events of special interest are included in APPENDIX 3.

The number and percentage of subjects with at least one TEAE of special interest will be presented. The number of events of special interest will also be summarized.

Listings will be provided for serious adverse events (SAEs), AEs leading to death, AEs leading to discontinuation of study drug and AEs of special interest.

13.3. CLINICAL LABORATORY EVALUATION

Laboratory evaluations that are done at study site visits will be collected and processed via a central laboratory, and presented in standard international (SI) units. 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.

Clinical laboratory evaluations include, but not limited to, the following:

- Chemistry:
  - Albumin
  - Alkaline phosphatase
  - Alanine aminotransferase
  - Amylase
  - Aspartate aminotransferase
  - Bicarbonate
  - Bilirubin (total, direct and indirect)
  - Blood urea nitrogen
  - Calcium (total)
  - Chloride
  - Cholesterol
  - C-reactive protein
  - Creatinine
  - Estimated glomerular filtration rate (Schwartz formula)
  - Gamma-glutamyl transferase
  - Glucose
  - Lipase
  - Magnesium
  - Phosphorus
  - Potassium
  - Sodium
  - Triglycerides
  - Uric acid
- Hematology:
  - Hematocrit
  - Hemoglobin
  - Platelet count
  - Red blood cell (RBC) count
  - RBC morphology, if needed
  - White blood cell count with differential
- Coagulation:
  - Prothrombin time/International normalized ratio
- Urinalysis:
  - Blood
  - Glucose
  - Leucocytes
  - Microscopic analysis

- pH and osmolality
- Protein
- Specific gravity

The laboratory summaries will be based on central lab results only and be presented for scheduled site visits only, i.e., baseline, weeks 1, 2, 4, 6, 8, 10, 12, 15, 18, 21, 24 and 28. In addition, laboratory results will also be presented at EOT.

Quantitative results will be summarized for hematology, serum chemistry, and selected urinalysis parameters by scheduled site visit. Both observed values and change from baseline will be summarized with descriptive statistics defined in Section 6.1. 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.

Markedly abnormal laboratory values are defined in APPENDIX 1. These criteria are based on lab normal ranges. The number and percentage of subjects with post-baseline results qualifying as markedly abnormal as defined in this table will be summarized by parameter and a subject level listing will be presented.

Laboratory results will be presented in an appendix data listing for each lab panel (chemistry, hematology, urinalysis) by subject, parameter, and date of collection. Laboratory values outside of the normal range will be flagged. Local lab test results, categorical test results and urine pregnancy results will be presented in appendix data listings only.

13.4. VITAL SIGNS

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

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Pulse Rate (bpm)
- Temperature (°C)
- Weight (kg)
- 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/m2) for children 2-15 years of age
- Weight for length ratio (kg/cm) for infants 4-<12 months corrected gestational age
- Height or length for age Z-score
- Weight for age Z-score
- BMI for age Z-score for children 2-15 years of age
- Weight for length Z-score for infants 4-<12 months corrected gestational age
- Head circumference for age Z-score for subjects ≤ 36 months of age

Descriptive statistics (e.g., mean, standard deviation, median, minimum and maximum values, the number and percent of subjects in specified categories) will be used to summarize the vital signs at each scheduled study site visit and at EOT. Both observed value and change from baseline will be summarized with descriptive statistics defined in Section 6.1. Mean ± SE plots of body weight, height or length, BMI and head circumference for age Z-scores and weight for length Z-score by visit will be generated.

The following specific derivations will be used:

- 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. BMI will only be presented for Children 2-15 years of age.

- Weight for length ratio

Weight for length ratio = Body weight (kg)/length (cm), where both body weight and length data are available at the same scheduled visit. Weight for length ratio will only be presented for the infant cohort.

- Height or length, Weight, Head Circumference, BMI for age Z-scores and weight for length Z-score

A z-score is the deviation of the value for an individual from the mean value of the reference population divided by the standard deviation for the reference population.

Z-scores are calculated using the formula below:

Z-score= [((observed value / M) ^ L) – 1] / (S * L), for L≠0

Z-score= ln(observed value / M) / S, for L=0

In which 'observed value' is the child's height or length, weight, head circumference or derived BMI. The L, M, and S values vary according to the child's sex, age or length. The following data tables containing the L, M and S values for child's height or length, weight, head circumference, derived BMI for age and weight for length will be used.

Age	Height or Length		Weight		BMI [3]	Weight for Length [4]	Head Circumference	
	Children 1-15 yrs [1]	Infants 4-<12 mos [2]	Children 1-15 yrs [1]	Infants 4-<12 mos [2]	Children 1-15 yrs [1]	Infants 4-<12 mos [2]	Children 1-15 yrs [1]	Infants 4-<12 mos [2]
0-<12 mos	NA	WHO	NA	WHO	NA	WHO	NA	Kato 2014
1-<2 yrs	Isojima 2016	WHO	Isojima 2016	WHO	NA	WHO	Kato 2014	Kato 2014
2-3 yrs	Isojima 2016	NA	Isojima 2016	NA	Kato 2011	NA	Kato 2014	NA
>3 yrs	Isojima 2016	NA	Isojima 2016	NA	Kato 2011	NA	NA	NA

[1] Actual (chronological) age at the time of assessment is used for Z-score calculation.

[2] Corrected gestational age at the time of assessment is used for Z-score calculation.

[3] BMI is only calculated for Children 2-15 years of age.

[4] Weight for length is only calculated for the cohort of infants.

NA = Not applicable; mos = Months; yrs = Years

To obtain the L, M, and S values using these data tables, the corrected gestational age will be used for infants and the actual (chronological) age for children 1-15 years of age. Note that the calculated age at each vital sign assessment date will be obtained using the date of birth as reference date for actual (chronological) age and (date of birth + difference in days between corrected gestational age and actual age at informed consent) as reference date for corrected gestational age.

Details of the Z-score calculation are provided in subsections below.

Z-scores will be rounded to 2 decimal places for reporting.

For more information on the LMS method, see

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC27365/.

Official and validated SAS programs created by Centers for Disease Control and Prevention (CDC) will be used to calculate the Z-scores for a child's sex and age (up to 20 years of age) for BMI, weight, height, and head circumference based on the L, M, S values referred above. For more information on the CDC SAS programs, see http://www.cdc.gov/growthcharts/computer_programs.htm.

13.4.1. Z-SCORES OF HEIGHT FOR AGE AND WEIGHT FOR AGE FOR CHILDREN 1-15 YEARS OF AGE

The L, M and S values of height and weight for age for Japanese children as given in Isojima et al. (2016) will be used. These values are also given in Table 1 (for height) and Table 2 (for weight) of APPENDIX 2.

