Title: An Open-Label, Extension Study of Teduglutide in Japanese Subjects with Short Bowel Syndrome who Completed 24 Weeks of Treatment in SHP633-306 or TED-C14-004

NCT Number: NCT03596164

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STATISTICAL ANALYSIS PLAN

Teduglutide
PHASE 3 Extension

An Open-Label, Extension Study of Teduglutide in Japanese Subjects with Short Bowel Syndrome who Completed 24 Weeks of Treatment in SHP633-306 or TED-C14-004

PROTOCOL IDENTIFIER: SHP633-307

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

Author (Company): [redacted]

Protocol: 27 SEP 2018, Amendment 1

SAP Version #:2.0

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Statistical Analysis Plan Signature Page

SAP Final V2.0 (dated 16Feb2022) for Protocol SHP633-307.

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

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REVISION HISTORY

Version	Issue Date	Summary of Changes
Draft 1.0	31May2019	New Document
Draft 2.0	17Jul2019	- Definition of prior medication has been deleted and definition of concomitant medication has been revised. - Summary of extent of exposure categorized into weeks has been added. - Definition and summary of extent of observation have been added. - Summary of adverse event by system organ class, preferred term and onset time has been added. - Summary of selected efficacy endpoints by antibody results and visit has been added.
Draft 3.0	1Oct2019	- Definition of Analysis Visit has been added to be used for summary tables. - Definition of total extent of exposure has been added. - Definition of treatment emergent adverse events (TEAEs) has been updated. The analysis for related treatment emergent serious adverse events (TESAEs) has been added.
Final 1.0	11Oct2019	- Version number - Date
Final 2.0	10Feb2022	- Section 5.5: updated the categories for Extent of Exposure and Extent of Observation. - Section 6.1: clarified that absolute value in weekly PN/IV volume is to be analyzed. - Section 7.1: added overall summary of TEAEs leading to study discontinuation. - Section 11.3: corrected the corresponding visits of subject from SHP633-306 from Analysis Visit Month 27/28/29.

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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 of 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
EOS	end of study
ET	early termination
GI	gastrointestinal
ICF	informed consent form
ICH	International Conference on Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
NCA	non-compartmental analysis
PK	pharmacokinetics
PN/IV	parenteral nutrition/intravenous
PT	preferred terms
SAE	serious adverse event
SAP	statistical analysis plan
SBS	short bowel syndrome
SE	standard error

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 27 Sep 2018 incorporating most recent amendment 1. 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 long-term safety and efficacy of teduglutide in Japanese subjects with parenteral nutrition/intravenous (PN/IV) dependent short bowel syndrome (SBS) who completed SHP633-306 or who were in the extension phase of the TED-C14-004 study.

2.2 Estimands

Number/percentage of subjects who achieved at least 20% reduction from baseline of the core studies (SHP633-306 and TED-C14-004) in weekly PN/IV volume based on diary data at end of study (EOS) in Japanese subjects with PN/IV – dependent SBS in the safety population.

Absolute change from baseline of the core studies (SHP633-306 and TED-C14-004) in weekly PN/IV volume based on diary data at EOS in Japanese subjects with PN/IV – dependent SBS in the safety population.

Relative change from baseline of the core studies (SHP633-306 and TED-C14-004) in weekly PN/IV volume based on diary data at EOS in Japanese subjects with PN/IV – dependent SBS in the safety population.

2.3 Endpoints

2.3.1 Efficacy Endpoints

The following efficacy endpoints will be analyzed at each study visit and at the EOS, relative to the baseline of the core studies (SHP633-306 and TED-C14-004):

- Reduction in PN/IV volume of at least 20%
- Absolute and relative change in PN/IV volume
- Complete weaning off PN/IV
- Change in days per week of PN/IV

- Change in plasma citrulline

2.3.2 Safety Endpoints

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 Endpoints

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 a long-term extension study to evaluate the safety and efficacy of teduglutide in Japanese subjects who completed study SHP633-306 or were in the extension phase of TED-C14-004 (core studies). A schematic representation of the study design is presented in Figure 1.

Once informed consent has been obtained, demographics, updates to medical history and short bowel syndrome history will be obtained. Teduglutide 0.05 mg/kg will be administered once daily until teduglutide is either commercially available, or the subject's participation in this study is discontinued, or the study is discontinued. At each site visit, efficacy (adjustments to PN/IV) and safety will be monitored.

