STATISTICAL ANALYSIS PLAN

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STATISTICAL ANALYSIS PLAN

Teduglutide
PHASE 3

A 24-Week Safety, Efficacy, Pharmacokinetic Study of Teduglutide in Japanese Subjects with Short Bowel Syndrome who are Dependent on Parenteral Support

PROTOCOL IDENTIFIER: SHP633-306

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Upon review of this document, the undersigned approves this version of the Tables, Listings, Figures Shell Template, authorizing that the content is acceptable for the reporting of this study.

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ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase, Equivalent To SGPT
AST	Aspartate Aminotransferase, Equivalent To SGOT
AUC	Area Under the Plasma Concentration-Time Curve
AUC_{0-t}	AUC From Zero to The Last Measurable Concentration
BLQ	Below the Lower Limit if Quantification
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CL/F	Apparent Clearance
C_{max}	Maximum Plasma Concentration
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGD	Esophagogastroduodenoscopy
EOT	End of Treatment
ET	Early Termination
GI	Gastrointestinal
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ITT	Intent-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Non-compartmental Analysis
PK	Pharmacokinetics
PP	Per Protocol
PN/IV	Parenteral Nutrition/Intravenous
PT	Preferred Terms
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SBS	Short Bowel Syndrome
SC	Subcutaneous
SI	Standard International
SOC	System Organ Class
$t_{1/2}$	Terminal-Phase Half-Life
t_{max}	Time to C_{max}
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
ULN	Upper Limit of Normal
ULQ	Above the Upper Limit of Quantification
V/F	Apparent Volume of Distribution

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety and pharmacokinetic (PK) data (descriptive summaries only) as described in the final study protocol dated 23 Jan 2018. Specifications for tables, figures, and listings are contained in a separate document. Pharmacokinetics analyses (other than descriptive summaries) will be described in a separate PK SAP.

2. OBJECTIVES, ESTIMAND(S), AND ENDPOINTS

2.1 Objectives

The objectives of this clinical study are to evaluate the safety, efficacy, and pharmacokinetics of teduglutide in Japanese subjects with short bowel syndrome (SBS) who are dependent on parenteral nutrition/intravenous (PN/IV) over a 24-week treatment period.

2.2 Estimand(s)

Absolute change from baseline in weekly PN/IV volume based on diary data at End of Treatment (EOT) in Japanese subjects with PN/IV – dependent SBS in the Intent-to-treat (ITT) Population.

Relative change from baseline in weekly PN/IV volume based on diary data at EOT in Japanese subjects with PN/IV – dependent SBS in the ITT Population.

Number/percentage of subjects who achieved at least 20% decrease from baseline in weekly PN/IV volume based on diary data at Week 20 and Week 24 in Japanese subjects with PN/IV – dependent SBS in the ITT Population.

Number/percentage of subjects who achieved at least 20% decrease from baseline in weekly PN/IV volume based on diary data at Week 20 and Week 24 in Japanese subjects with PN/IV – dependent SBS in the PP Population.

Number/percentage of subjects who achieve at least a 20% reduction from baseline in weekly PN/IV volume based on diary data at each visit in Japanese subjects with PN/IV – dependent SBS in the ITT Population.

2.3 Endpoints

2.3.1 Efficacy Endpoint(s)

The following efficacy endpoints will be analyzed:

- Absolute and relative change from baseline in weekly PN/IV volume by visit and at EOT.
- Percentage of subjects who achieve at least 20% reduction from baseline in weekly PN/IV volume at both Weeks 20 and 24.
- Percentage of subjects who achieve at least a 20% reduction from baseline in weekly PN/IV volume at each visit
- Change in days per week of PN/IV support from baseline by visit.
- Change in plasma citrulline from baseline by visit.
- Number of subjects who are able to completely wean off of PN/IV support.

2.3.2 Safety Endpoint(s)

The safety endpoints include adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, laboratory safety data, antibodies to teduglutide, and 48-hour urine output, body weight, body mass index (BMI) and gastrointestinal-specific tests.

2.3.3 Pharmacokinetic Endpoint(s)

The following parameters will be derived as described in a separate PK SAP and reported separately:

Area under the plasma concentration–time curve from zero to the last measurable concentration (AUC_{0-t})

Maximum plasma concentration (C_{max})

Time to C_{max} (t_{max})

terminal-phase half-life ($t_{1/2}$)

Apparent clearance (CL/F)

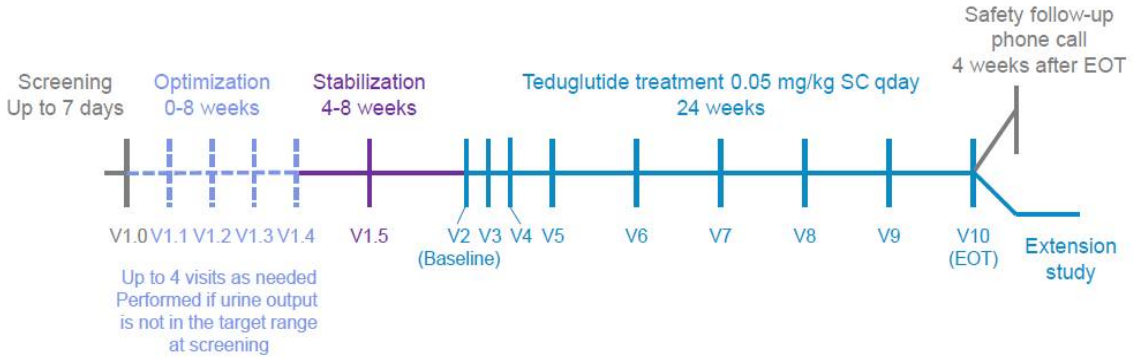
Apparent volume of distribution (V/F)

3. STUDY DESIGN

3.1 General Description

This is an open-label, multicenter study, consisting of a conditional PN/IV optimization period, a mandatory PN/IV stabilization period, and a 24-week treatment period. A schematic representation of the study design is presented in Figure 1.

Figure 1: Study Schematic



3.1.1 Optimization and Stabilization Periods

If at screening, a subject does not have an optimized PN/IV volume, defined as a 48-hour urine output between 2 and 4 L, he/she will enter the optimization period, during which the minimally tolerated stable PN/IV volume will be determined during a period of up to 8 weeks.

All subjects will then enter the stabilization period, during which the target PN/IV volume will be maintained for at least 4 consecutive weeks (8 weeks maximum). Those subjects who fail to stabilize will not proceed further and will not be included in the treatment period.

Schedules of evaluations for the optimization/stabilization period can be found in the protocol.

3.1.2 Treatment Period

Following the stabilization period, subjects will enter a 24-week dosing period, during which all subjects will receive teduglutide 0.05 mg/kg subcutaneously (SC) once daily. At each site visit during the treatment phase, efficacy (adjustments to PN/IV) and safety will be monitored.

Subjects will have blood samples taken for teduglutide PK analysis at predose and 15, 30 minutes and 1, 2, 3, 4, 6, 8, 10, and 12 hours post dose at the baseline visit (Visit 2). Subjects will also have blood samples taken for teduglutide PK analysis at predose and 1 and 2 hours post dose at Week 4 (Visit 5) or Week 12 (Visit 7) of the treatment period.

All subjects who complete the study may participate in a long-term extension study in which eligible subjects will continue to receive teduglutide.

Schedules of evaluations for the Treatment Period can be found in the protocol.

3.2 Randomization

Not applicable for this single arm study.

3.3 Blinding

Not applicable for this open-label study.

3.4 Sample Size and Power Considerations

The sample size of the SHP633-306 study is based on patient prevalence and study design elements; no statistical estimation was involved. Possible medical institutes for SBS studies are limited, given the rarity of the disease and the very limited number of patients with SBS (<1000) in Japan. The applicant considers that 5 treated subjects in SHP633-306 should provide sufficient basic information concerning the efficacy, safety and tolerability as well as PK of teduglutide in the Japanese study population.

4. STATISTICAL ANALYSIS SETS

4.1 All-enrolled Population

All subjects who provided a signed Informed Consent Form (ICF) will be included in the All-enrolled Population.

4.2 Intent-to-treat (ITT) Population

The Intent-to-treat Population will include all subjects who are deemed eligible for teduglutide treatment at the baseline visit (Visit 2).

4.3 Per Protocol (PP) Population

The Per Protocol Population will include all subjects in the ITT Population who complete the treatment period without any major protocol violations that could potentially affect the efficacy conclusions of the study. These situations include the following:

- Missing baseline and/or Week 24 for the weekly PN/IV volume efficacy data based on diary data.

- Non-compliance to study drug administration as defined in Section 5.7

Reasons for exclusion from the PP Population will be presented in the listings for the ITT population.

4.4 Safety Population

The Safety Population will include all subjects in the ITT Population who receive at least 1 dose of study drug.

4.5 Pharmacokinetic (PK) Population

The PK Population will include all subjects who receive at least 1 dose of teduglutide and have at least 1 evaluable post-dose pharmacokinetic concentration value.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

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

For the ITT and Safety Populations, the number and percentage of subjects who completed or prematurely discontinued the treatment period will be presented. Reasons for premature discontinuation from the treatment period as recorded on the end of treatment page of the electronic case report form (eCRF) will be summarized (number and percentage). The number and percentage of subjects who completed the treatment period and enrolled in the extension study will also be presented. A subject data listing will present subject disposition for the All Enrolled Population.

Inclusion and exclusion criteria violations, if any, will be presented in a listing for the All Enrolled Population.

5.2 Demographic and Other Baseline Characteristics

The baseline and demographic characteristics will be summarized for the ITT, PP, and Safety Populations with descriptive statistics defined in Section 11.1. Demographic and baseline characteristics to be presented include:

- Age (at informed consent date) in years, both as a continuous parameter and by categories of <45, 45-<65, and ≥65.
- Sex
- Race
- Ethnicity
- Height (cm) at the Screening visit
- Weight (kg) at the Baseline visit
- BMI (kg/m^2) at the Baseline visit

BMI is calculated as weight (kg)/ $[height (m)]^2$.

The following SBS history information collected at the Screening visit will be summarized with the descriptive statistics defined in Section 11.1 for the ITT, PP and Safety Populations:

- Duration of SBS (years)
- Primary reason for the diagnosis of SBS (Crohn's disease, vascular disease, injury, volvulus, cancer, and other)
- Secondary reason for the diagnosis of SBS (Y/N), secondary reason (Crohn's disease, vascular disease, injury, volvulus, cancer, and other)
- Stoma (Y/N), stoma type (jejunostomy, ileostomy, colostomy, other)
- Remaining colon (Y/N), estimated percent colon remaining, and colon in continuity (Y/N)
- Total estimated remaining small intestinal length (cm) and category (< 25 cm, ≥ 25 cm; < 40 cm, ≥ 40 cm; < 60 cm, ≥ 60 cm)
- Distal/terminal ileum (Y/N) and ileocecal valve (Y/N)

- Method to determine remaining anatomy length (surgery, radiology, and other)

Duration of SBS will be calculated as (Date of ICF Signed – Date of Diagnosis of SBS +1)/365.25.