For ages (in years) that fall between two age categories given in Table 1 and Table 2, the following interpolation will be used to calculate the L, M, S values:

LMS value=LMS_lower + [(actual age in years – age_lower) * (LMS_upper – LMS_lower)] / (age_upper – age_lower).

Where LMS_lower is the L, M or S value corresponding to the lower age category in the age interval, i.e., age_lower, and LMS_upper is the L, M or S value corresponding to the upper age category in the age interval, i.e., age_upper.

For example, according to Table 1 in APPENDIX 2, the M values of height are 135.9 for a 10 years old male and 138.8 for a 10.5 years old male. Therefore, to obtain the M value of height for a 10.2 years old male, the following calculation is applied:

M=135.9 + [(10.2 – 10) * (138.8 – 135.9)] / (10.5 – 10) = 137.06

13.4.2. Z-SCORES OF LENGTH FOR AGE AND WEIGHT FOR AGE FOR INFANTS 4-12 MONTHS CORRECTED GESTATIONAL AGE

L, M, S values for WHO growth charts will be used:

https://www.cdc.gov/growthcharts/who_charts.htm

13.4.3. Z-SCORES OF HEAD CIRCUMFERENCE FOR ALL STUDY SUBJECTS ≤36 MONTHS OF AGE

The L, M and S values of head circumference for age for Japanese population as given in Kato et al. (2014) will be used. These values are also given in Table 5 of APPENDIX 2.

Corrected gestational age will be used for infants and the actual (chronological) age for children 1-3 years of age.

For ages (in months) that fall between two age categories given in Table 5, a similar interpolation as described in Section 13.4.1 will be used to calculate the L, M, S values.

13.4.4. Z-SCORES OF BMI FOR CHILDREN 2-15 YEARS OF AGE

The L, M and S values of BMI for age for Japanese children as given in Kato et al. (2011) will be used. These values are also given in Table 3 (for male) and Table 4 (for female) of APPENDIX 2. BMI for age Z-scores will only be presented for the children 2-15 years of age.

13.4.5. Z-SCORES OF WEIGHT FOR LENGTH FOR INFANTS

L, M, S values for WHO growth charts will be used:

https://www.cdc.gov/growthcharts/who_charts.htm

Weight for length Z-scores will only be presented for the infant cohort.

13.5. ECG VARIABLES

The number and percentage of subjects with each type of ECG finding (Normal/Abnormal, Not Clinically Significant/Abnormal, Clinically Significant) will be presented at baseline, weeks 12, 24 and 28 as well as at EOT for the Safety population.

13.6. PHYSICAL EXAMINATION

Physical exam findings will be presented in the listings for the Safety population.

13.7. ANTIBODIES TO TEDUGLUTIDE

A summary table will provide the number of subjects with a sample analyzed for baseline, Week 24, EOT and Week 28. The summary table will also provide the number of subjects with an antibody finding (Antibodies to teduglutide Negative/Positive and No Neutralizing Antibodies Present/Neutralizing Antibodies Present) at each of those visits.

13.8. GASTROINTESTINAL-SPECIFIC TESTING

The results of GI-specific testing including UGI/SBFT, abdominal ultrasound, fecal occult blood testing, and colonoscopy/ sigmoidoscopy will be reported as 'Normal', 'Abnormal, not clinically significant', 'Abnormal, clinically significant' or 'Negative', 'Positive, not clinically significant', 'Positive, clinically significant'. For the infant cohort, only UGI/SBFT is to be reported. The number of patients and percentage will be presented by visit for each GI-specific testing parameter and result category.

13.9. FECAL AND URINE OUTPUT

Output diary 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. For

the analysis, the latest 48-hour period of output diary data entered prior to each visit will be used (The 48-hour period does not need to be within 48 hours of the visit). Any additional output diary data collected out of this 48-hour window will only be presented in the listings.

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) / most recent body weight (kg) prior to or on 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 over 48 hours. Values will not be calculated if the urine output is not available at the visit.

The average daily fecal output will be summarized separately by the number of stools per day, the typical stool form score using Bristol Stool Form Scale, the total daily stool/mixed stool diaper weight (g/kg/day) and the total ostomy output per day (mL/kg/day). The 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 a formula analogous to that used to calculate the average daily urine output.

The change and the percent change in average daily output for urine and fecal from baseline to each scheduled visit, as well as at EOT, will be presented using descriptive statistics defined in Section 6.1.

13.10. PRIOR AND CONCOMITANT MEDICATIONS

Prior and concomitant medications will be coded to indication-specific preferred name using the World Health Organization Drug Dictionary. Investigator verbatim as well as coded terms will be included in the listings.

Prior medications are defined as any medication discontinued prior to the administration of study treatment. Concomitant medications are defined as any medication taken during the course of the study including medications with onset dates on or after the first dose of study medication, medications with onset dates prior to first dose of study medication without a stop date, or medications with a stop date after first dose of study medication.

Partial date imputation for medications is described in Section 6.3.

Prior and concomitant medication use will be summarized by preferred name using the number and percentage of subjects. 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.

A listing of all medications, both prior and concomitant, will be presented. The listing will be sorted by subject identifier and will include reported name, dose, route of administration,

dosing frequency, start date, end date, indication, and period of medication (prior or concomitant).

14. CHANGES IN THE STATISTICAL METHODOLOGY PRESENTED IN THE PROTOCOL

There is no change of analysis from protocol.

15. GENERAL PROGRAMMING INFORMATION

15.1. GENERAL

All programmed table, figure and listing outputs, unless specified otherwise, will be generated using the SAS version 9.4 or later. The programmed outputs will be similar to the format/appearance of the table and listing shells. However, space/formatting limitations may dictate changes in the programmed output. The footnotes specified in the table and listing shells may be changed as necessary for clarifying table entries or the explanation of algorithms or methods used for producing the entries. Significant changes in footnotes will be discussed prior to their implementation.

15.2. FORMAT OF TABLES/LISTINGS

Tables will present subject cohorts, including all subjects and subset of subjects who began treatment after protocol amendment 3.0, in the following order: “Children (1 - 15 years) After Amendment 3”, “Total Children (1 - 15 years)”, “Infants (4 - <12 months)”, unless otherwise specified. Note that all subjects in the infant cohort will be enrolled after protocol amendment 3.0 and thus the subset of subjects who began treatment after protocol amendment 3.0 will not be presented for the infant cohort. The following footnote will be presented in all tables/listings: "Infants are of 4 - <12 months corrected gestational age”.

All output should have a 1-line footer with the SAS program name, including the path, and the date and time the output was produced at the lower left margin of the footer.

