Statistical Analysis Plan

Protocol TED-C14-004

A 4-Stage Open-label, Multicenter Study Including Long-term Extension to Evaluate the Safety, Efficacy and Pharmacokinetics of Teduglutide in Japanese Subjects with PN-dependent Short Bowel Syndrome

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The signatures below indicate approval of the Statistical Analysis Plan for Protocol TED-C14-004 dated 03 April 2017. Any changes or modifications to the Statistical Analysis Plan following approval, with the exception of minor editorial changes to table, figure or listing shells or clarification of shells for the programmers require an amendment with the corresponding approval signatures.

Statistical Analysis Plan 29 October 2018 Version 2.0

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Document History

Version/Date	History
Version 1.0 / 05 October 2012	Original Document
Version / 01 December 2016	Statistical Analysis Plan for the 12-Month interim analysis
Version 2.0 / 29 October 2018	Updated SAP to incorporate Stage 4 data for the final CSR

TABLE OF CONTENTS

ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0–inf}$	Area under the plasma concentration–time curve of zero to infinity
AUC_{0-t}	AUC from zero to the last measurable concentration
CCK	Cholecystokinin
C_{max}	Maximum plasma concentration
CL/F	Apparent clearance
CSR	Clinical Study Report
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECP	*Escherichia coli* protein
eCRF	Electronic case report form
EOT	End of Treatment
FDA	Food and Drug Administration
GI	Gastrointestinal
GLC	Gas liquid chromatography
GLP-2	Glucagon-like peptide 2
IB	Investigator's Brochure
IBD	Inflammatory bowel disease
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MS	Mass spectrometry
NOAEL	No Observed Adverse Effect Level
PD	Pharmacodynamic
PK	Pharmacokinetic
PN	Parenteral nutrition
QD	Once daily
SAE	Serious adverse event
SAP	Statistical Analysis Plan

SBS	Short bowel syndrome
SC	Subcutaneous
SMT	Safety Management Team
SOT	Start of Treatment
SUSAR	Suspected, unexpected, serious, adverse reaction
t1/2λz	Terminal phase half-life
tmax	Time to maximum plasma concentration
ULN	Upper limit of normal
Vλz/F	Apparent volume of distribution
WHODD	World Health Organization Drug Dictionary
WMA	World Medical Association

1 INTRODUCTION AND BACKGROUND INFORMATION

2.1 Study Design

This is an open-label, multicenter, 4-stage study consisting of an optimization/stabilization period (Stage 1), a 24-week treatment period in which all subjects will receive teduglutide 0.05 mg/kg/day (Stage 2), and a long-term extension (Stages 3 and 4).

At least 5 subjects may be enrolled during the recruitment period, which ends approximately 6 months after the initiation of the study.

Main Treatment Period (Stages 1 and 2)

Stage 1 will include a screening visit; a maximum 8-week PN/I.V. optimization period (if required); and a stabilization period that demonstrates stable PN/I.V. support for a minimum of 4 weeks to a maximum of 8 weeks.

If at screening a subject does not have a stable PN/I.V volume, defined as a 48-hour urine output within 2 to 4 L, he/she will enter the optimization period, during which the minimally tolerated stable PN/I.V. volume will be determined during a period of up to 8 weeks. If it is not possible to keep the subject adequately hydrated and nourished within the target urine output range, the minimally tolerated PN/I.V. volume will be documented.

All subjects will then enter the stabilization period, during which the target volume will be maintained for at least 4 consecutive weeks (8 weeks maximum) prior to entering the dosing period (Stage 2).

If a subject fails to maintain a stable PN/I.V. volume for at least 4 consecutive weeks, the subject may start the optimization period again, beginning with Week 2 (Visit 1.1). Those subjects who fail to stabilize after 2 attempts will not proceed further and will not be included in Stage 2.

Stage 2 will be a 24-week dosing period, during which subjects will self-administer teduglutide 0.05 mg/kg/day at home. Stage 2 will begin with baseline assessments of hydration and nutritional status once the subjects have demonstrated PN/I.V. stability for 4 to 8 weeks. At least 5 subjects will be enrolled. The on-treatment study visits will occur at Weeks 2, 4, 8, 12, 16 and 20, with the last scheduled visit at Week 24 of Stage 2.