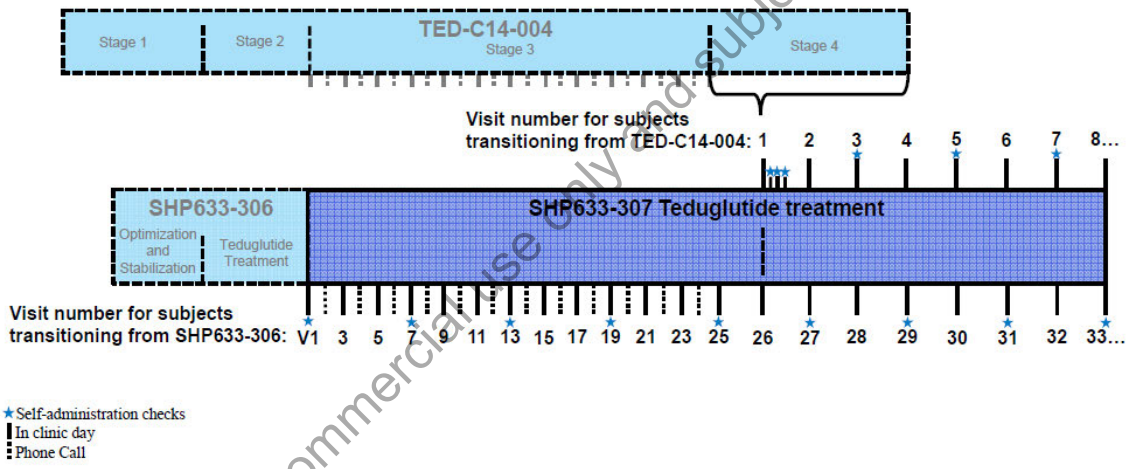
For subjects transitioning from SHP633-306, the SHP633-306 EOS visit assessments will be combined with the assessments for the first visit in SHP633-307. Clinic and phone visits will then alternate on a monthly basis through Month 24; thereafter, clinic visits will occur

every 3 months. For subjects transitioning from TED-C14-004, the TED-C14-004 EOS visit assessments will be combined with the assessments for the first visit in SHP633-307; thereafter clinic visits will occur every 3 months.

Subjects enrolling from TED-C14-004 will have blood samples taken for teduglutide PK analysis at predose and at 15, 30 minutes and 1, 2, 3, 4, 6, 8, 10, and 12 hours post dose at the first visit that they enter in this study. Subjects enrolling from SHP633-306 will have blood samples taken for teduglutide PK analysis at predose and 1 and 2 hours post dose at the first clinic visit in this study.

Study schedules for subjects enrolling from SHP633-306 and for subjects enrolling from TED-C14-004 can be found in the protocol.

Figure 1: Study Schematic



Subjects from SHP633-306: Between V1-V25 study visits occur monthly alternating between clinic visits and phone calls Starting at V25 clinic visits occur every 3 months

Interim safety visits after PN/IV adjustments are not shown

Subjects from TED-C14-004: End of study assessments for TED-C14-004 are combined with the SHP633-307 assessments at V1 The study physician will administer the first dose The study physician must observe the subject administering the study drug in compliance with the study drug administration checklist at least twice before the parent/guardian is allowed to administer the drug without direct observation by the physician Refer to the criteria for self-administration in the Site Training Guide

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 number of subjects in this study is not based on statistical power considerations as this is an extension study of the core study SHP633-306 and TED-C14-004. Approximately 5 subjects who completed study SHP633-306 and 7 subjects in the extension phase of TED-C14-004 may enroll in this extension study.

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 Safety Population

The safety population will include all enrolled subjects in the study. A subject will be considered enrolled in the study once the informed consent has been obtained and the subject meets all of the study inclusion criteria. Safety population will be used for both safety and efficacy analyses.

4.3 Pharmacokinetic (PK) Population

The PK population will include all subjects who receive at least 1 dose of teduglutide in this SHP633-307 study and have at least 1 evaluable post-dose pharmacokinetic concentration value.

5. STUDY SUBJECTS

5.1 Disposition of Subjects

The number and percentage of subjects in each study analysis population (i.e., screened, safety and PK), and of which core studies were subjects transitioning from will be presented for the screened population.

For the safety population, the number and percentage of subjects who completed or prematurely discontinued the study will be presented. Reasons for premature discontinuation from the study as recorded on the end of study page of the electronic case report form (eCRF) will be summarized (number and percentage). A subject data listing will present subject disposition for the safety population.