The following Parenteral Nutrition history information collected at the Screening visit will be summarized with the descriptive statistics defined in Section 11.1 for the ITT, PP and Safety Populations:

- Years since start of PN dependency
- Prescribed weekly PN/IV volume
- Prescribed weekly number of days of PN/IV

Years since start of PN dependency will be calculated as (Date of ICF Signed – Start Date of PN dependency +1)/365.25.

The following Crohn's Disease Evaluation information collected at the Screening visit will be summarized with the descriptive statistics defined in Section 11.1 for the ITT, PP and Safety Populations:

- Medical history of Crohn's disease (Y/N), and current clinical status of Crohn's disease (Active, Inactive)

The following gastrointestinal (GI)–specific testing information collected during the stabilization period will be summarized with the descriptive statistics defined in Section 11.1 for the ITT, PP and Safety Populations:

- For subjects with Crohn's disease, upper GI contrast series with small bowel follow-through: normal, abnormal not clinically significant, abnormal clinically significant
- abdominal ultrasound: normal, abnormal not clinically significant, abnormal clinically significant
- colonoscopy: normal, abnormal not clinically significant, abnormal clinically significant

- sigmoidoscopy: normal, abnormal not clinically significant, abnormal clinically significant

- Esophagogastroduodenoscopy (EGD): normal, abnormal not clinically significant, abnormal clinically significant

Colonoscopy, sigmoidoscopy and EGD will also be presented at Dosing Week 24/early termination (ET).

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

5.3 Medical History

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

5.4 Prior Treatment and Medication

Prior medications will be coded using the World Health Organization Drug Dictionary.

Prior medications are defined as medications taken prior to the first dose of study medication. Partial date imputation for medications is described in Section 11.5.2.

Prior medication use will be summarized by preferred name using the number and percentage of subjects for the Safety Population. Medications will be sorted by descending incidence 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 preferred name, reported name, dose, route of administration, dosing frequency, start date, end date, indication, and type of medication (prior only, concomitant only, prior and concomitant).

5.5 Concomitant Treatment and Medication

Concomitant medications will also be coded using the World Health Organization Drug Dictionary.

Concomitant medications are defined as 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 11.5.2.

Concomitant medications will be summarized in the same way as prior medications (refer to Section 5.4).

Diagnostic, surgical, or therapeutic procedures during the study will be listed.

5.6 Exposure to Investigational Product

The extent of exposure is defined as the number of days on treatment, including any periods of temporary dose interruption, 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 with the descriptive statistics defined in Section 11.1. 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 for the ITT, PP and Safety Populations.

5.7 Measurements of Treatment Compliance

Percent compliance will be calculated as 100 times the number of doses administered (either by the investigator or by the subject per instructions) divided by the number of days on treatment, excluding any periods of temporary dose interruptions due to adverse event that were deemed necessary by the investigator. Number of days on treatment is then calculated as (last dose date – first dose date +1) and the number of days of dose interruption due to adverse event will be excluded, i.e., the sum of (Date of study drug resumed – start date of interruption due to adverse event +1) as recorded on the Study Drug Interruption eCRF form. The information whether the study treatment was administered per instructions is captured on the study drug administration daily diary.

Drug accountability information, first dose date, last dose date, and study medication interruptions (start date of interruption, date study medication resumed, and reason for interruption) will be included in the listings.

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 the descriptive statistics defined in Section 11.1 and the number and percentage of subjects who are ≥ 80% compliant for both the ITT, PP and Safety Populations. Treatment compliance by visit will not be calculated.

5.8 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 provided as part of the CTMS transfer to Biostatistics. Protocol deviations will be summarized for the ITT Population and all protocol deviations will be listed.

6. EFFICACY ANALYSES

All efficacy analyses will be based on the ITT Population and PP Population and be displayed in tables side by side for these two populations. The PP Population will be used for sensitivity analysis purpose. Unless stated otherwise, the baseline for all efficacy analyses will be as defined in Section 11.2.

All efficacy analyses will be descriptive only and there will be no statistical testing.

6.1 Analyses of Efficacy Endpoints

The efficacy endpoints are the following:

- Absolute and relative change from baseline in weekly PN/IV volume by visit and at EOT.
- Percentage of subjects who achieve at least 20% reduction from baseline in weekly PN/IV volume at both Weeks 20 and 24.
- Percentage of subjects who achieve at least a 20% reduction from baseline in weekly PN/IV volume at each visit
- Change in days per week of PN/IV support from baseline by visit.
- Change in plasma citrulline from baseline by visit.
- Number of subjects who were able to completely wean off of PN/IV support.

Analyses on weekly PN/IV support are based on two data sources: the subject diary data and the investigator prescribed data.

The diary weekly PN/IV volume will be calculated based on the daily volumes recorded in subjects' diaries within 14 days prior to each scheduled visit. The calculation will follow the formula below.

Weekly volume = (sum of daily volumes in the diary/number of days with values) *7

Missing daily PN/IV volumes will not be imputed. A maximum of 5 missing days (or at least 9 days of non-missing data) from the 14-day intervals are allowable, otherwise the interval will be classified as missing. One exception to this rule is the baseline interval, which will be filtered back up to 28 days prior to first dose until 9 data points are obtained.

Investigator prescribed data is captured in the PN/IV baseline and PN/IV adjustment in eCRF. Investigator prescribed weekly PN/IV volume reported at each visit will be the most recent PN/IV prescription (from either baseline or prescription adjustments) prior to or on the date of visit.

Data will be summarized at all scheduled visits during the 24-week treatment period. An EOT time point will also be added. Therefore,

- PN/IV weekly volume and days per week of PN/IV support will be summarized at Baseline, Weeks 2, 4, 8, 12, 16, 20, 24 and EOT.

- Plasma citrulline will be summarized at Baseline, Weeks 4, 8, 16, 24 and EOT.

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.

Change in weekly PN/IV volume from baseline

The absolute and percent change in weekly PN/IV volume from baseline to each scheduled visit during the 24-week treatment period, as well as at EOT, will be presented using the descriptive statistics defined in Section 11.1.

Percent change in weekly PN/IV volume from baseline at each scheduled visit will be calculated using the formula below:

% change in weekly PN/IV volume at the visit = [(weekly PN/IV volume at the visit – weekly PN/IV volume at baseline) / weekly PN/IV volume at baseline] * 100

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

Mean ± SE plots of absolute and percent change from baseline in weekly PN/IV volume will be generated. In addition, individual absolute and percent change from baseline in weekly PN/IV volume will be presented for each subject.

Response to Teduglutide at both Weeks 20 and 24

The number and percentage of subjects who demonstrate a response at Week 20 and again at Week 24 will be presented. A response is defined as the achievement of at least a 20% reduction from baseline in weekly PN/IV volume.

Binary response to Teduglutide by visit

The number and percentage of subjects who demonstrate a response at each scheduled visit during the 24-week treatment period, as well as EOT, will be presented. A response is defined as the achievement of at least a 20% reduction from baseline in weekly PN/IV volume.

Change in days per week of PN/IV support from baseline

The absolute and percent change in days per week of PN/IV support from baseline to each scheduled visit during the 24-week treatment period, as well as at EOT, will be presented based on diary and investigator prescribed data using descriptive statistics defined in Section 11.1.

Changes in plasma citrulline from baseline

The absolute and percent change in plasma citrulline from baseline to each scheduled visit during the 24-week treatment period, as well as at EOT, will be presented using descriptive statistics defined in Section 11.1.

Number of subjects who are able to completely wean off PN/IV support

A subject will be considered to have achieved independence from PN/IV (completely weaned off PN/IV) if the investigator prescribes no PN/IV at week 24/EOT and there is no use of PN/IV recorded in the subject diary during the 2 weeks prior to the last dosing visit.

The number and percentage of subjects who completely wean off PN/IV support by Week 24/EOT will be presented.

6.1.1 Sensitivity Analyses of Efficacy Endpoint(s)

The PP Population will be used for sensitivity analysis purpose.

6.2 Multiplicity Adjustment

As there will be no statistical testing given the small sample size, no adjustment for multiple comparisons will be made.

6.3 Subgroup Analyses

No subgroup analysis will be performed.

7. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Population. Safety variables include AEs, clinical laboratory variables, vital signs, ECG variables, physical examination, 48-hour urine output and antibodies to Teduglutide. For each safety variable, the last value collected before the first dose of the investigational product will be used as the baseline for all analyses of that safety variable.

7.1 Adverse Events

AEs will be coded using MedDRA. Investigator verbatim as well as PT and SOC will be included in the listings.

Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens, or intensity increases after receiving the study medication. AEs with an unknown date of onset and a stop date after the start of the study treatment or unknown stop date will be included as TEAEs. 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 11.5.3. 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 TEAEs, severity of TEAEs, 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, and TEAEs leading to discontinuation.

TEAEs 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 presented. Categories summarized are as follows:

- TEAEs,
- Severity of TEAEs,
- Investigator assessment of relationship of TEAEs to study treatment,
- TESAEs.

Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending incidence.

Listings will be provided for serious adverse events (SAEs), AEs leading to death, and AEs leading to discontinuation of study drug. The listings will be sorted by subject identifier and will include SOC, PT, reported term, start date/time, end date/time, frequency, severity, relationship, action taken, and outcome.

For AEs with partial dates, the imputed dates described in Section 11.5.3 will be used to determine the onset interval.

7.1.1 Adverse Events of Special Interest

The preferred terms corresponding to central line systemic infection AEs will be identified by Shire and provided to IQVIA Biostatistics for the analysis. These TEAEs will be presented by PT, sorted by descending incidence.

7.2 Clinical Laboratory Data

Clinical laboratory tests are to be performed at site visits with results processed by a central laboratory. Laboratory tests include the following (Table 2):

Table 2 List of Laboratory Tests

Hematology:

- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- Red blood cell morphology, if needed
- White blood cell count with differential

Urinalysis:

- Blood
- Glucose
- Leucocytes
- Microscopic analysis
- pH
- Protein
- Specific gravity
- Urine Sodium

Pregnancy tests (females of childbearing potential):

- Urine β-HCG

Biochemistry:

- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bilirubin (total, direct and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- Citrulline (plasma)
- C-reactive protein
- Creatinine
- Creatinine clearance
- Gamma-glutamyl transferase
- Glucose
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Triglycerides
- Uric acid

Laboratory parameters will be presented in standard international (SI) units. The summaries will be based on central lab results only.

Quantitative results will be summarized for hematology, serum chemistry, and urinalysis parameters at each scheduled visit during the 24-week treatment period (Baseline, Weeks 2, 4, 8, 12, 16, 20 and 24) and at EOT. Both actual values and change from baseline will be summarized with descriptive statistics defined in Section 11.1.

Clinical laboratory test values are markedly abnormal if they meet either the low or high markedly abnormal criterion listed in Table 3. These criteria are based on lab normal ranges and discussions with the experts. The number and percentage of subjects with post-baseline markedly abnormal values will be summarized by parameter. The

percentages will be calculated relative to the number of subjects with available baseline values and at least 1 post-baseline assessment for the associated parameter. The numerator is the total number of subjects with at least 1 post-baseline markedly abnormal value. A supportive listing of subjects with post-baseline markedly abnormal values will be provided including the subject number, site, parameter, lab dates, baseline, and post-baseline values. This listing will present all values for a subject and laboratory parameter if at least one post-baseline value for that subject and parameter is identified as being markedly abnormal.