Tables and listings should be internally paginated in relation to the total length for that table or listing (i.e., Page n of N, where n is the page number within the table or listing and N is the total number of pages for that table or listing).

The table, figure and listing numbering will be based on the International Conference on Harmonization (ICH) guidelines.

A number should identify each table/listing, and the table designation (e.g., Table 1) should be centered above the title. A decimal system (e.g., x, x.y, x.y.z) should be used to identify

tables/listings with related contents. The title should be centered and in mixed-case characters. The title and table/listing designation should be single-spaced, but are separated from the content of the table/listing by a space and a solid underline. The study population and/or subgroup (e.g., ITT population) should be identified on the line immediately following the title.

Column headings should be in title case characters. For numeric variables, the unit should be included in the column heading when appropriate.

Footnotes should be single spaced, but separated by an underline and a space from the text of the table/listing. The notes should be aligned vertically by the left vertical border of the table/listing. Numeric references, which can be confused with data, should not be used. Rather asterisks and other non-numeric symbols should be used to refer to footnotes.

The dictionary (e.g., MedDRA, WHO-DRUG) and the dictionary version numbers should be identified in the footnotes to the tables/listings for data coded with a dictionary.

For summarizations of categorical data, an Unknown or Missing category should be added to any variable for which information is not available for all subjects. 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.

Individual data listings will be sorted and presented by cohort, subject number, parameter (if applicable) and visit/collection date.

15.3. DATA FORMATS

Unless otherwise specified, means (arithmetic, geometric and 95% CI of the mean) and medians will be rounded and presented to 1 decimal place more than the raw data and standard deviations and standard errors to 2 decimal places more than the raw data. Minimum and maximum values will be presented to the same number of decimal places as the raw data. Coefficient of variation shall always be reported as a percent with 1 decimal.

Unless otherwise specified, percentages should be presented to one decimal place. Less than signs (i.e., '<') should be presented as appropriate (e.g., 0.04% should be presented as < 0.1%, not 0.0%).

Standard deviations will be calculated when the number of subjects is 2 or more.

16. TABLE, FIGURE AND DATA LISTING SHELLS

16.1. TABLE SHELLS

See separate file.

16.2. FIGURE SHELLS

See separate file.

16.3. DATA LISTING SHELLS

See separate file.

17. REFERENCES

- Isojima, T., Kato, N., Ito, Y., Kanzaki, S., and Murata, M. (2016). Growth standard charts for Japanese children with mean and standard deviation (SD) values based on the year 2000 national survey. Clin Pediatr Endocrinol 2016; 25(2), 71–76.
- Kato, N., Takimoto, H., and Sudo, N. (2011). The Cubic Functions for Spline Smoothed L, S and M Values for BMI Reference Data of Japanese Children. Clin Pediatr Endocrinol 2011; 20(2), 47-49.
- Kato, N., Takimoto, H., Yokoyama, T., Yokoya, S., Tanaka, T., and Tada, H. (2014). Updated Japanese growth references for infants and preschool children, based on historical, ethnic and environmental characteristics. Acta Paediatrica 2014; 103, e251-e261.

APPENDIX 1. MARKEDLY ABNORMAL LABORATORY CRITERIA

Lab Parameter	Unit	Infants (4 - <12 months corrected gestational age)		Children (1 - 15 years)	
		Lower Limit Criteria	Upper Limit Criteria	Lower Limit Criteria	Upper Limit Criteria
Chemistry					
Albumin	g/L	<20	>68	<20	>68
Alkaline Phosphatase	U/L		>5 x ULN		>5 x ULN
Alanine Aminotransferase (ALT)	U/L		>8 x ULN		>8 x ULN
Aspartate Aminotransferase (AST)	U/L		>8 x ULN		>8 x ULN
Amylase	U/L		>3 x ULN		>3 x ULN
Lipase	U/L		>3 x ULN		>3 x ULN
Bilirubin Total	umol/L		>5 x ULN		>3 x ULN
Direct Bilirubin	umol/L		>68.4147		>34.208
Blood Urea Nitrogen	mmol/L		>12.495		>12.495
Calcium	mmol/L	<1.5	>3	<1.5	>3
Creatinine	umol/L		>132.6		>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		>=100
Glucose	mmol/L	<2.22	>13.875	<2.22	>13.875
Magnesium	mmol/L	<0.4114	>1.2342	<0.4114	>1.2342
Phosphorus	mmol/L	<0.644	>2.254	<0.644	>2.254

Potassium	mmol/L	<2.5	>6.5	<2.5	>6.5
Sodium	mmol/L	<120	>160	<120	>160
Triglycerides	mmol/L		>5.65		>5.65
Hematology					
Hemoglobin	g/L	<70	>200	<70	>200
Hematocrit	fraction of 1	<0.21	>0.60	<0.21	>0.60
Platelets	10^9/L	<75	>700	<75	>700
Leukocytes	10^9/L	<2	>30	<2	>30
Neutrophils, absolute	10^9/L	<0.5		<0.5	