Inclusion 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 safety population with descriptive statistics defined in Section 11.1. Demographic and baseline characteristics to be presented include:

- Age (at informed consent date of core studies) in years, both as a continuous parameter and by categories of <45, 45-<65, and ≥65.
- Sex
- Race
- Ethnicity
- Baseline Height (cm) of core studies (SHP633-306 and TED-C14-004)
- Baseline Weight (kg) of core studies (SHP633-306 and TED-C14-004)
- Baseline BMI (kg/m^2) of core studies (SHP633-306 and TED-C14-004)

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

The following SBS history information collected at the first visit will be summarized with the descriptive statistics defined in Section 11.1 for subjects in the safety population whose SBS history were updated since the enrollment of the core studies and prior to the current study's first visit:

Any update in SBS history since core studies' (SHP633-306 and TED-C14-004) screening visit will be collected and summarized. If there is no update in the SBS history from the core studies, the data from core studies screening visit will be used in the SBS history summary below.

- Duration of SBS at baseline of core studies (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 at core studies – date of diagnosis of SBS +1)/365.25.

Partial dates for the start 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 supplement the medical history information collected at the start of the core studies (SHP633-306 and TED-C14-004) and will consist of the following:

- New medical conditions not related to SBS since core study participation
- Ongoing adverse events at the time of core study completion
- Update to a previously reported medical history

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Type of medical or surgical history, 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 Concomitant Treatment and Medication

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

All medications collected part of the extension study are concomitant medications. Medication use will be summarized by preferred name using the number and percentage of subjects for the Safety Population. Medications will be sorted categories alphabetically then 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 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.

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

5.5 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 of SHP633-307 - date of first dose of SHP633-307) + 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 months (<15, 15-<21, 21-<27, 27-<33, >=33). Exposure summaries will be presented for the safety population.

The total extent of exposure (core + extension combined) is defined as the number of days on treatment, including any periods of temporary dose interruption, calculated as:

Extent of exposure in extension study + extent of exposure in core study.

The total extent of exposure will be summarized with descriptive statistics and number and percentages of subjects based on months.

The total extent of observation is defined as the number of days on study and calculated as:

(date of last visit/data cut-off date) - date of ICF of SHP633-307 + 1.

The number and percentages of subject will be tabulated for total extent of observation categorized months (<24, 24-<30, 30-<36, 36-<42, >=42).

5.6 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) 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) as recorded on the Study Drug Interruption eCRF form. The information whether the study treatment was administered 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 the safety population. Treatment compliance by visit will not be calculated.

5.7 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 safety population and all protocol deviations will be listed.

6. EFFICACY ANALYSES

All efficacy analyses will be based on the safety population and will be separated in two columns based on subjects' enrollment from the core studies (SHP633-306 and TED-C14-004). For subjects transitioning from SHP633-306, data will be presented on a bi-monthly basis through Month 24; thereafter, on every 3-monthly basis until EOS as defined in Section 11.4. For subjects transitioning from TED-C14-004, data will be presented on a 3-monthly basis until EOS as defined in Section 11.4.

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

6.1 Analyses of Efficacy Endpoints

The efficacy endpoints will be analyzed at each study visit and at the EOS, relative to the baseline of the core studies (SHP633-306 and TED-C14-004):

- Reduction in PN/IV volume of at least 20%
- Absolute values and relative change in PN/IV volume
- Complete weaning off PN/IV
- Change in days per week of PN/IV
- Change in plasma citrulline

Unless stated otherwise, the baseline for all efficacy analyses will be as defined in Section 11.2.

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

The diary PN/IV volume will be calculated based on the daily volumes recorded in subjects' diaries within 14 days prior to each scheduled clinic and interim safety 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.

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

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.

Reduction of at least 20% in weekly PN/IV volume

The number and percentage of subjects who achieved at least a 20% reduction from baseline of core studies (SHP633-306 or TED-C14-004) to each scheduled visit until EOS, in weekly PN/IV volume will be presented.

Change in weekly PN/IV volume from baseline

The absolute values and percent change in weekly PN/IV volume from baseline of core studies (SHP633-306 or TED-C14-004) to each scheduled visit until EOS, will be presented using the descriptive statistics defined in Section 11.1.

Percent change in weekly PN/IV volume from baseline of core studies (SHP633-306 or TED-C14-004) at each scheduled visit until EOS 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 EOS as defined in Section 11.4.

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

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 prescribed no PN/IV at EOS 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 will be presented. There will be a listing of those who completely weaned off PN/IV.

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 of the core studies (SHP633-306 and TED-C14-004) to each scheduled visit until EOS, 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 of the core studies (SHP633-306 and TED-C14-004) to each scheduled visit throughout the treatment period, as well as at EOS, will be presented using descriptive statistics defined in Section 11.1.

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 of core studies (SHP633-306 or TED-C14-004) will be used as the baseline for all analyses of that safety variable.