Table 3: Markedly Abnormal Laboratory Criteria

Lab parameter	Unit	Lower Limit	Upper Limit
Chemistry			
Albumin	g/L	<=20	>=90
Alkaline Phosphatase	U/L	NA	>2*ULN
ALT	U/L	NA	>3*ULN
Amylase	U/L	<=15	>=350
AST	U/L	NA	>3*ULN
Bilirubin (total)	µmol/L	NA	>2*ULN
BUN	mmol/L	NA	>=10.7
Calcium (total)	mmol/L	<=2.1	>=3.0
Chloride	mmol/L	<=80	>=125
Cholesterol (total)	mmol/L	NA	>=12.9
Creatinine	µmol/L	NA	>=177
C Reactive Protein	mg/L	NA	>=21
Glucose	mmol/L	<=1.7	>=13.9
Gamma glutamyl transferase	U/L	NA	>100
Lipase	U/L	NA	>3*ULN
Magnesium	mmol/L	<LLN	>ULN
Phosphate	mmol/L	NA	>=2.0
Potassium	mmol/L	<=2.5	>=6.5
Sodium	mmol/L	<=120	>=165
Triglycerides	mmol/L	NA	>=5.6
Uric acid	µmol/L	NA	>=624 (males) >=505 (females)
Hematology			
Hematocrit	L/L	<=0.37 (males) <=0.32 (females)	>0.54 (males) NA (females)
Hemoglobin	g/L	<=115 (males) <=95 (females)	NA
Platelets	10^9/L	<=75	>=700

ULN = upper limit of normal
ALT = Alanine Aminotransferase, Equivalent to SGPT
AST = Aspartate Aminotransferase, Equivalent to SGOT
BUN = Blood Urea Nitrogen

Laboratory results will be presented in a listing for each lab panel (chemistry, hematology, and urinalysis) by subject, visit, and parameter. Laboratory values outside of the normal range will be flagged. Categorical urinalysis findings and urine pregnancy results will be presented in a listing only.

7.3 Vital Signs, Body Weight and BMI

The descriptive statistics defined in Section 11.1 will be used to summarize the vital signs (i.e., systolic blood pressure, diastolic blood pressure (mmHg), pulse rate, body temperature, weight, and BMI) by scheduled visit during the 24-week treatment period (Baseline, Weeks 2, 4, 8, 12, 16, 20 and 24) and at EOT for the Safety Population. Both actual values and changes from baseline will be summarized.

7.4 Electrocardiogram

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 4 and 24, and EOT for the Safety Population. All ECG data will be listed.

7.5 Other Safety Data

7.5.1 Physical Examination

Physical examination results will be presented in a listing only.

7.5.2 Antibodies to Teduglutide

A summary table will provide the number of subjects with a sample analyzed for Baseline, Weeks 12, 24 and EOT. The summary table will also provide the number of subjects with an antibody finding at each of those visits in the Safety Population.

All antibody data including neutralizing antibodies and antibody titers will be listed.

7.5.3 48 Hour Oral Fluid Intake and Urine Output

Oral/enteral intake and urine output measurements collected during 48 hours prior to each visit will be summarized by scheduled visit during the 24-week treatment period (Weeks 2, 4, 8, 12, 16, 20 and 24) and at EOT. Oral/enteral intake and urine output measurements for Day 1 and Day2 will be captured in the eCRF. The sum of the measurements of Day 1 and Day 2 in mL will be summarized.

Actual values and both absolute and percent change from baseline will be summarized in the Safety Population with descriptive statistics defined in Section 11.1.

8. PHARMACOKINETIC ANALYSIS

8.1 Pharmacokinetic Parameters

The PK parameters will be derived and estimated based on measured teduglutide plasma concentrations using Non-compartmental analysis (NCA) by a Shire designated vendor in accordance with the PK SAP and generated separately.

8.2 Statistical Analysis of Pharmacokinetic Data

The PK concentration data will be summarized on the PK Population for the protocol scheduled sampling time points:

At Baseline:

- 0 hour (predose) draw: any time prior to the dose
- 15 minutes postdose ±5 minutes
- 30 minutes postdose ±5 minutes
- 1 hour postdose ±10 minutes
- 2 hours postdose ±10 minutes
- 3 hours postdose ±10 minutes
- 4 hours postdose ±30 minutes
- 6 hours postdose ±30 minutes
- 8 hours postdose ±30 minutes
- 10 hours postdose ±30 minutes

- 12 hours postdose ±30 minutes

At Week 4 or Week 12:

- 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
- 1 hour postdose ±10 minutes
- 2 hours postdose ±10 minutes

Descriptive statistics of PK concentration (number of subjects, mean, standard deviation, coefficient of variation (CV) %, geometric mean, geometric CV (%), median, minimum and maximum values) will be calculated at each time point. Mean (±SD) PK concentration by time curves will be provided for the PK population. PK concentration by time will also be plotted by individual subject. A listing for PK concentration data will also be provided.

9. OTHER ANALYSES

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

10. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

Interim analyses may be conducted during the study, as needed. Analyses will be descriptive in nature. No formal comparisons are planned, and no hypotheses will be formally tested. Due to the open-label nature of this study, personnel involved in conducting the interim analyses will have access to treatment assignments.

11. DATA HANDLING CONVENTIONS

11.1 General Data Reporting Conventions

The small sample size resulting from the small study population requires the use of descriptive statistics with a goal of summarizing the sample and thus discourages the use of inferential statistics.

Data from all healthcare setting study sites that participate in this protocol will be combined so that an adequate number of subjects will be available for analysis.

Descriptive statistics will be presented as follows:

- Continuous variables, including those assessed on a discrete scale, will be summarized using the following descriptive statistics: the number of subjects, mean, median, standard deviation, minimum, maximum and 95% confidence interval where needed.

- Categorical variables will be summarized by the number and percentage of subjects in each category (with a category for missing data as needed). Unless otherwise stated, the denominator for percentages is N (the number of subjects in the analysis population).

The following rules will be followed for decimal places and rounding:

- Unless otherwise specified, means (arithmetic and geometric) and medians will be rounded and presented to 1 decimal place more than the raw data and standard deviations 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.

- 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%). This rule also applies to %CV.

- BMI, duration of SBS and years since start of PN dependency should be rounded to 1 decimal place for reporting.

Study day will be calculated as follows;

- If the evaluation date is on or after the date of first day of study medication:

  Study day = date of evaluation – first day of study medication + 1

- If the evaluation date is before the date of first day of study medication:

  Study day = date of evaluation – first day of study medication

All output should have a 3-line header at the upper left margin:

Shire
SHP633-306
Confidential

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 14.x) 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, WHODD) and the dictionary version numbers should be identified in the footnotes to the tables/listings for data coded with a dictionary.

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 subject number and visit/event date.

Dates will be presented in a DDMONYYYY format. Dates with partial missing data will be presented with a dash (i.e., ‘-’) for the missing data (e.g., --JAN2019).

In general, analyses on PP population will be conducted if PP population is different from ITT population.

For the following analyses, data for ITT, PP and Safety will be presented side by side in tables:

- Demographic and other baseline characteristics
- Short bowel syndrome history
- Parenteral nutrition history
- Crohn's disease evaluation
- Gastrointestinal specific testing
- Exposure of investigational product
- Treatment compliance

11.2 Definition of Baseline

For summary purposes, the baseline value will be defined as the last available pre-dose value.

11.3 Definition of Visit Windows

Although there is a visit window from 2 to 7 days around the expected visit date, nominal visits will be used for the per-visit analyses. Therefore, no windowing of visits by actual study day will be done for data obtained at the scheduled visits. For subjects who withdraw from the study pre-maturely, if the ET visit falls into the window of a scheduled visit as defined in the protocol, the ET visit is also summarized for that scheduled visit, unless the scheduled visit already took place.

11.4 Derived Efficacy Endpoints

An EOT time point, defined as the last determination of endpoint or last available measurement from the date of first dose, will be analyzed in addition to the scheduled visits. Unscheduled measurements will not be included in by-visit summaries but can contribute to the EOT value where applicable.

11.5 Handling of Missing, Unused, and Spurious Data

No imputation for missing data (e.g., last observation carried forward) will be applied except for the partial dates to derive treatment emergent adverse events and flagging prior/concomitant medications.

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

11.5.1 Missing Date of Investigational Product

No imputation will be applicable to missing date of investigational product.

11.5.2 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed.

11.5.2.1 Incomplete Start Date

The following derivations will be applied to impute the missing start dates. In each section, dates will be defined using the hierarchy of the derivations. Should any of the following 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.

11.5.2.1.1 Missing Day and Month

1. If only year is known, and it is previous to the year of the informed consent, use June 30th of that year.

2. If only year is known, and it is the year of the first dose date, use the first dose date

3. If only year is known, and it is after the year of the first dose date, then use Jan 1st of that year.

4. If only year is known, and it is the year of the informed consent, use the informed consent date.

11.5.2.1.2 Missing Month Only

The day will be treated as missing and both month and day will be replaced according to the above procedures.

11.5.2.1.3 Missing Day Only

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 the month and year of the informed consent, use the informed consent date.

3. If year and month are known, and the month is not the month and year of the first dose or informed consent, use the first day of the month.

For other incomplete dates, leave as missing.

11.5.2.2 Incomplete Stop Date

The following derivations will be applied to impute the missing stop dates. In each section, dates will be defined using the hierarchy of the derivations. Should any of the following stop dates created be before a start date (either a complete date or an imputed one,), use the (imputed) start date instead of the date that would otherwise be created.

11.5.2.2.1 Missing Day and Month

1. If only year is known and study medication stopped during that year, use the stop date of study medication.

2. If only year is known and study medication stopped after that year, use December 31st of that year.

3. If only year is known and study medication stopped prior to that year, use the first day of the year.

11.5.2.2.2 Missing Month Only

The day will be treated as missing and both month and day will be replaced according to the above procedures.

11.5.2.2.3 Missing Day Only

1. If year and month are known and study medication stopped during that month and year, use the stop date of study medication.

2. If year and month are known and informed consent was provided during that month and year, use the date of informed consent.

3. If only year and month are known and study medication stopped after that year and month, use the last day of the month.

4. If only year and month are known and study medication stopped prior to that year and month, use the first day of the month.

For other incomplete dates, leave as missing.

11.5.3 Missing Date Information for Adverse Events

If any AE records contain only partial dates, these will be handled by imputation, as described in the subsections below.

11.5.3.1 Incomplete Start Date

The following derivations will be applied to impute the missing dates. In each section, dates will be defined using the hierarchy of the derivations. Should any of the following 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.

11.5.3.1.1 Missing Day and Month

1. If only year is known, and it is previous to the year of the informed consent, use June 30th of that year.

2. If only year is known, and it is the year of the first dose date, use the first dose date

3. If only year is known, and it is after the year of the first dose date, then use Jan 1st of that year.

4. If only year is known, and it is the year of the informed consent, use the informed consent date.

11.5.3.1.2 Missing Month Only

The day will be treated as missing and both month and day will be replaced according to the above procedures.

11.5.3.1.3 Missing Day Only

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 the month and year of the informed consent, use the informed consent date.

3. If year and month are known, and the month is not the month and year of the first dose or informed consent, use the first day of the month.

Otherwise, if a start date is unknown, leave as missing.