APPENDIX 2. L, M AND S VALUES OF HEIGHT, BODY WEIGHT, BMI AND HEAD CIRCUMFERENCE FOR AGE FOR JAPANESE

Table 1 L, M and S Values of Height for Age for Japanese Children

Age (yr)	Male			Female		
	L	M	S	L	M	S
0	2.300	49.0	0.0417	1.200	48.5	0.0390
0.25	2.212	61.5	0.0378	1.159	60.1	0.0361
0.5	2.124	67.7	0.0351	1.117	66.2	0.0341
0.75	2.036	71.6	0.0335	1.076	70.2	0.0327
1	1.948	74.8	0.0328	1.034	73.5	0.0318
1.25	1.861	77.8	0.0328	0.993	76.6	0.0316
1.5	1.773	80.7	0.0332	0.952	79.5	0.0317
1.75	1.685	83.4	0.0340	0.910	82.2	0.0321
2	1.597	85.8	0.0348	0.869	84.6	0.0328
2.5	1.421	89.7	0.0364	0.786	88.4	0.0344
3	1.245	93.5	0.0378	0.703	91.8	0.0361
3.5	1.069	97.1	0.0386	0.620	95.4	0.0376
4	0.894	100.4	0.0392	0.538	99.4	0.0389
4.5	0.718	103.6	0.0397	0.455	103.2	0.0399
5	0.542	106.8	0.0403	0.372	106.7	0.0406
5.5	0.366	110.1	0.0410	0.289	109.7	0.0411
6	0.190	113.3	0.0417	0.206	112.7	0.0414
6.5	0.015	116.4	0.0423	0.124	115.5	0.0416
7	–0.161	119.5	0.0426	0.041	118.3	0.0418
7.5	–0.337	122.4	0.0426	–0.042	121.2	0.0421
8	–0.513	125.1	0.0424	–0.114	124.1	0.0428
8.5	–0.689	127.8	0.0421	–0.036	127.2	0.0438
9	–0.864	130.4	0.0420	0.213	130.4	0.0451
9.5	–1.040	133.1	0.0424	0.599	133.8	0.0466
10	–1.216	135.9	0.0435	1.055	137.2	0.0477
10.5	–1.392	138.8	0.0453	1.506	140.6	0.0481
11	–1.401	142.0	0.0476	1.879	144.0	0.0472
11.5	–0.965	145.4	0.0500	2.118	147.2	0.0447
12	–0.275	149.0	0.0519	2.190	150.0	0.0410
12.5	0.428	153.1	0.0526	2.090	152.1	0.0367
13	0.931	157.0	0.0517	1.843	153.8	0.0342
13.5	1.090	160.5	0.0491	1.498	155.1	0.0324
14	0.865	163.4	0.0453	1.124	155.9	0.0314
14.5	0.323	165.6	0.0414	0.801	156.6	0.0310
15	–0.370	167.3	0.0382	0.602	157.0	0.0310
15.5	–0.982	168.6	0.0358	0.579	157.3	0.0310
16	–1.267	169.5	0.0344	0.742	157.5	0.0310
16.5	–1.031	170.1	0.0340	1.032	157.7	0.0310
17	–0.516	170.5	0.0340	1.295	157.8	0.0310
17.5	0.000	170.8	0.0340	1.250	157.8	0.0310

Table 2 L, M and S Values of Weight for Age for Japanese Children

Age (yr)	Male			Female		
	L	M	S	L	M	S
0	0.774	3.00	0.149	0.754	2.95	0.146
0.25	0.490	6.31	0.131	0.375	5.86	0.126
0.5	0.262	7.93	0.119	0.083	7.32	0.113
0.75	0.082	8.80	0.110	–0.139	8.14	0.106
1	–0.062	9.38	0.105	–0.303	8.72	0.103
1.25	–0.177	9.91	0.102	–0.422	9.26	0.102
1.5	–0.269	10.4	0.101	–0.506	9.82	0.102
1.75	–0.344	11.0	0.102	–0.563	10.4	0.104
2	–0.408	11.5	0.103	–0.602	11.0	0.105
2.5	–0.513	12.5	0.108	–0.646	12.1	0.110
3	–0.607	13.5	0.113	–0.677	13.1	0.114
3.5	–0.703	14.5	0.119	–0.718	14.0	0.118
4	–0.804	15.5	0.123	–0.778	15.1	0.122
4.5	–0.913	16.5	0.127	–0.861	16.1	0.127
5	–1.026	17.5	0.131	–0.960	17.1	0.131
5.5	–1.136	18.5	0.134	–1.068	18.2	0.137
6	–1.236	19.6	0.138	–1.171	19.4	0.142
6.5	–1.321	20.9	0.142	–1.259	20.6	0.148
7	–1.384	22.2	0.146	–1.319	21.9	0.154
7.5	–1.420	23.5	0.152	–1.344	23.2	0.159
8	–1.429	25.0	0.159	–1.328	24.5	0.164
8.5	–1.407	26.4	0.166	–1.269	25.9	0.169
9	–1.358	28.0	0.174	–1.169	27.4	0.174
9.5	–1.284	29.6	0.182	–1.037	29.2	0.180
10	–1.191	31.4	0.189	–0.884	31.2	0.185
10.5	–1.084	33.4	0.195	–0.722	33.6	0.190
11	–0.971	35.6	0.200	–0.572	36.3	0.194
11.5	–0.862	38.1	0.204	–0.448	39.0	0.195
12	–0.764	40.7	0.206	–0.368	41.5	0.194
12.5	–0.686	43.6	0.205	–0.346	43.8	0.187
13	–0.636	46.3	0.201	–0.389	45.8	0.176
13.5	–0.619	49.0	0.196	–0.496	47.5	0.164
14	–0.642	51.6	0.187	–0.653	48.8	0.154
14.5	–0.705	54.0	0.178	–0.830	49.8	0.147
15	–0.809	55.9	0.169	–0.976	50.6	0.142
15.5	–0.952	57.5	0.161	–1.012	51.2	0.139
16	–1.127	58.8	0.155	–1.072	51.6	0.138
16.5	–1.325	59.7	0.151	–1.132	51.9	0.137
17	–1.534	60.4	0.147	–1.192	52.1	0.135
17.5	–1.739	60.9	0.141	–1.252	52.3	0.134

Table 3 L, M and S Values of BMI for Age for Japanese Children (Male)

Months of age	Smoothed L	Smoothed S	Smoothed M
0			$0.032048517\ x^3 + -0.493433273\ x^2 + 2.551397766\ x + 12.62254537$
2.5			$0.007972878\ x^3 + -0.201998877\ x^2 + 1.54342034\ x + 13.697217$
9.5	$1.4345E-06\ x^3 + -0.000119864\ x^2 + -0.037620259\ x + 0.624077322$	$-7.58553E-08\ x^3 + 2.1302E-05\ x^2 + -0.001094812\ x + 0.090651064$	$-7.67459E-05\ x^3 + 0.007173901\ x^2 + -0.251765964\ x + 18.77518828$
26.75			
78			$-3.88384E-06\ x^3 + 0.001076046\ x^2 + -0.081944537\ x + 17.20118685$
90	$-3.06037E-06\ x^3 + 0.001387949\ x^2 + -0.190798754\ x + 5.531514491$		
150		$1.99415E-08\ x^3 + -1.37006E-05\ x^2 + 0.002877807\ x + -0.053198893$	$-3.94748E-06\ x^3 + 0.001761925\ x^2 + -0.203856428\ x + 22.66402577$
210	$9.04656E-07\ x^3 + -0.00066203\ x^2 + 0.156555714\ x + -13.82908985$		

Table 4 L, M and S Values of BMI for Age for Japanese Children (Female)