7.1 Adverse Events

Adverse events 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 all AEs captured in this study.

Treatment emergent AEs will be summarized overall using descriptive statistics (e.g., number and percentage 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, TEAEs leading to study treatment discontinuation and TEAEs leading to study discontinuation.

TEAEs will be summarized using number and percentage of subjects. Subject incidence for TEAEs 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.
- Related TESAEs.

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

Listings will be provided for treatment emergent serious adverse events (TESAEs), TEAEs leading to death, TEAEs leading to study treatment discontinuation and TEAEs 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 captured 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.

TEAEs will be summarized by AE onset time in 3 months increments (6-<9 months, 9-<12 months, 12-<15 months, etc.). The denominator for each interval would be the number of subjects who reached same interval of treatment duration.

AE onset time in months will be calculated as (AE start date – Date of first dose in SHP633-306 or TED-C14-004 + 1) / 30.4375. The treatment duration in months, used for the denominators, will be calculated as (Last visit date – Date of first dose in SHP633-306 or TED-C14-004 + 1) / 30.4375.

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 TEAE 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 to be performed during the treatment period can be found in Table 1.

Analyses will be presented in two columns based on subjects' enrollment from the core studies (SHP633-306 and TED-C14-004). For subjects transitioning from SHP633-306, data will be presented on a bi-monthly basis through Month 24; thereafter, on every 3-monthly basis until EOS as defined in Section 11.4. For subjects transitioning from TED-C14-004, data will be presented on a 3-monthly basis until EOS.

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 throughout the treatment period and at EOS. Both actual values and change from baseline will be summarized with descriptive statistics defined in Section 11.1. Unless stated otherwise, the baseline will be as defined in Section 11.2.

Table 1 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

Clinical laboratory test values are markedly abnormal if they meet either the low or high markedly abnormal criterion listed in Table 2. The number and percentage of subjects with post-baseline markedly abnormal values will be summarized by parameter. Subjects with post-baseline markedly abnormal values at unscheduled visits will also be included in the summary. 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.

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.

Table 2: 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

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

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 [mmHg], diastolic blood pressure [mmHg], pulse rate [bpm], body temperature [degree Celsius], weight [kg], and BMI [kg/m^2]) at each scheduled visit throughout the treatment period and at EOS as defined in Section 11.4 for the safety population.

Analyses will be presented in two columns based on subjects' enrollment from the core studies (SHP633-306 and TED-C14-004). For subjects transitioning from SHP633-306, data will be presented on a bi-monthly basis through Month 24; thereafter, on every 3-monthly basis until EOS. For subjects transitioning from TED-C14-004, data will be presented on a 3-monthly basis until EOS.

Both actual values and changes from baseline will be summarized. Unless stated otherwise, the baseline will be as defined in Section 11.2.

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 each scheduled visit throughout the treatment period and at EOS as defined in Section 11.4 for the safety population. All ECG data will be listed.

Analyses will be presented in two columns based on subjects' enrollment from the core studies (SHP633-306 and TED-C14-004). For subjects transitioning from SHP633-306, data will be presented on a six-monthly basis through Month 24 and at EOS. For subjects transitioning from TED-C14-004, data will only be presented at first visit and EOS.

7.5 Other Safety Data

7.5.1 Physical Examination

Physical examination dates will be presented in a listing only. New, clinically significant physical exam findings are recorded as adverse events.

7.5.2 Antibodies to Teduglutide

A summary table will provide the number of subjects with a sample analyzed at each scheduled visit and at EOS as defined in Section 11.4 for the safety population. The summary table will also provide the number of subjects with an antibody finding.

Analyses will be based on subjects' enrollment from the core studies (SHP633-306 and TED-C14-004). For subjects transitioning from SHP633-306, data will be presented on a six-monthly basis throughout the treatment period until EOS. For subjects transitioning from TED-C14-004, data will also be presented on a six-monthly basis throughout the treatment period until EOS.

Observed value, change and percentage change from baseline for selected efficacy endpoints (Diary PS Volume, Prescribed PS Volume, Diary Days per Week of PS, Prescribed Days per Week of PS) will be analysed by antibody to teduglutide result (positive/negative) by semi-annually, relative to the baseline of the core study (SHP633-306/TED-C14-004). This by-visit analysis will be done for subjects with both efficacy endpoint and antibody data.

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 scheduled visit and interim safety visit will be summarized throughout the treatment period and at EOS as defined in Section 11.4. Oral/enteral intake and urine output measurements for Day 1 and Day 2 will be captured in the eCRF. The average of Day 1 and Day 2 measurement in mL will be summarized.