11.5.3.2 Incomplete Stop Date

No imputation is applied to incomplete stop date.

11.5.4 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries only and will not be reported in the data listings.

11.5.5 Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to the investigational product will be used for incidence summaries only and will not be reported in the data listings.

11.5.6 Character Values of Clinical Laboratory Variables

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

12. ANALYSIS SOFTWARE

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

13. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

There is no change of analysis from protocol.

14. REFERENCES

No references used in this SAP.

15. APPENDICES

No appendices listed in this section.

STATISTICAL ANALYSIS PLAN

Teduglutide
PHASE 3

A 24-Week Safety, Efficacy, Pharmacokinetic Study of Teduglutide in Japanese Subjects with Short Bowel Syndrome who are Dependent on Parenteral Support

PROTOCOL IDENTIFIER: SHP633-306

Study Sponsor(s): Takeda Human Genetic Therapies, Inc.
300 Shire Way Lexington, MA 02421
USA

Author (Company): [redacted] (IQVIA)

Protocol: 23 JAN 2018

SAP Version #:2.0

SAP Date: 15Apr2019

Status: Final

Statistical Analysis Plan Signature Page

SAP Final V2.0 (dated 15Apr2019) for Protocol SHP633-306.

	Name	Signature	Date (DDMMMYYYY)
Author:	[redacted]	[redacted]	[redacted]
Position:	[redacted]		
Company:	IQVIA		

Upon review of this document, the undersigned approves this version of the Tables, Listings, Figures Shell Template, authorizing that the content is acceptable for the reporting of this study.

Approved By:	[redacted]
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Position:	[redacted]
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Position:	[redacted]
Company:	Takeda
Approved By:	[redacted]
Position:	[redacted]
Company:	Takeda

REVISION HISTORY

Version	Issue Date	Summary of Changes
Final 1.0	12Dec2018	New Document
Final 1.1	3Mar2019	**7.1** Added a clarification that TEAEs leading to study treatment discontinuation is summarized and listed. In addition to the listing of AE leading to study drug discontinuation, a new listing of AE leading to study discontinuation is also added. **7.1.1** This whole section of AE of special interest is now updated according to protocol (date 23Jan2018) section 8.3. **7.2** The calculation for percentages of subjects with post-baseline markedly abnormal values is updated by removing the necessity for including baseline values in the calculation. **7.5.3** Revised method of calculating urine output measurement by taking the average of Day 1 and Day 2 urine output measurement, instead of the sum of Day 1 and Day 2.
Final 2.0	15Apr2019	**Statistical Analysis Plan Signature Page** Added [redacted] to signature page. **Throughout the document** Updated branding from Shire to Takeda. **4.1** and throughout the document Changed the wording 'All-enrolled Population' to 'Screened Population'. **6.1**

		Added a listing to the 'Number of subjects who are able to completely wean off PN/IV support' analysis. **7.1.1** Added a reference to indicate that a listing indicating the MedDRA terms to AE of Special Interest can be found in Appendix I. Also added that PT will also be presented within each grouping of AE of Special Interest. **7.2** White Blood Cells is now added to Table 3 Markedly Abnormal Laboratory Criteria table. **11.1** Standard errors required in tables when a corresponding figure is generated.

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase, Equivalent To SGPT
AST	Aspartate Aminotransferase, Equivalent To SGOT
AUC	Area Under the Plasma Concentration-Time Curve
AUC_{0-t}	AUC From Zero to The Last Measurable Concentration
BLQ	Below the Lower Limit if Quantification
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CL/F	Apparent Clearance
C_{max}	Maximum Plasma Concentration
CTMS	Clinical Trial Management System
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EGD	Esophagogastroduodenoscopy
EOT	End of Treatment
ET	Early Termination
GI	Gastrointestinal
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ITT	Intent-To-Treat
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Non-compartmental Analysis
PK	Pharmacokinetics
PP	Per Protocol
PN/IV	Parenteral Nutrition/Intravenous
PT	Preferred Terms
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SBS	Short Bowel Syndrome
SC	Subcutaneous
SI	Standard International
SOC	System Organ Class
$t_{1/2}$	Terminal-Phase Half-Life
t_{max}	Time to C_{max}
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
ULN	Upper Limit of Normal
ULQ	Above the Upper Limit of Quantification
V/F	Apparent Volume of Distribution

1. INTRODUCTION

This statistical analysis plan (SAP) provides a technical and detailed elaboration of the statistical analyses of efficacy, safety and pharmacokinetic (PK) data (descriptive summaries only) as described in the final study protocol dated 23 Jan 2018. Specifications for tables, figures, and listings are contained in a separate document. Pharmacokinetics analyses (other than descriptive summaries) will be described in a separate PK SAP.

2. OBJECTIVES, ESTIMAND(S), AND ENDPOINTS

2.1 Objectives

The objectives of this clinical study are to evaluate the safety, efficacy, and pharmacokinetics of teduglutide in Japanese subjects with short bowel syndrome (SBS) who are dependent on parenteral nutrition/intravenous (PN/IV) over a 24-week treatment period.

2.2 Estimand(s)

Absolute change from baseline in weekly PN/IV volume based on diary data at End of Treatment (EOT) in Japanese subjects with PN/IV – dependent SBS in the Intent-to-treat (ITT) Population.

Relative change from baseline in weekly PN/IV volume based on diary data at EOT in Japanese subjects with PN/IV – dependent SBS in the ITT Population.

Number/percentage of subjects who achieved at least 20% decrease from baseline in weekly PN/IV volume based on diary data at Week 20 and Week 24 in Japanese subjects with PN/IV – dependent SBS in the ITT Population.

Number/percentage of subjects who achieved at least 20% decrease from baseline in weekly PN/IV volume based on diary data at Week 20 and Week 24 in Japanese subjects with PN/IV – dependent SBS in the PP Population.

Number/percentage of subjects who achieve at least a 20% reduction from baseline in weekly PN/IV volume based on diary data at each visit in Japanese subjects with PN/IV – dependent SBS in the ITT Population.

2.3 Endpoints

2.3.1 Efficacy Endpoint(s)

The following efficacy endpoints will be analyzed:

- Absolute and relative change from baseline in weekly PN/IV volume by visit and at EOT.
- Percentage of subjects who achieve at least 20% reduction from baseline in weekly PN/IV volume at both Weeks 20 and 24.
- Percentage of subjects who achieve at least a 20% reduction from baseline in weekly PN/IV volume at each visit
- Change in days per week of PN/IV support from baseline by visit.
- Change in plasma citrulline from baseline by visit.
- Number of subjects who are able to completely wean off of PN/IV support.

2.3.2 Safety Endpoint(s)

The safety endpoints include adverse events (AEs), 12-lead electrocardiogram (ECG), vital signs, laboratory safety data, antibodies to teduglutide, and 48-hour urine output, body weight, body mass index (BMI) and gastrointestinal-specific tests.

2.3.3 Pharmacokinetic Endpoint(s)

The following parameters will be derived as described in a separate PK SAP and reported separately:

Area under the plasma concentration–time curve from zero to the last measurable concentration (AUC_{0-t})

Maximum plasma concentration (C_{max})

Time to C_{max} (t_{max})

terminal-phase half-life ($t_{1/2}$)

Apparent clearance (CL/F)

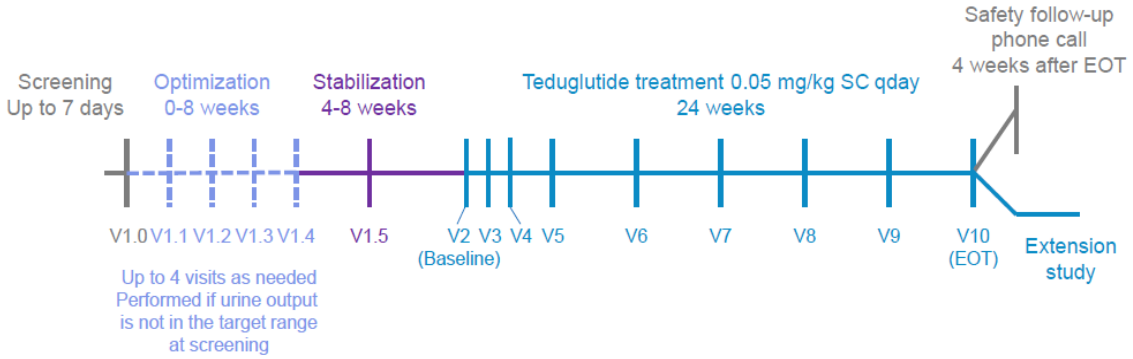
Apparent volume of distribution (V/F)

3. STUDY DESIGN

3.1 General Description

This is an open-label, multicenter study, consisting of a conditional PN/IV optimization period, a mandatory PN/IV stabilization period, and a 24-week treatment period. A schematic representation of the study design is presented in Figure 1.

Figure 1: Study Schematic



3.1.1 Optimization and Stabilization Periods

If at screening, a subject does not have an optimized PN/IV volume, defined as a 48-hour urine output between 2 and 4 L, he/she will enter the optimization period, during which the minimally tolerated stable PN/IV volume will be determined during a period of up to 8 weeks.

All subjects will then enter the stabilization period, during which the target PN/IV volume will be maintained for at least 4 consecutive weeks (8 weeks maximum). Those subjects who fail to stabilize will not proceed further and will not be included in the treatment period.

Schedules of evaluations for the optimization/stabilization period can be found in the protocol.

3.1.2 Treatment Period

Following the stabilization period, subjects will enter a 24-week dosing period, during which all subjects will receive teduglutide 0.05 mg/kg subcutaneously (SC) once daily.

At each site visit during the treatment phase, efficacy (adjustments to PN/IV) and safety will be monitored.

Subjects will have blood samples taken for teduglutide PK analysis at predose and 15, 30 minutes and 1, 2, 3, 4, 6, 8, 10, and 12 hours post dose at the baseline visit (Visit 2). Subjects will also have blood samples taken for teduglutide PK analysis at predose and 1 and 2 hours post dose at Week 4 (Visit 5) or Week 12 (Visit 7) of the treatment period.

All subjects who complete the study may participate in a long-term extension study in which eligible subjects will continue to receive teduglutide.

Schedules of evaluations for the Treatment Period can be found in the protocol.

3.2 Randomization

Not applicable for this single arm study.

3.3 Blinding

Not applicable for this open-label study.

3.4 Sample Size and Power Considerations

The sample size of the SHP633-306 study is based on patient prevalence and study design elements; no statistical estimation was involved. Possible medical institutes for SBS studies are limited, given the rarity of the disease and the very limited number of patients with SBS (<1000) in Japan. The applicant considers that 5 treated subjects in SHP633-306 should provide sufficient basic information concerning the efficacy, safety and tolerability as well as PK of teduglutide in the Japanese study population.

4. STATISTICAL ANALYSIS SETS

4.1 Screened Population

All subjects who provided a signed Informed Consent Form (ICF) will be included in the Screened Population.

4.2 Intent-to-treat (ITT) Population

The Intent-to-treat Population will include all subjects who are deemed eligible for teduglutide treatment at the baseline visit (Visit 2).