Months of age	Smoothed L	Smoothed S	Smoothed M
0			0.019399718 x^3 + -0.359429206 x^2 + 2.139236779 x + 12.56896799
2.5			0.007312299 x^3 + -0.194108219 x^2 + 1.537772117 x + 13.22824693
9.5	3.47613E-07 x^3 + -2.38575E-05 x^2 + -0.037631412 x + 0.795846301	-1.0218E-07 x^3 + 2.31971E-05 x^2 + -0.000923983 x + 0.08896935	-0.000168505 x^3 + 0.013702125 x^2 + -0.385286062 x + 19.15626964
26.75			-4.80005E-07 x^3 + 0.000350143 x^2 + -0.031651293 x + 16.03450105
69	-5.83768E-06 x^3 + 0.002194825 x^2 + -0.255465003 x + 7.295142629		
90		2.10831E-08 x^3 + -1.43497E-05 x^2 + 0.002839146 x + -0.035441889	-3.03967E-06 x^3 + 0.001541344 x^2 + -0.183867689 x + 21.95124139
150	5.41432E-06 x^3 + -0.002965041 x^2 + 0.532984646 x + -32.85082504		-2.5069E-06 x^3 + 0.000642483 x^2 + 0.049828797 x + 5.323050314
210			

Table 5 L, M and S Values of Head Circumference for Age for Japanese Population

	Boys			Girls		
	LMS			LMS		
Age	*L*	*M*	*S*	*L*	*M*	*S*
Birth	3.57516	33.5340	0.041033	3.16302	33.0616	0.039349
30 days	3.51357	36.6508	0.038015	3.31746	35.8649	0.036895
1.5 months	3.47738	37.9537	0.036657	3.38432	37.0473	0.035782
2.5 months	3.39959	39.9479	0.034410	3.48864	38.8785	0.033925
3.5 months	3.31270	41.3592	0.032639	3.56084	40.2025	0.032438
4.5 months	3.21754	42.3408	0.031291	3.60300	41.1507	0.031282
5.5 months	3.11495	43.0462	0.030314	3.61724	41.8547	0.030417
6.5 months	3.00576	43.6255	0.029657	3.60563	42.4433	0.029803
7.5 months	2.89081	44.1563	0.029267	3.57027	42.9833	0.029401
8.5 months	2.77094	44.6439	0.029092	3.51326	43.4792	0.029171
9.5 months	2.64698	45.0903	0.029081	3.43670	43.9330	0.029074
10.5 months	2.51976	45.4977	0.029181	3.34267	44.3466	0.029069
11.5 months	2.39013	45.8680	0.029340	3.23327	44.7219	0.029118
12.5 months	2.25893	46.2032	0.029508	3.11059	45.0609	0.029182
13.5 months	2.12698	46.5059	0.029658	2.97674	45.3658	0.029240
14.5 months	1.99512	46.7783	0.029791	2.83380	45.6395	0.029293
15.5 months	1.86419	47.0232	0.029906	2.68386	45.8847	0.029340
16.5 months	1.73503	47.2431	0.030005	2.52903	46.1042	0.029381
17.5 months	1.60847	47.4406	0.030088	2.37140	46.3008	0.029418
18.5 months	1.48535	47.6181	0.030156	2.21305	46.4772	0.029448
19.5 months	1.36650	47.7783	0.030210	2.05609	46.6363	0.029474
20.5 months	1.25277	47.9238	0.030249	1.90261	46.7807	0.029496
21.5 months	1.14498	48.0570	0.030276	1.75470	46.9134	0.029512
22.5 months	1.04397	48.1806	0.030290	1.61446	47.0370	0.029524
23.5 months	0.95058	48.2970	0.030292	1.48399	47.1543	0.029531
27 months	0.69015	48.6746	0.030216	1.12237	47.5434	0.029525
33 months	0.45065	49.2382	0.029846	0.80613	48.1547	0.029414
39 months	0.39445	49.7113	0.029298	0.76467	48.7035	0.029206
45 months	0.43079	50.1119	0.028712	0.87148	49.1982	0.028934
51 months	0.46891	50.4577	0.028230	1.00006	49.6471	0.028633
57 months	0.41804	50.7642	0.027995	1.02390	50.0499	0.028337
63 months	0.18741	51.0444	0.028148	0.81650	50.3975	0.028081
69 months	−0.31374	51.3113	0.028831	0.25137	50.6807	0.027898
75 months	−1.17618	51.5780	0.030185	−0.79801	50.8899	0.027824

APPENDIX 3. MEDDRA TERMS CORRESPONDING TO EACH GROUPING OF ADVERSE EVENTS OF SPECIAL INTEREST

Groupings	System Organ Class (SOC)	Preferred Terms (PT)	Higher Level Group Terms (HLGT)
Tumor-promoting ability	Neoplasms benign, malignant and unspecified		
Growth of pre-existing polyps of the colon		Duodenal polyp	
		Intestinal polyp	
		Rectal Polyp	
		Large intestine polyp	
		Gastrointestinal polyp	
Benign neoplasia of the GI tract including the hepatobiliary system			Gastrointestinal neoplasms benign
			Hepatic and biliary neoplasms benign
		Abdominal wall cyst	
		Abdominal wall neoplasm benign	
		Benign abdominal neoplasm	
		Benign gastrointestinal neoplasm	
		Benign mesenteric neoplasm	
		Benign pancreatic neoplasm	
		Benign peritoneal neoplasm	
		Benign small intestinal neoplasm	
		Gastric haemangioma	
		Gastrointestinal polyp	
		Gastrointestinal polyp haemorrhage	
		Gastrointestinal tract adenoma	
		Gingival cyst	

Groupings	System Organ Class (SOC)	Preferred Terms (PT)	Higher Level Group Terms (HLGT)
		Intestinal angioma	
		Intestinal cyst	
		Intestinal polyp	
		Intra-abdominal haemangioma	
		Intraductal papillary mucinous neoplasm	
		Large intestine benign neoplasm	
		Mesenteric cyst	
		Pancreatic cyst	
		Pancreatic cyst rupture	
		Peutz-Jeghers syndrome	
		Retroperitoneum cyst	
		Small intestine polyp	
		Stoma site polyp	
		Adenolymphoma	
		Ameloblastoma	
		Benign keratocystic odontogenic neoplasm	
		Benign salivary gland neoplasm	
		Buccal polyp	
		Cementoblastoma	
		Dental cyst	
		Gingival polyp	
		Lip neoplasm benign	
		Mouth cyst	
		Odontogenic cyst	
		Oral fibroma	
		Oral haemangioma	
		Oral neoplasm benign	
		Oral papilloma	
		Papillary cystadenoma lymphomatosum	
		Pleomorphic adenoma	