Analyses will be presented in columns based on subjects' enrollment from the core studies (SHP633-306 and TED-C14-004). For subjects transitioning from SHP633-306, data will be presented on a bi-monthly basis through Month 24; thereafter, on every 3-monthly basis until EOS. For subjects transitioning from TED-C14-004, data will be presented on 3-monthly basis until EOS.

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.

7.5.4 Gastrointestinal-specific Testing

Colonoscopy/Sigmoidoscopy

Data for colonoscopy/Sigmoidoscopy collected during the treatment period will be summarized with the descriptive statistics defined in Section 11.1.

Analyses will be presented in two columns based on subjects' enrollment from the core studies (SHP633-306 and TED-C14-004). For subjects transitioning from SHP633-306, data will be presented for Visit 1, Month 24 and EOS as defined in Section 11.4. For subjects transitioning from TED-C14-004, data will be presented for Visit 1 and EOS.

Esophagogastroduodenoscopy

Data for EGD collected during the treatment period will be summarized with the descriptive statistics defined in Section 11.1.

For subjects transitioning from SHP633-306, data will be presented for Visit 1, Month 24 and EOS as defined in Section 11.4. For subjects transitioning from TED-C14-004, data will be presented for Visit 1 and EOS.

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 following scheduled sampling time points.

Subjects enrolling from SHP633-306 at the first visit (Visit 1) in this study:

- 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

Subjects enrolling from TED-C14-004 at the first visit (Visit 1) in this study:

- 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
- 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

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, and presented in two separated tables based on enrollment from core studies. 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

An interim analysis will be conducted when the last subject who enters the study from SHP633-306 reaches the Month 6 visit (Visit 7) and the last subject from TED-C14-004 reaches Visit 1. Additional 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

For subjects transitioning from SHP633-306 and TED-C14-004, the EOS visit assessments will be combined with the assessments for the first visit in SHP633-307.

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 study sites that participate in this protocol will be combined.

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 and duration of SBS 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 core studies' 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 core studies' study medication

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

Takeda
SHP633-307
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., safety 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 using 8601 format. Dates with partial missing data will be presented with a dash (i.e., '-') for the missing data (e.g., YYYY-MM---).

For tables columns, subjects from the two core studies (i.e. SHP633-306 and TED-C14-004) will be identified.

11.2 Definition of Baseline

For summary purposes, baseline values are taken from baseline values defined at the respective core studies (SHP633-306 and TED-C14-004). Baseline values will be obtained from the analysis datasets of the core studies.

11.3 Definition of Analysis Visit and Visit Windows

Analysis visits will be used for all by-visit analysis. This will be aligned with months of exposure on teduglutide from the core study. This is achieved by aligning the first visit in the extension study to be equivalent to the last exposure month from the core study. From

the first visit in the extension study, exposure month will be translated based on the nominal visits in the core study.

The only exception would be PK analysis. It will be based on protocol defined visits.

Although there is a visit window of ± 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.

Below tables are examples of visits in the extension studies corresponding to the analysis visits (i.e. nominal months of exposures in teduglutide).

Analysis Visit	Visit of Subject from SHP633-306	Visit of Subject from TED-014-004 Scenario 1	Visit of Subject from TED-014-004 Scenario 2
Month 6	Visit 1		
Month 7	Visit 2		
Month 8	Visit 3		
Month …			
Month 27	Visit 22		
Month 28	Visit 23		
Month 29	Visit 24		
Month 30	Visit 25*		
Month 31			
Month 32			
Month 33	Visit 26		
Month 34			
Month 35			
Month 36	Visit 27		
Month 37			
Month 38			
Month 39	Visit 28	Visit 1	
Month 40			
Month 41			
Month 42	Visit 29	Visit 2	Visit 1
Month 43			
Month 44			
Month 45	Visit 30	Visit 3	Visit 2

*Visiting frequency for subjects enrolled from SHP633-306 switch to every 3-month after Visit 25.

11.4 Derived Efficacy Endpoints

An EOS time point is 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 EOS 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.

Imputation will be performed for partial dates of AEs solely for the purpose of defining treatment emergence for AEs, determining whether an AE started in the treatment period and for calculating the onset time of adverse events. Details on how to handle partial dates for adverse events 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 Adverse Events

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

11.5.2.1 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.

11.5.2.1.1 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.

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

11.5.2.2 Incomplete Stop Date

No imputation is applied to incomplete stop date.

11.5.3 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.

11.5.4 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.

11.5.5 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 SAS Grid in Windows Server 2012 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.