4.3 Per Protocol (PP) Population

The Per Protocol Population will include all subjects in the ITT Population who complete the treatment period without any major protocol violations that could potentially affect the efficacy conclusions of the study. These situations include the following:

- Missing baseline and/or Week 24 for the weekly PN/IV volume efficacy data based on diary data.
- Non-compliance to study drug administration as defined in Section 5.7

Reasons for exclusion from the PP Population will be presented in the listings for the ITT population.

4.4 Safety Population

The Safety Population will include all subjects in the ITT Population who receive at least 1 dose of study drug.

4.5 Pharmacokinetic (PK) Population

The PK Population will include all subjects who receive at least 1 dose of teduglutide and have at least 1 evaluable post-dose pharmacokinetic concentration value.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

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

For the ITT and Safety Populations, the number and percentage of subjects who completed or prematurely discontinued the treatment period will be presented. Reasons for premature discontinuation from the treatment period as recorded on the end of treatment page of the electronic case report form (eCRF) will be summarized (number and percentage). The number and percentage of subjects who completed the treatment period and enrolled in the extension study will also be presented. A subject data listing will present subject disposition for the Screened Population.

Inclusion and exclusion criteria violations, if any, will be presented in a listing for the Screened Population.

5.2 Demographic and Other Baseline Characteristics

The baseline and demographic characteristics will be summarized for the ITT, PP, and Safety Populations with descriptive statistics defined in Section 11.1. Demographic and baseline characteristics to be presented include:

- Age (at informed consent date) in years, both as a continuous parameter and by categories of <45, 45-<65, and ≥65.
- Sex
- Race
- Ethnicity
- Height (cm) at the Screening visit
- Weight (kg) at the Baseline visit
- BMI (kg/m^2) at the Baseline visit

BMI is calculated as weight (kg)/ $[height (m)]^2$.

The following SBS history information collected at the Screening visit will be summarized with the descriptive statistics defined in Section 11.1 for the ITT, PP and Safety Populations:

- Duration of SBS (years)
- Primary reason for the diagnosis of SBS (Crohn's disease, vascular disease, injury, volvulus, cancer, and other)
- Secondary reason for the diagnosis of SBS (Y/N), secondary reason (Crohn's disease, vascular disease, injury, volvulus, cancer, and other)
- Stoma (Y/N), stoma type (jejunostomy, ileostomy, colostomy, other)

- Remaining colon (Y/N), estimated percent colon remaining, and colon in continuity (Y/N)
- Total estimated remaining small intestinal length (cm) and category (< 25 cm, ≥ 25 cm; < 40 cm, ≥ 40 cm; < 60 cm, ≥ 60 cm)
- Distal/terminal ileum (Y/N) and ileocecal valve (Y/N)
- Method to determine remaining anatomy length (surgery, radiology, and other)

Duration of SBS will be calculated as (Date of ICF Signed – Date of Diagnosis of SBS +1)/365.25.

The following Parenteral Nutrition history information collected at the Screening visit will be summarized with the descriptive statistics defined in Section 11.1 for the ITT, PP and Safety Populations:

- Years since start of PN dependency
- Prescribed weekly PN/IV volume
- Prescribed weekly number of days of PN/IV

Years since start of PN dependency will be calculated as (Date of ICF Signed – Start Date of PN dependency +1)/365.25.

The following Crohn's Disease Evaluation information collected at the Screening visit will be summarized with the descriptive statistics defined in Section 11.1 for the ITT, PP and Safety Populations:

- Medical history of Crohn's disease (Y/N), and current clinical status of Crohn's disease (Active, Inactive)

The following gastrointestinal (GI)–specific testing information collected during the stabilization period will be summarized with the descriptive statistics defined in Section 11.1 for the ITT, PP and Safety Populations:

- For subjects with Crohn's disease, upper GI contrast series with small bowel follow-through: normal, abnormal not clinically significant, abnormal clinically significant

- abdominal ultrasound: normal, abnormal not clinically significant, abnormal clinically significant

- colonoscopy: normal, abnormal not clinically significant, abnormal clinically significant

- sigmoidoscopy: normal, abnormal not clinically significant, abnormal clinically significant

- Esophagogastroduodenoscopy (EGD): normal, abnormal not clinically significant, abnormal clinically significant

Colonoscopy, sigmoidoscopy and EGD will also be presented at Dosing Week 24/early termination (ET).

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

5.3 Medical History

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

5.4 Prior Treatment and Medication

Prior medications will be coded using the World Health Organization Drug Dictionary.

Prior medications are defined as medications taken prior to the first dose of study medication. Partial date imputation for medications is described in Section 11.5.2.

Prior medication use will be summarized by preferred name using the number and percentage of subjects for the Safety Population. Medications will be sorted by descending incidence 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 preferred name, reported name, dose, route of administration, dosing frequency, start date, end date, indication, and type of medication (prior only, concomitant only, prior and concomitant).

5.5 Concomitant Treatment and Medication

Concomitant medications will also be coded using the World Health Organization Drug Dictionary.

Concomitant medications are defined as 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 11.5.2.

Concomitant medications will be summarized in the same way as prior medications (refer to Section 5.4).

Diagnostic, surgical, or therapeutic procedures during the study will be listed.

5.6 Exposure to Investigational Product

The extent of exposure is defined as the number of days on treatment, including any periods of temporary dose interruption, 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 with the descriptive statistics defined in Section 11.1. 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 for the ITT, PP and Safety Populations.

5.7 Measurements of Treatment Compliance

Percent compliance will be calculated as 100 times the number of doses administered (either by the investigator or by the subject per instructions) divided by the number of days on treatment, excluding any periods of temporary dose interruptions due to adverse event that were deemed necessary by the investigator. Number of days on treatment is then calculated as (last dose date – first dose date +1) and the number of days of dose interruption due to adverse event will be excluded, i.e., the sum of (Date of study drug resumed – start date of interruption due to adverse event +1) as recorded on the Study Drug Interruption eCRF form. The information whether the study treatment was administered per instructions is captured on the study drug administration daily diary.

Drug accountability information, first dose date, last dose date, and study medication interruptions (start date of interruption, date study medication resumed, and reason for interruption) will be included in the listings.

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 the descriptive statistics defined in Section 11.1 and the number and percentage of subjects who are ≥ 80% compliant for both the ITT, PP and Safety Populations. Treatment compliance by visit will not be calculated.

5.8 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 provided as part of the CTMS transfer to Biostatistics. Protocol deviations will be summarized for the ITT Population and all protocol deviations will be listed.

6. EFFICACY ANALYSES

All efficacy analyses will be based on the ITT Population and PP Population and be displayed in tables side by side for these two populations. The PP Population will be used for sensitivity analysis purpose. Unless stated otherwise, the baseline for all efficacy analyses will be as defined in Section 11.2.

All efficacy analyses will be descriptive only and there will be no statistical testing.

6.1 Analyses of Efficacy Endpoints

The efficacy endpoints are the following:

- Absolute and relative change from baseline in weekly PN/IV volume by visit and at EOT.
- Percentage of subjects who achieve at least 20% reduction from baseline in weekly PN/IV volume at both Weeks 20 and 24.
- Percentage of subjects who achieve at least a 20% reduction from baseline in weekly PN/IV volume at each visit
- Change in days per week of PN/IV support from baseline by visit.
- Change in plasma citrulline from baseline by visit.
- Number of subjects who were able to completely wean off of PN/IV support.

Analyses on weekly PN/IV support are based on two data sources: the subject diary data and the investigator prescribed data.

The diary weekly PN/IV volume will be calculated based on the daily volumes recorded in subjects' diaries within 14 days prior to each scheduled visit. The calculation will follow the formula below.

Weekly volume = (sum of daily volumes in the diary/number of days with values) *7

Missing daily PN/IV volumes will not be imputed. A maximum of 5 missing days (or at least 9 days of non-missing data) from the 14-day intervals are allowable, otherwise the interval will be classified as missing. One exception to this rule is the baseline interval, which will be filtered back up to 28 days prior to first dose until 9 data points are obtained.

Investigator prescribed data is captured in the PN/IV baseline and PN/IV adjustment in eCRF. Investigator prescribed weekly PN/IV volume reported at each visit will be the most recent PN/IV prescription (from either baseline or prescription adjustments) prior to or on the date of visit.

Data will be summarized at all scheduled visits during the 24-week treatment period. An EOT time point will also be added. Therefore,

- PN/IV weekly volume and days per week of PN/IV support will be summarized at Baseline, Weeks 2, 4, 8, 12, 16, 20, 24 and EOT.

- Plasma citrulline will be summarized at Baseline, Weeks 4, 8, 16, 24 and EOT.

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.

Change in weekly PN/IV volume from baseline

The absolute and percent change in weekly PN/IV volume from baseline to each scheduled visit during the 24-week treatment period, as well as at EOT, will be presented using the descriptive statistics defined in Section 11.1.

Percent change in weekly PN/IV volume from baseline at each scheduled visit will be calculated using the formula below:

% change in weekly PN/IV volume at the visit = [(weekly PN/IV volume at the visit – weekly PN/IV volume at baseline) / weekly PN/IV volume at baseline] * 100

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

Mean ± SE plots of absolute and percent change from baseline in weekly PN/IV volume will be generated. In addition, individual absolute and percent change from baseline in weekly PN/IV volume will be presented for each subject.

Response to Teduglutide at both Weeks 20 and 24

The number and percentage of subjects who demonstrate a response at Week 20 and again at Week 24 will be presented. A response is defined as the achievement of at least a 20% reduction from baseline in weekly PN/IV volume.

Binary response to Teduglutide by visit

The number and percentage of subjects who demonstrate a response at each scheduled visit during the 24-week treatment period, as well as EOT, will be presented. A response

is defined as the achievement of at least a 20% reduction from baseline in weekly PN/IV volume.

Change in days per week of PN/IV support from baseline

The absolute and percent change in days per week of PN/IV support from baseline to each scheduled visit during the 24-week treatment period, as well as at EOT, will be presented based on diary and investigator prescribed data using descriptive statistics defined in Section 11.1.

Changes in plasma citrulline from baseline

The absolute and percent change in plasma citrulline from baseline to each scheduled visit during the 24-week treatment period, as well as at EOT, will be presented using descriptive statistics defined in Section 11.1.

Number of subjects who are able to completely wean off PN/IV support

A subject will be considered to have achieved independence from PN/IV (completely weaned off PN/IV) if the investigator prescribes no PN/IV at week 24/EOT and there is no use of PN/IV recorded in the subject diary during the 2 weeks prior to the last dosing visit.

The number and percentage of subjects who completely wean off PN/IV support by Week 24/EOT will be presented. There will be a listing of those who completely weaned off PN/IV.

6.1.1 Sensitivity Analyses of Efficacy Endpoint(s)

The PP Population will be used for sensitivity analysis purpose.

6.2 Multiplicity Adjustment

As there will be no statistical testing given the small sample size, no adjustment for multiple comparisons will be made.

6.3 Subgroup Analyses

No subgroup analysis will be performed.

7. SAFETY ANALYSIS

The safety analysis will be performed using the Safety Population. Safety variables include AEs, clinical laboratory variables, vital signs, ECG variables, physical examination, 48-hour urine output and antibodies to Teduglutide. For each safety variable, the last value collected before the first dose of the investigational product will be used as the baseline for all analyses of that safety variable.

7.1 Adverse Events

AEs will be coded using MedDRA. Investigator verbatim as well as PT and SOC will be included in the listings.

Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens, or intensity increases after receiving the study medication. AEs with an unknown date of onset and a stop date after the start of the study treatment or unknown stop date will be included as TEAEs. 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 11.5.3. 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 TEAEs, severity of TEAEs, 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, and TEAEs leading to study treatment discontinuation.

TEAEs 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 presented. Categories summarized are as follows:

- TEAEs,
- Severity of TEAEs,
- Investigator assessment of relationship of TEAEs to study treatment,
- TESAEs.

Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending incidence.

Listings will be provided for serious adverse events (SAEs), AEs leading to death, AEs leading to study treatment discontinuation and AEs leading to study discontinuation. Adverse events leading to study discontinuation are not captured in the AE eCRF page, however primary reason for study discontinuation due to AE is capture in the End of Study eCRF page with the relevant AE number. This data will be used to present the AE leading to study discontinuation. The listings will be sorted by subject identifier and will include SOC, PT, reported term, start date/time, end date/time, frequency, severity, relationship, action taken, and outcome.

For AEs with partial dates, the imputed dates described in Section 11.5.3 will be used to determine the onset interval.

7.1.1 Adverse Events of Special Interest

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

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

- Growth of preexisting 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 preferred terms corresponding to each grouping of events of special interest will be identified by Takeda. A listing indicating the MedDRA terms corresponding to each grouping of events of special interest can be found in Appendix I .

For each grouping of events of special interest, PT, 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.

Listing for AE of special interest will also be provided.

7.2 Clinical Laboratory Data

Clinical laboratory tests are to be performed at site visits with results processed by a central laboratory. Laboratory tests include the following (Table 2):

Table 2 List of Laboratory Tests

Hematology:
- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- Red blood cell morphology, if needed
- White blood cell count with differential

Urinalysis:
- Blood
- Glucose
- Leucocytes
- Microscopic analysis
- pH
- Protein
- Specific gravity
- Urine Sodium

Pregnancy tests (females of childbearing potential):
- Urine β-HCG

Biochemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Amylase
- Aspartate aminotransferase
- Bilirubin (total, direct and indirect)
- Blood urea nitrogen
- Calcium (total)
- Chloride
- Cholesterol
- Citrulline (plasma)
- C-reactive protein
- Creatinine
- Creatinine clearance
- Gamma-glutamyl transferase
- Glucose
- Lipase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Triglycerides
- Uric acid

Laboratory parameters will be presented in standard international (SI) units. The summaries will be based on central lab results only.

Quantitative results will be summarized for hematology, serum chemistry, and urinalysis parameters at each scheduled visit during the 24-week treatment period (Baseline, Weeks 2, 4, 8, 12, 16, 20 and 24) and at EOT. Both actual values and change from baseline will be summarized with descriptive statistics defined in Section 11.1.

Clinical laboratory test values are markedly abnormal if they meet either the low or high markedly abnormal criterion listed in Table 3. These criteria are based on lab normal ranges and discussions with the experts. The number and percentage of subjects with post-baseline markedly abnormal values will be summarized by parameter. The

percentages will be calculated relative to the number of subjects with at least 1 post-baseline assessment for the associated parameter. The numerator is the total number of subjects with at least 1 post-baseline markedly abnormal value. A supportive listing of subjects with post-baseline markedly abnormal values will be provided including the subject number, site, parameter, lab dates, baseline, and post-baseline values. This listing will present all values for a subject and laboratory parameter if at least one post-baseline value for that subject and parameter is identified as being markedly abnormal.

Table 3: Markedly Abnormal Laboratory Criteria

Lab parameter	Unit	Lower Limit	Upper Limit
Chemistry			
Albumin	g/L	<=20	>=90
Alkaline Phosphatase	U/L	NA	>2*ULN
ALT	U/L	NA	>3*ULN
Amylase	U/L	<=15	>=350
AST	U/L	NA	>3*ULN
Bilirubin (total)	µmol/L	NA	>2*ULN
BUN	mmol/L	NA	>=10.7
Calcium (total)	mmol/L	<=2.1	>=3.0
Chloride	mmol/L	<=80	>=125
Cholesterol (total)	mmol/L	NA	>=12.9
Creatinine	µmol/L	NA	>=177
C Reactive Protein	mg/L	NA	>=21
Glucose	mmol/L	<=1.7	>=13.9
Gamma glutamyl transferase	U/L	NA	>100
Lipase	U/L	NA	>3*ULN
Magnesium	mmol/L	<LLN	>ULN
Phosphate	mmol/L	NA	>=2.0
Potassium	mmol/L	<=2.5	>=6.5
Sodium	mmol/L	<=120	>=165
Triglycerides	mmol/L	NA	>=5.6
Uric acid	µmol/L	NA	>=624 (males) >=505 (females)
Hematology			
Hematocrit	L/L	<=0.37 (males) <=0.32 (females)	>0.54 (males) NA (females)
Hemoglobin	g/L	<=115 (males) <=95 (females)	NA
Platelets	10^9/L	<=75	>=700

White Blood Cells	10^9/L	<=2.8	>=16.0

ULN = upper limit of normal
ALT = Alanine Aminotransferase, Equivalent to SGPT
AST = Aspartate Aminotransferase, Equivalent to SGOT
BUN = Blood Urea Nitrogen

Laboratory results will be presented in a listing for each lab panel (chemistry, hematology, and urinalysis) by subject, visit, and parameter. Laboratory values outside of the normal range will be flagged. Categorical urinalysis findings and urine pregnancy results will be presented in a listing only.

7.3 Vital Signs, Body Weight and BMI

The descriptive statistics defined in Section 11.1 will be used to summarize the vital signs (i.e., systolic blood pressure, diastolic blood pressure (mmHg), pulse rate, body temperature, weight, and BMI) by scheduled visit during the 24-week treatment period (Baseline, Weeks 2, 4, 8, 12, 16, 20 and 24) and at EOT for the Safety Population. Both actual values and changes from baseline will be summarized.

7.4 Electrocardiogram

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 4 and 24, and EOT for the Safety Population. All ECG data will be listed.

7.5 Other Safety Data

7.5.1 Physical Examination

Physical examination results will be presented in a listing only.

7.5.2 Antibodies to Teduglutide

A summary table will provide the number of subjects with a sample analyzed for Baseline, Weeks 12, 24 and EOT. The summary table will also provide the number of subjects with an antibody finding at each of those visits in the Safety Population.

All antibody data including neutralizing antibodies and antibody titers will be listed.

7.5.3 48 Hour Oral Fluid Intake and Urine Output

Oral/enteral intake and urine output measurements collected during 48 hours prior to each visit will be summarized by scheduled visit during the 24-week treatment period (Weeks 2, 4, 8, 12, 16, 20 and 24) and at EOT. Oral/enteral intake and urine output measurements for Day 1 and Day2 will be captured in the eCRF. The average of Day 1 and Day 2 measurement in mL will be summarized.

Actual values and both absolute and percent change from baseline will be summarized in the Safety Population with descriptive statistics defined in Section 11.1.

8. PHARMACOKINETIC ANALYSIS

8.1 Pharmacokinetic Parameters

The PK parameters will be derived and estimated based on measured teduglutide plasma concentrations using Non-compartmental analysis (NCA) by a Takeda designated vendor in accordance with the PK SAP and generated separately.

8.2 Statistical Analysis of Pharmacokinetic Data

The PK concentration data will be summarized on the PK Population for the protocol scheduled sampling time points:

At Baseline:

- 0 hour (predose) draw: any time prior to the dose
- 15 minutes postdose ±5 minutes
- 30 minutes postdose ±5 minutes
- 1 hour postdose ±10 minutes
- 2 hours postdose ±10 minutes
- 3 hours postdose ±10 minutes
- 4 hours postdose ±30 minutes
- 6 hours postdose ±30 minutes
- 8 hours postdose ±30 minutes

- 10 hours postdose ±30 minutes
- 12 hours postdose ±30 minutes

At Week 4 or Week 12:

- 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
- 1 hour postdose ±10 minutes
- 2 hours postdose ±10 minutes

Descriptive statistics of PK concentration (number of subjects, mean, standard deviation, coefficient of variation (CV) %, geometric mean, geometric CV (%), median, minimum and maximum values) will be calculated at each time point. Mean (±SD) PK concentration by time curves will be provided for the PK population. PK concentration by time will also be plotted by individual subject. A listing for PK concentration data will also be provided.

9. OTHER ANALYSES

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

10. INTERIM ANALYSIS/ DATA MONITORING (REVIEW) COMMITTEE

Interim analyses may be conducted during the study, as needed. Analyses will be descriptive in nature. No formal comparisons are planned, and no hypotheses will be formally tested. Due to the open-label nature of this study, personnel involved in conducting the interim analyses will have access to treatment assignments.

11. DATA HANDLING CONVENTIONS

11.1 General Data Reporting Conventions

The small sample size resulting from the small study population requires the use of descriptive statistics with a goal of summarizing the sample and thus discourages the use of inferential statistics.

Data from all healthcare setting study sites that participate in this protocol will be combined so that an adequate number of subjects will be available for analysis.

Descriptive statistics will be presented as follows:

- Continuous variables, including those assessed on a discrete scale, will be summarized using the following descriptive statistics: the number of subjects, mean, median, standard deviation, minimum, maximum and 95% confidence interval where needed. The standard errors will be calculated in the tables if a corresponding figure is generated (e.g., efficacy tables).

- Categorical variables will be summarized by the number and percentage of subjects in each category (with a category for missing data as needed). Unless otherwise stated, the denominator for percentages is N (the number of subjects in the analysis population).

The following rules will be followed for decimal places and rounding:

- Unless otherwise specified, means (arithmetic and geometric) and medians will be rounded and presented to 1 decimal place more than the raw data and standard deviations 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.

- 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%). This rule also applies to %CV.

- BMI, duration of SBS and years since start of PN dependency should be rounded to 1 decimal place for reporting.

Study day will be calculated as follows;

- If the evaluation date is on or after the date of first day of study medication:

  Study day = date of evaluation – first day of study medication + 1

- If the evaluation date is before the date of first day of study medication:

  Study day = date of evaluation – first day of study medication

All output should have a 3-line header at the upper left margin:

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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 14.x) 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, WHODD) and the dictionary version numbers should be identified in the footnotes to the tables/listings for data coded with a dictionary.

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 subject number and visit/event date.

Dates will be presented in a DDMONYYYY format. Dates with partial missing data will be presented with a dash (i.e., '-') for the missing data (e.g., --JAN2019).

In general, analyses on PP population will be conducted if PP population is different from ITT population.

For the following analyses, data for ITT, PP and Safety will be presented side by side in tables:

- Demographic and other baseline characteristics
- Short bowel syndrome history
- Parenteral nutrition history
- Crohn's disease evaluation
- Gastrointestinal specific testing
- Exposure of investigational product
- Treatment compliance

11.2 Definition of Baseline

For summary purposes, the baseline value will be defined as the last available pre-dose value.

11.3 Definition of Visit Windows

Although there is a visit window from 2 to 7 days around the expected visit date, nominal visits will be used for the per-visit analyses. Therefore, no windowing of visits by actual study day will be done for data obtained at the scheduled visits. For subjects who withdraw from the study pre-maturely, if the ET visit falls into the window of a scheduled visit as defined in the protocol, the ET visit is also summarized for that scheduled visit, unless the scheduled visit already took place.