Groupings	System Organ Class (SOC)	Preferred Terms (PT)	Higher Level Group Terms (HLGT)
		Salivary gland adenoma	
		Salivary gland cyst	
		Tongue cyst	
		Tongue neoplasm benign	
		Tongue polyp	
		White sponge naevus	
		Anal polyp	
		Appendix adenoma	
		Benign anorectal neoplasm	
		Colon adenoma	
		Large intestine fibroma	
		Large intestine polyp	
		Rectal adenoma	
		Rectal polyp	
		Benign duodenal neoplasm	
		Benign gastric neoplasm	
		Benign oesophageal neoplasm	
		Duodenal polyp	
		Gastric adenoma	
		Gastric cyst	
		Gastric polyps	
		Oesophageal cyst	
		Oesophageal papilloma	
		Oesophageal polyp	
		Biliary cyst	
		Biliary polyp	
		Choledochal cyst	
		Congenital cystic disease of liver	
		Gallbladder polyp	
		Haemorrhagic hepatic cyst	
		Hepatic cyst	

Groupings	System Organ Class (SOC)	Preferred Terms (PT)	Higher Level Group Terms (HLGT)
		Hepatic cyst infection	
		Hepatic cyst ruptured	
		Benign biliary neoplasm	
		Benign hepatic neoplasm	
		Benign hepatobiliary neoplasm	
		Benign neoplasm of ampulla of Vater	
		Biliary adenoma	
		Biliary hamartoma	
		Cholangioadenoma	
		Focal nodular hyperplasia	
		Gallbladder adenoma	
		Gallbladder papilloma	
		Haemangioma of liver	
		Hepatic adenoma	
		Hepatic haemangioma rupture	

Note: MedDRA terms are based on MedDRA version 20.0.

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Strategic Consulting

PK ANALYSIS PLAN

A 24-week Safety, Efficacy, Pharmacodynamic, and Pharmacokinetic Study of Teduglutide in Japanese Pediatric Subjects, Aged 4 Months through 15 Years, with Short Bowel Syndrome who are Dependent on Parenteral Support

Sponsor Protocol No.: SHP633-302 (Amendment 4: 12-Jun-2018)
Investigational Product: SHP633 (Teduglutide)

Final
Date: 13-Sep-2019

CSC Reference No.: SHIR-PCS-129

Takeda Pharmaceutical Company Limited
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SIGNATURE PAGE

Protocol No.: SHP633-302 (Amendment 4: 12-Jun-2018)

Project Title: Pharmacokinetic Analysis Plan (Protocol SHP633-302)

CSC Reference No.: SHIR-PCS-129

Review and Approval

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Certara Strategic Consulting

[redacted] Date

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Certara Strategic Consulting

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Sponsor Review and Approval

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Research & Development
Takeda Pharmaceutical Company Limited
Shire is now part of Takeda

[redacted] Date

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2 LIST OF ABBREVIATIONS

Term	Definition
BLQ	Below limit of quantification
CSC	Certara Strategic Consulting
CV%	Coefficient of variation
eCRF	Electronic case report form
EDT	Electronic Data Transmission
GLP-2	Glucagon-like peptide-2
LLOQ	Lower limit of quantitation
Max	Maximum
Mean	Arithmetic mean
Min	Minimum
N	Sample size
PD	Pharmacodynamic(s)
PK	Pharmacokinetics(s)
PN	Parenteral Support
SBS	Short bowel syndrome
SC	Subcutaneous
SD	Standard deviation
sFTP	Secure File Transfer Protocol
SOP	Standard operating procedures

3 BACKGROUND

This pharmacokinetic (PK) Analysis Plan was created using the study protocol SHP633-302 (Amendment 4, dated 12-Jun-2018). Any further changes to the protocol may require updates to the current analysis plan.

Teduglutide is a novel, recombinant analog of naturally occurring human glucagon-like peptide-2 (GLP-2) that regulates the functional and structural integrity of the cells lining the gastrointestinal tract. Teduglutide is a 33-amino acid peptide that differs from native GLP-2 in the substitution of glycine for alanine at the second position at the N-terminus. As a result, teduglutide demonstrates resistance to degradation by dipeptidyl peptidase 4 and therefore maintains a longer elimination half-life ($t_{1/2}$) of approximately 2 hours compared to the native peptide, which has a $t_{1/2}$ of approximately 7 minutes. Teduglutide has been shown in animal studies and previous human clinical trials to increase villus height and crypt depth in the intestinal epithelium, thereby increasing the absorptive surface area of the intestines.

This analysis plan addresses the multiple-dose PK of teduglutide 0.05 mg/kg administered subcutaneously in Japanese pediatric subjects, aged 4 months through 15 years, with short bowel syndrome who are dependent on parenteral support. The intended methods of data analysis and reporting are included in the current analysis plan.

This document provides guidance to the extent, scope, and method of analysis. However, due to uncertainty of the nature of the data a priori, deviations from this plan may be necessary and will be documented.

4 ANALYSIS PLAN OBJECTIVES

The specific objective of this project is to summarize the concentrations of teduglutide after single and repeated subcutaneous (SC) administration of teduglutide 0.05 mg/kg in Japanese pediatric subjects, aged 4 months through 15 years with short bowel syndrome who are dependent on parenteral support. PK parameters will not be derived due to the sparse data collected (ie, only 2 concentrations post-dose).

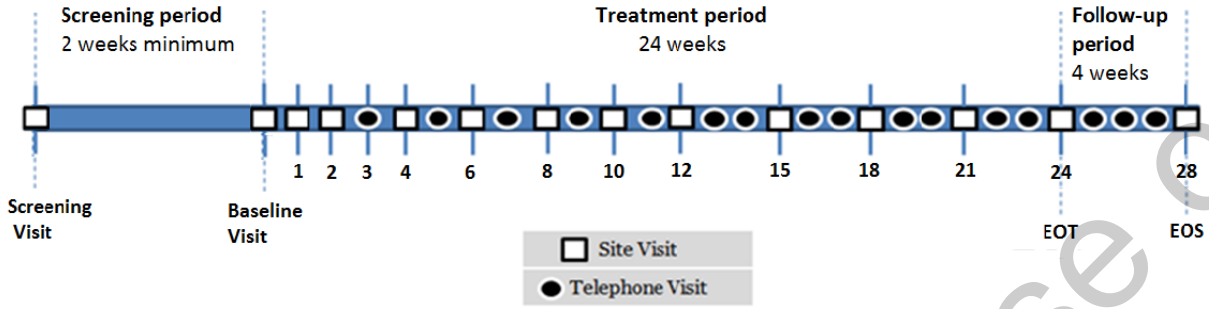
A population PK analysis will be performed after combining multiple studies. The data collected in the current study will be included in the population PK analysis. Details on the population PK analysis are covered in a separate analysis plan.

5 STUDY DESIGN

Protocol SHP633-302 was a 24-week safety, efficacy, pharmacodynamic, and PK study of teduglutide in Japanese pediatric subjects, aged 4 months through 15 years, with short bowel syndrome (SBS) who are dependent on parenteral support. Planned enrollment is a minimum of 5 subjects aged 1 through 15 years and a minimum of 2 subjects of 4 to <12 months corrected for gestational age.