11.4 Derived Efficacy Endpoints

An EOT time point, defined as the last determination of endpoint or last available measurement from the date of first dose, will be analyzed in addition to the scheduled visits. Unscheduled measurements will not be included in by-visit summaries but can contribute to the EOT value where applicable.

11.5 Handling of Missing, Unused, and Spurious Data

No imputation for missing data (e.g., last observation carried forward) will be applied except for the partial dates to derive treatment emergent adverse events and flagging prior/concomitant medications.

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

11.5.1 Missing Date of Investigational Product

No imputation will be applicable to missing date of investigational product.

11.5.2 Missing Date Information for Prior or Concomitant Medications

For prior or concomitant medications, incomplete (i.e., partially missing) start date and/or stop date will be imputed.

11.5.2.1 Incomplete Start Date

The following derivations will be applied to impute the missing start dates. In each section, dates will be defined using the hierarchy of the derivations. Should any of the following 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.

11.5.2.1.1 Missing Day and Month

1. If only year is known, and it is previous to the year of the informed consent, use June 30th of that year.

2. If only year is known, and it is the year of the first dose date, use the first dose date

3. If only year is known, and it is after the year of the first dose date, then use Jan 1st of that year.

4. If only year is known, and it is the year of the informed consent, use the informed consent date.

11.5.2.1.2 Missing Month Only

The day will be treated as missing and both month and day will be replaced according to the above procedures.

11.5.2.1.3 Missing Day Only

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 the month and year of the informed consent, use the informed consent date.

3. If year and month are known, and the month is not the month and year of the first dose or informed consent, use the first day of the month.

For other incomplete dates, leave as missing.

11.5.2.2 Incomplete Stop Date

The following derivations will be applied to impute the missing stop dates. In each section, dates will be defined using the hierarchy of the derivations. Should any of the following stop dates created be before a start date (either a complete date or an imputed one,), use the (imputed) start date instead of the date that would otherwise be created.

11.5.2.2.1 Missing Day and Month

1. If only year is known and study medication stopped during that year, use the stop date of study medication.

2. If only year is known and study medication stopped after that year, use December 31st of that year.

3. If only year is known and study medication stopped prior to that year, use the first day of the year.

11.5.2.2.2 Missing Month Only

The day will be treated as missing and both month and day will be replaced according to the above procedures.

11.5.2.2.3 Missing Day Only

1. If year and month are known and study medication stopped during that month and year, use the stop date of study medication.

2. If year and month are known and informed consent was provided during that month and year, use the date of informed consent.

3. If only year and month are known and study medication stopped after that year and month, use the last day of the month.

4. If only year and month are known and study medication stopped prior to that year and month, use the first day of the month.

For other incomplete dates, leave as missing.

11.5.3 Missing Date Information for Adverse Events

If any AE records contain only partial dates, these will be handled by imputation, as described in the subsections below.

11.5.3.1 Incomplete Start Date

The following derivations will be applied to impute the missing dates. In each section, dates will be defined using the hierarchy of the derivations. Should any of the following 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.

11.5.3.1.1 Missing Day and Month

1. If only year is known, and it is previous to the year of the informed consent, use June 30th of that year.

2. If only year is known, and it is the year of the first dose date, use the first dose date

3. If only year is known, and it is after the year of the first dose date, then use Jan 1st of that year.

4. If only year is known, and it is the year of the informed consent, use the informed consent date.

11.5.3.1.2 Missing Month Only

The day will be treated as missing and both month and day will be replaced according to the above procedures.

11.5.3.1.3 Missing Day Only

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 the month and year of the informed consent, use the informed consent date.

3. If year and month are known, and the month is not the month and year of the first dose or informed consent, use the first day of the month.

Otherwise, if a start date is unknown, leave as missing.

11.5.3.2 Incomplete Stop Date

No imputation is applied to incomplete stop date.

11.5.4 Missing Severity Assessment for Adverse Events

If severity is missing for an AE starting prior to the date of the first dose of investigational product, then a severity of "Mild" will be assigned. If the severity is missing for an AE starting on or after the date of the first dose of investigational product, then a severity of "Severe" will be assigned. The imputed values for severity assessment will be used for incidence summaries only and will not be reported in the data listings.

11.5.5 Missing Relationship to Investigational Product for Adverse Events

If the relationship to investigational product is missing for an AE starting on or after the date of the first dose of investigational product, a causality of "Related" will be assigned. The imputed values for relationship to the investigational product will be used for incidence summaries only and will not be reported in the data listings.

11.5.6 Character Values of Clinical Laboratory Variables

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

12. ANALYSIS SOFTWARE

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

13. CHANGES TO ANALYSIS SPECIFIED IN PROTOCOL

There is no change of analysis from protocol.

14. REFERENCES

No references used in this SAP.

15. APPENDICES

Appendix I – MedDRA Terms Corresponding to Each Grouping of Adverse Event of Special Interest

Groupings	System Organ Class (SOC)	Preferred Terms (PT)	Higher Level Group Terms (HLGTs)
Tumor promoting ability	Neoplasms benign, malignant and unspecified		
Growth preexisting polyps		Duodenal polyp	
		Intestinal polyp	
		Rectal Polyp	
		Large intestine polyp	
		Gastrointestinal polyp	
Benign neoplasia GI			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	

Groupings	System Organ Class (SOC)	Preferred Terms (PT)	Higher Level Group Terms (HLGTs)
		Gastrointestinal tract adenoma	
		Gingival cyst	
		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 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	

Groupings	System Organ Class (SOC)	Preferred Terms (PT)	Higher Level Group Terms (HLGTs)
		Pleomorphic adenoma	
		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 leiomyoma	
		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 (HLGTs)
		Hepatic cyst infection	
		Hepatic cyst ruptured	
		Hepatobiliary cyst	
		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	
		Hepatic hamartoma	

Note: MedDRA terms are based on MedDRA version 21.0.

CERTARA®

Strategic Consulting

PK ANALYSIS PLAN

A 24-Week Safety, Efficacy, Pharmacokinetic Study of Teduglutide in Japanese Subjects with Short Bowel Syndrome who are Dependent on Parenteral Support

Sponsor Protocol No.: SHP633-306 (Amendment 1: 27-Sep-2018)
Investigational Product: SHP633 (Teduglutide)

Final
Date: 13-Sep-2019

CSC Reference No.: SHIR-PSC-129

Takeda Pharmaceutical Company Limited
Shire is now part of Takeda
650 East Kendall Street, Cambridge, MA 02142, USA

SIGNATURE PAGE

Protocol No.: SHP633-306 (Amendment 1: 27 Sep 2018)

Project Title: Pharmacokinetic Analysis Plan (Protocol SHP633-306)

CSC Reference No.: SHIR-PSC-129

Review and Approval

[redacted] PhD, DABT

Certara Strategic Consulting

[redacted]

Date

[redacted] PhD, FCP

Certara Strategic Consulting

[redacted]

Date

Sponsor Review and Approval

[redacted] MPH, PhD

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

[redacted]

Date

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS

Term	Definition
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable concentrations, calculated using the linear trapezoid rule.
AUC_{0-inf}	Area under the plasma concentration time curve from time zero to infinity
BLQ	Below limit of quantification
CL/F	Apparent clearance
C_{max}	Maximum plasma concentration
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
λ_z	Lambda z, first-order rate constant of the terminal elimination phase
Max	Maximum
Mean	Arithmetic mean
Min	Minimum
N	Sample size
NCA	Non-compartmental analysis
PK	Pharmacokinetics(s)
PN/IV	Parenteral nutrition or intravenous
QD	Once daily
SBS	Short bowel syndrome
SC	Subcutaneous
SD	Standard deviation
sFTP	Secure File Transfer Protocol
SOP	Standard operating procedures
$t_{1/2}$	Terminal elimination half-life
T_{last}	Time of time of the last quantifiable concentration
T_{max}	Time of maximum observed plasma concentration
Vz/F	Apparent volume of distribution

3 BACKGROUND

This pharmacokinetic (PK) Analysis Plan was created using the study protocol SHP633-306 (Amendment 1, dated 27 Sep 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 PK of teduglutide (0.05 mg/kg) following subcutaneous (SC) administration in Japanese subjects with short bowel syndrome (SBS) who are dependent on parenteral nutrition or intravenous (PN/IV) 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 PK of teduglutide after a SC administration of teduglutide 0.05 mg/kg in adult Japanese subjects with SBS who are dependent on PN/IV support. PK parameters will be derived using non-compartmental analysis (NCA).

5 STUDY DESIGN

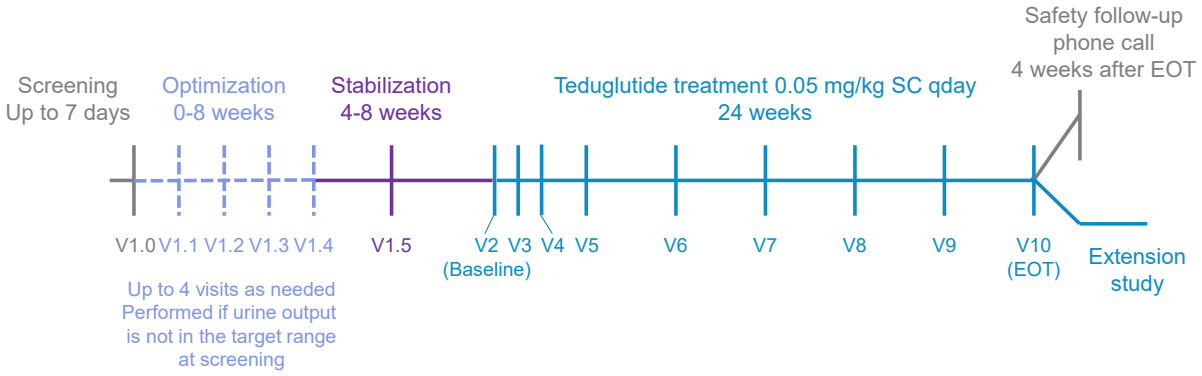
Protocol SHP633-306 was an open-label, multicenter study, consisting of a conditional PN/IV optimization period, a mandatory PN/IV stabilization period, and a 24-week treatment period.

Japanese male or female subjects 16 years of age or older (at the time of signing informed consent) were considered eligible for the study. If at screening, a subject did not have an optimized PN/IV volume, defined as a 48-hour urine output between 2 and 4 L, he/she entered the optimization period, during which the minimally tolerated stable PN/IV volume was determined during a period of up to 8 weeks. If it was not possible to keep the subject adequately hydrated and nourished within the target urine output range, the minimally tolerated PN/IV volume was documented.

All subjects entered the stabilization period, during which the target PN/IV volume was maintained for at least 4 consecutive weeks (8 weeks maximum). Following the stabilization period, subjects entered a 24-week dosing period, during which all subjects received teduglutide 0.05 mg/kg SC once daily. At each site visit during the treatment phase, efficacy (adjustments to PN/IV) and safety was monitored.

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

Figure 1. Study Design (SHP633-302)



SC=subcutaneous; qday=once daily; EOT=end of treatment

Teduglutide (0.05 mg/kg) was administered SC once daily into 1 of the 4 quadrants of the abdomen or either thigh or arm for 24 weeks. Subjects had blood samples taken for teduglutide PK analysis at predose, at 15, 30 minutes and 1, 2, 3, 4, 6, 8, 10, and 12 hours post dose at Visit 2. Subjects also had blood samples taken for teduglutide PK analysis at predose and 1 and 2 hours post dose at Visit 5 (Week 4) or Visit 7 (Week 12) of the treatment period. The first dose of teduglutide was administered by the study physician at the baseline visit (Visit 2). At this visit, subjects had blood samples taken for teduglutide PK analysis:

- 0-hour (predose) draw: any time prior to the dose
- 15 minutes postdose: ±5 minutes
- 30 minutes postdose: ±5 minutes
- 1 hour postdose: ±10 minutes
- 2 hours postdose: ±10 minutes
- 3 hours postdose: ±10 minutes
- 4 hours postdose: ±30 minutes
- 6 hours postdose: ±30 minutes
- 8 hours postdose: ±30 minutes
- 10 hours postdose: ±30 minutes
- 12 hours postdose: ±30 minutes

Subjects also had blood samples taken for teduglutide PK analysis at Week 4 (Visit 5) or Week 12 (Visit 7):

- 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
- 1 hour postdose: ±10 minutes
- 2 hours postdose: ±10 minutes

All subjects who completed the study may have participated in a long-term extension study (SHP633-307) in which they continued receiving teduglutide.

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 profile.

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. The Electronic Data Transmission (EDT) contact at Takeda is:

[redacted], MPH, PhD
[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]

The following CSC designates are the EDT contacts:

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

[redacted], PhD, FCP
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 Noncompartmental PK Analysis

7.2.1 Concentration Data

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.

7.2.2 Pharmacokinetic Parameters of Teduglutide

All plasma PK parameters will be derived using actual or nominal times (when actual time is not available) relative to the time of study drug administration. PK parameters will be derived using NCA methods[1] based on individual plasma concentration-time data for teduglutide collected at baseline (day 0) (or at any other future site visit if subject was unable to provide blood samples at day 0) as described in Table 1.

Table 1. PK Parameters Teduglutide in Plasma

Parameters	Definitions
AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the last measurable concentrations, calculated using the linear trapezoid rule.
AUC_{0-inf}	Area under the plasma concentration time curve from time zero to infinity, calculated using the formula $AUC_{0-t} + (C_{last} / \lambda_Z)$, where C_{last} is the last quantifiable concentration. The AUC_{0-inf} will be calculated using the linear trapezoid rule. If the percent of extrapolation (% AUC_{Extrap}) is > 20%, the value of AUC_{0-inf} (and other derived parameters such as CL/F and V_Z/F) will be reported but not taken into account in the calculation of descriptive statistics.
λ_Z	First-order rate constant of the terminal elimination phase, calculated by log-linear regression analysis over the terminal log-linear segment of the plasma concentration-time curve. Assessments of λ_Z included the key considerations listed below this table.
$t_{1/2}$	Terminal elimination half-life, calculated as $ln(2)/ \lambda_z$. Assessments of $t_{1/2}$ followed the key considerations for λ_Z, as listed below this table.
% AUC_{Extrap}	The percentage of AUC_{0-inf} estimated by extrapolation from T_{last} to infinity, calculated as $(AUC_{0-inf} - AUC_{0-t})/ AUC_{0-inf}$ x 100.
CL/F	Apparent clearance, calculated as Dose / AUC_{0-inf}.
V_Z/F	Apparent volume of distribution, calculated as Dose / AUC_{0-inf} x λ_z.

The assessments of λ_z will include the following considerations:

- At least 3 time points (in which the first time point must be greater than t_{max}) with measurable serum concentrations were required for the calculation of λ_Z.
- λ_z must be positive, and calculated from at least three data points in the terminal phase of the concentration-time profile.
- Points prior to C_{max} are not used.
- $R^2_{adj} \geq 0.7$ for the log-linear regression analysis of λ_z.

No value for λ_Z and related parameters (eg, AUC_{0-inf}, $t_{1/2}$, CL/F and/or V_Z/F) will be reported for concentration-time profiles that do not exhibit an elimination phase in the concentration versus time profile (ie, if $R^2_{adj} < 0.7$ for the log-linear regression analysis of λ_Z).

7.3 Statistical Methods

7.3.1 Concentrations of Teduglutide

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 by treatment for single dose (day 0) and multiple doses (ie, unscheduled visit, if applicable).

7.3.2 PK Parameters of Teduglutide

Individual plasma teduglutide PK parameters will be listed and summarized in accordance with the grouping factors (ie, by treatment and for single dose and multiple doses, if applicable) with the following descriptive statistics: n, Mean, SD, CV%, Median, Min, Max, Geometric Mean and CV% Geometric Mean.

Reporting rules for the PK (with the exception of C_{max}) and summary statistics will be as follows:

- Individual values with the number of decimals that will allow 3 significant figures to be presented for the minimum value of the parameter, except for t_{max} which are parameters of time to be reported with 2 decimals.
- Mean and Geometric Mean: 1 more decimal than the individual value

- SD: 1 more decimal than the mean
- CV% and CV% Geometric Mean: always 1 decimal
- Median, Min, Max: same number of decimals as the individual value

Individual and summary statistics for the PK parameter C_{max} will follow the reporting rules described for teduglutide concentrations (Section 7.3.1).

Mean concentrations will be reported as zero if all values are zero, and no descriptive statistics will be reported. A minimum of three values will be required for calculation of descriptive statistics.

7.4 Data Handling

7.4.1 Handling of Missing Plasma Concentrations

PK parameters will be calculated for subjects with sufficient plasma sample data to assess PK parameters, ie with at least 2 postdose concentrations. Concentrations for subjects with missing samples will not be excluded from the concentration summary statistics.

For the PK parameter calculations following a single dose (Day 0), a missing predose value will be set to zero. For the PK parameter calculations following multiple doses (ie, any other future site visit after day 0), a missing predose value will be set to the median value observed in the treatment group, if available.

Unless otherwise noted, data summaries will be performed only on observed data.

7.4.2 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.

7.4.3 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.

Multiple observations at the same time point will be averaged for the calculation of PK parameters.

7.5 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.

7.6 Quality Control and Quality Assurance

Data sets, table and figures will be quality-controlled by two scientists at CSC (i.e., by the originator of the work and by a reviewer) as per CSC SOP[redacted] entitled, "Managing Data in CSC" and CSC SOP[redacted] 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 REFERENCES

1. Gabrielsson, J., Weiner, D. (2016). Pharmacokinetic & Pharmacodynamic Data Analysis: Concepts and Applications (5th Edition). Swedish Pharmaceutical Society, Stockholm, Sweden.

10 APPENDIX 1: LIST OF TABLES, FIGURES AND LISTINGS

14. PHARMACOKINETIC TABLES AND FIGURES

14.1. Plasma Teduglutide Mean Concentration-Time Profiles

14.2. Plasma Teduglutide Concentration-Time Tables

14.3. Plasma Teduglutide Pharmacokinetic Parameter Tables

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)

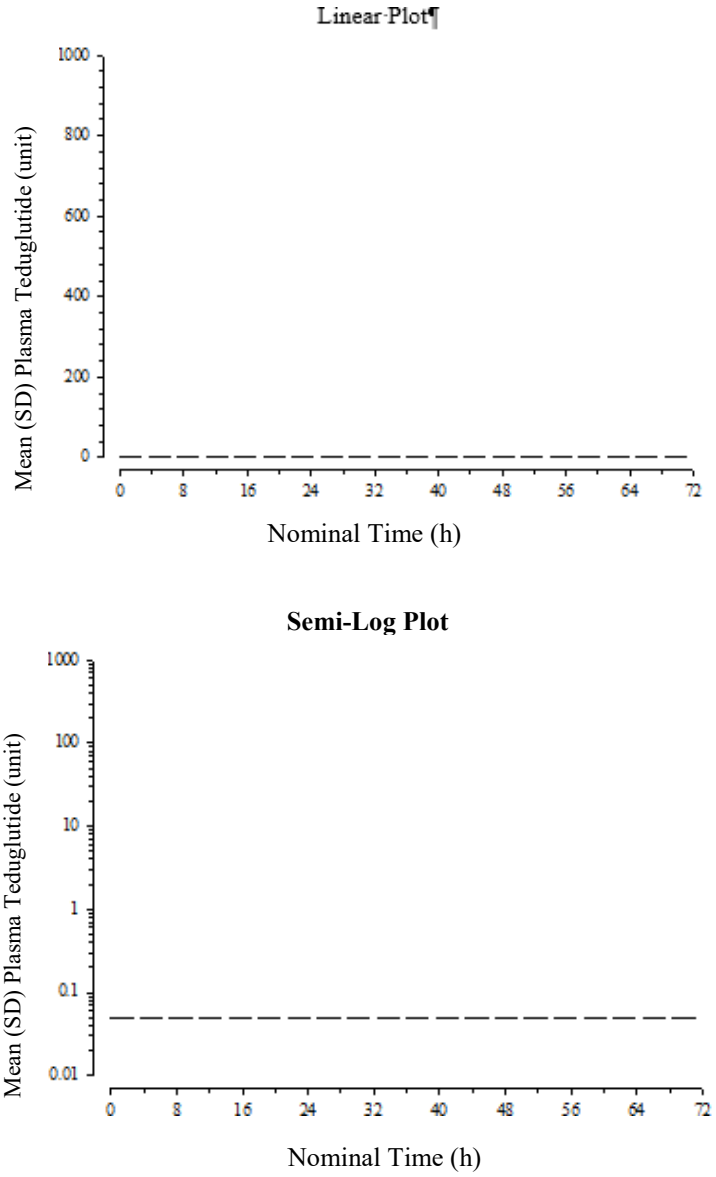
APPENDIX

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

11 APPENDIX 2: TABLE AND FIGURE SHELLS

Concentration-Time Profiles

Figure 14.1.1 Mean (+SD) Plasma Teduglutide Concentrations vs. Time after a Single SC Administration of Teduglutide by Treatment – Day 0 (Linear and Semi-Log)



Note: These are for presentation purpose, axis titles and range will be set accordingly (i.e. 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 Single SC Administration of Teduglutide 0.05 mg/kg – Day 0

Subject ID	Plasma Teduglutide Concentrations (Unit) over Nominal Time (h)			
	0.0	1.0	2.0	4.0
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 for Teduglutide 0.05 mg/kg at day 0 and for both treatments following multiple doses (unscheduled visit), if applicable.

Individual and Summary PK Parameter Tables

Table 14.3.1. Plasma Teduglutide PK Parameters after a Single SC Administration of Teduglutide 0.05 mg/kg – Day 0

Subject ID	AUC_{0-t} (ng.h/mL)	AUC_{0-inf} (ng.h/mL)	C_{max} (ng/mL)	T_{max} (h)	T_{last} (h)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
1 2 3 4 5 6 7 8 9 10 11 …								
N **Mean** **SD** **Min** **Median** **Max** **CV%** **Geometric Mean** **CV%** **Geometric Mean**								

Note: Similar tables will be used for Teduglutide 0.05 mg/kg at day 0 and for both treatments following multiple doses (unscheduled visit), if applicable.