A schematic representation of the study design is presented in Figure 1.

Figure 1. Study Design (SHP633-302)



EOS=end of study; EOT=end of treatment

During the treatment period, a SC dose of 0.05 mg/kg/day of teduglutide was administered once daily to the subjects for 24 weeks. The dose calculation was based on body weight measured at the baseline visit (visit 2) and may be adjusted at Week 12 (visit 14).

Subjects participated in a minimum 2-week screening period from the time of the screening visit to the baseline visit, followed by 24 weeks of treatment. Attempts were made to limit the screening period to 4 weeks. The EOS visit was scheduled at Week 28, 4 weeks after the EOT visit (Week 24).

Following reconstitution, teduglutide was administered by SC injection once daily into 1 of the 4 quadrants of the abdomen (in subjects without a stoma) or into either the thigh or arm. For subjects with a stoma, the quadrant of the abdomen containing the stoma was not used. Each day, the injection site was to be rotated. The site of administration (arm, thigh, or abdomen) of the first teduglutide dose was specified and recorded in the eCRF.

Blood samples for teduglutide concentrations were collected at the baseline and at the Week 4 visits as presented in Table 1.

Table 1. Blood Sample Collection Schedule for Pharmacokinetic Testing

Study week	**Baseline**			**Week 4**		
Visit Number	**2**			**6**		
Hour	0[a]	1	6	0[a]	2	4

[a] Prior to investigational product administration

Some deviations from the above timepoints may have occurred. The investigator or designee kept deviations to a minimum and guided by the following collection windows:

- 0-h (predose) draw: any time prior to the daily dose, on the day of dosing, but at least 14 h after the previous dose (at the week 4 draw).
- 1-h postdose draw: ±10 min
- 2-h postdose draw: ±10 min
- 4-h postdose draw: ±30 min
- 6-h postdose draw: ±30 min

If a blood sample was not collected at Week 4, the uncollected sample could be collected during any future site visit while the subject is still receiving the investigational product. In smaller children for whom blood sampling may impose unacceptable phlebotomy volume, the number of PK samples may have been reduced.

At PK timepoints, the date and time of investigational product administration and blood collection must be recorded on the eCRF.

6 ANALYSIS SET

The PK Population will consist of all enrolled subjects who received at least one SC injection of teduglutide and have evaluable and interpretable PK data.

7 METHODS

7.1 Data Transfer

Electronic files from Takeda will be transferred to Certara Strategic Consulting (CSC) via a Secure File Transfer Protocol (sFTP) site. Electronic Data Transmission (EDT) contact at Takeda will be:

[redacted], **MPH, PhD**
[redacted]
[redacted]
Research & Development
Takeda Pharmaceutical Company Limited
Shire is now part of Takeda
650 East Kendall Street, Cambridge, MA 02142, USA
Tel: [redacted]
Mobile: [redacted]
[redacted]

The following CSC designates will be the EDT contacts:

[redacted], **PhD, DABT**
[redacted]
Certara Strategic Consulting
Montreal, Quebec, Canada H3A 2W5
Tel: [redacted]
Email: [redacted]

[redacted] **PhD, FCP**
[redacted]
Certara Strategic Consulting
Montreal, Quebec, Canada H3A 2W5
Tel. [redacted]
Email: [redacted]

Data will be provided as .csv, sas7dat or SAS transport files by Takeda. A dataset including the subject ID, time of blood sample collection and of treatment (Visit, Date, and Hour), Dose, Treatment, and plasma concentrations of teduglutide.

7.2 Concentrations of Teduglutide

7.2.1 Handling of Incomplete and/or Non-Compliant Data

Subjects with incomplete dosing information or plasma concentration-time profiles will be reviewed by CSC and Takeda for inclusion/exclusion into the PK Population.

Missing dose or sampling dates and/or times may be imputed using nominal times. The imputation strategy will be discussed with Takeda. All samples associated to a missing dosing date and/or time that cannot be imputed will be excluded from the analysis.

7.2.2 Unexpected Data

After database lock, a visual inspection of concentration-time profiles will be performed to determine dataset integrity and potential outliers. Subjects with potential outlier data will be reviewed by CSC and Takeda for inclusion/exclusion from the descriptive statistics on a case-by-case basis.

Any plasma concentrations that cannot be uniquely and unequivocally attributed to a particular subject, visit, or time point based on eCRF records or other observed data records in the study will be treated as incomplete data. Such data will be compiled, commented, and listed separately in the appendix of the report. Incomplete and/or non-compliant data, if any, will be excluded from analysis datasets; no analyses, summaries or graphs will be produced using these data.

7.3 Summarization of Teduglutide Concentrations

Observed concentration values of plasma teduglutide that are reported as below the limit of quantitation (BLQ) will be set to zero for PK analysis and summary statistics.

Individual teduglutide concentrations will be listed and summarized in accordance with the grouping factors (ie, by treatment and for single dose and multiple doses, if applicable). Each data subset will be listed by subject and summarized for each nominal time point. If the actual time of blood collection post-dose deviates by >20% from the nominal time, those sample concentrations will be reported and included in the PK analysis but excluded from summary statistics of concentration tables and mean figures.

Concentration data will be summarized at each nominal time point with the following descriptive statistics: sample size (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), median (Median), minimum (Min), maximum (Max).

Individual concentrations of teduglutide will be reported at the level of significance presented in the observed data files. Reporting rules for the concentrations and summary statistics, will be as follows:

- Mean: 1 more level of significance than the individual value
- SD: 1 more level of significance than the mean
- CV%: always 1 decimal

- Median, Min, Max: at the level of significance reported for the individual value.

Mean concentrations will be reported as zero if all values are zero, and no descriptive statistics will be reported. If the calculated mean concentration is less than the lower limit of quantitation (LLOQ = 1 ng/mL), the value will be reported as calculated. A minimum of three values will be required for calculation of descriptive statistics.

Mean (+SD) teduglutide concentrations vs. nominal sampling time will be presented on linear-linear and log-linear scales at Visit 2 and 6. Results will be presented overall, and by age groups (4 to <12 months and 1 to 15 years).

No PK parameters will be derived considering the sparse data collected at Visit 2 and 6 (ie, only 2 samples after dosing are available).

7.4 Software

Dataset set construction, tables and figures will be generated using Phoenix NLME (Version 7.2 or higher), Phoenix™ WinNonlin® (6.3 or later), R® (Version 3.3.1 or higher) or SAS.

7.5 Quality Control and Quality Assurance

Data sets, table and figures will be quality-controlled by two scientists at CSC (ie, by the originator of the work and by a reviewer) as per CSC SOP-104 entitled, "Managing Data in CSC" and CSC SOP-114 entitled, "Analysis Workflow in CSC".

8 ARCHIVING

The project documentation (documents, report, records, and data) will be retained in hardcopy for a period of 3 years following project completion at CSC (Montreal, Quebec, Canada). During these retention periods, electronic versions of project documentation will be retained on CSC servers, with access limited to personnel assigned to the project. After completion of the retention period, sponsor approval will be requested and documented before destruction of documents.

9 APPENDIX 1: LIST OF TABLES, FIGURES AND LISTINGS

14. PHARMACOKINETIC TABLES AND FIGURES

14.1. Plasma Teduglutide Concentration-Time Tables by Visit

Table 14.2.1. Plasma Teduglutide Concentrations vs. Time after a SC Administration of Teduglutide 0.05 mg/kg – Baseline (Visit 2)
Table 14.2.2. Plasma Teduglutide Concentrations vs. Time after a SC Administration of Teduglutide 0.05 mg/kg – Visit 4 (Week 6)

Table 14.2.3. Plasma Teduglutide Concentrations vs. Time after a SC Administration of Teduglutide 0.05 mg/kg – Baseline (Visit 2) - Unscheduled Visit (if applicable)
Table 14.2.4. Plasma Teduglutide Concentrations vs. Time after a SC Administration of Teduglutide 0.05 mg/kg – Visit 4 (Week 6) - Unscheduled Visit (if applicable)

14.2. Plasma Teduglutide Concentration-Time Tables by Visit and Age

Table 14.2.5. Plasma Teduglutide Concentrations vs. Time after a SC Administration of Teduglutide 0.05 mg/kg – Baseline (Visit 2, 4 to <12 months)
Table 14.2.6. Plasma Teduglutide Concentrations vs. Time after a SC Administration of Teduglutide 0.05 mg/kg – Baseline (Visit 2, 1 to 15 years)

Table 14.2.7. Plasma Teduglutide Concentrations vs. Time after a SC Administration of Teduglutide 0.05 mg/kg – Visit 4 (Week 6, 4 to <12 months)
Table 14.2.8. Plasma Teduglutide Concentrations vs. Time after a SC Administration of Teduglutide 0.05 mg/kg – Visit 4 (Week 6, 1 to 15 years)

16. INDIVIDUAL DATA

16.1. Individual Concentration-Time Plots

Figure 16.1.1. Individual Plasma Teduglutide Concentrations vs. Time after Administration of Teduglutide (Linear and Semi-Log)

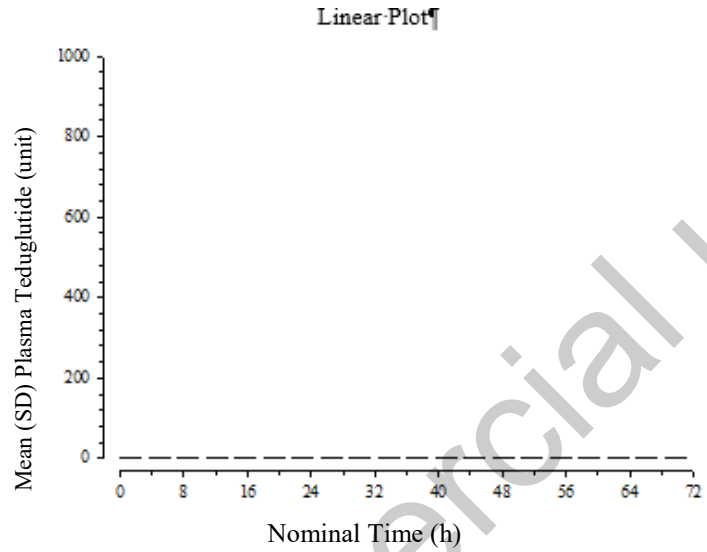
APPENDIX

Appendix 1 Listing of Plasma Teduglutide Concentrations vs. Time after SC Administration of Teduglutide - Unscheduled Visit (if applicable)

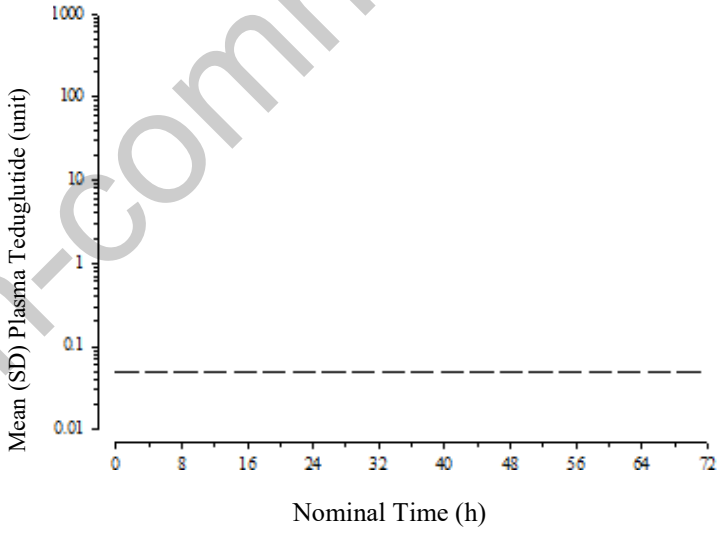
10 APPENDIX 2: TABLE AND FIGURE SHELLS

Concentration-Time Profiles

Figure 14.1.1 Mean (+SD) Plasma Teduglutide Concentrations vs. Time after SC Administration of Teduglutide by Treatment – Baseline (Visit 2) (Linear and Semi-Log)



Semi-Log Plot



Note: These are for presentation purpose, axis titles and range will be set accordingly (ie, to 4 h). BLQ reference line may not be presented. Similar figures will be created for multiple dose administration, if applicable.

Individual and Summary Concentration-Time Tables

Table 14.2.1 Plasma Teduglutide Concentrations vs. Time after a SC Administration of Teduglutide 0.05 mg/kg – Baseline (Visit 2)

Subject ID	Plasma Teduglutide Concentrations (Unit) over Nominal Time (h)		
	0.0	1.0	6.0
1 2 3 4 5 6 7 8 9 10 11 …			
N **Mean** **SD** **Min** **Median** **Max** **CV%**			

. = No data

NC = Not calculated

<0.00 = Below limit of quantification. Set to zero for calculation of summary statistics

/t = Blood draw time deviation >20% of nominal time relative to the start of infusion, excluded from summary statistics

Note: Similar tables will be used at Visit 4