Extension Treatment Period (Stages 3 and 4)

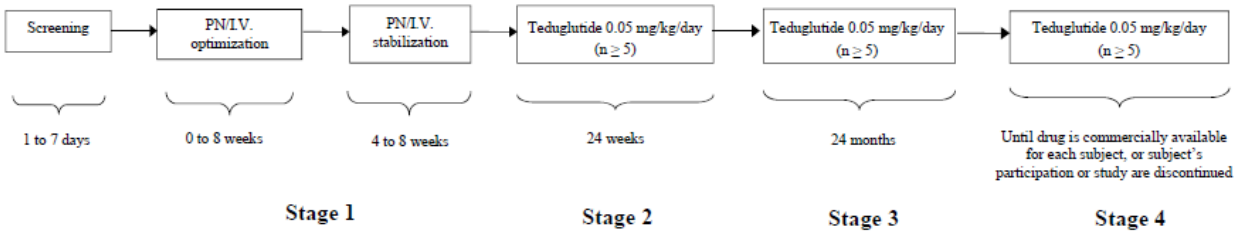
Stages 3 and 4 constitute the long-term extension portion of the study. Stage 3, which will begin immediately following Stage 2, will include subjects who complete the main treatment period and who are willing to continue with treatment teduglutide 0.05 mg/kg/day SC for up to an additional 24 months. In Stage 4, which will begin immediately following Stage 3, subjects will continue treatment with teduglutide 0.05 mg/kg/day SC in Study TED-C14-004 until teduglutide is commercially available for each subject, the subject's participation in this study is discontinued, or the study is discontinued.

Any subject who achieves complete independence from PN/I.V. support at any time during the Stages 2, 3 or 4 treatment periods will continue to receive teduglutide treatment. If a subject relapses following achievement of PN/I.V. independence, PN/I.V. support will be re-initiated and the subject will continue receiving teduglutide.

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

The Schedule of Evaluations and Procedures for each stage are outlined in Section 6.4 of the protocol.

Figure 1 Study Diagram



2.2 Objective

The objectives of this clinical study are to evaluate the safety, efficacy and pharmacokinetics of teduglutide in Japanese subjects with PN/I.V.-dependent SBS over a 24-week period (Stage 2) followed by a long-term extension (Stages 3 and 4) to evaluate safety and continued efficacy.

2.2.1 Efficacy and Pharmacodynamic Endpoints – Stage 2

The efficacy endpoints are as follows:

- Absolute and percent change from baseline in weekly PN/I.V. volume over 24 weeks (by visits and at end of treatment [EOT]). Weekly PN/I.V. volume will be based on the subject diary recordings.
- Percentage of subjects who demonstrate a response at Week 20 and again at Week 24. A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.
- Change in days per week of PN/I.V. support
- Changes in plasma citrulline levels from baseline to Week 24 (or EOT)

2.2.2 Efficacy and Pharmacodynamic Endpoints – Stages 3 and 4

For Stages 3 and 4, absolute and percent change from baseline in weekly PN/I.V. volume and changes in days per week of PN/I.V. support and plasma citrulline levels will continue to be evaluated throughout the long-term extension.

2.2.3 Pharmacokinetic Endpoints – Stage 2 Only

Pharmacokinetic Endpoints are described and analyzed in the interim report.

2.2.4 Safety Objectives

The safety and tolerability of teduglutide treatment will be assessed by evaluation of adverse events (AEs); 12-lead electrocardiogram (ECG); vital signs; laboratory safety data; antibodies to teduglutide and to *Escherichia coli* protein (ECP) and changes in 48-hour urine output, body weight and body mass index (BMI). An abdominal ultrasound and colonoscopy/sigmoidoscopy of remnant colon will be done during the stabilization period if these procedures were not performed during the 6 months prior to screening. Colonoscopy/sigmoidoscopy will be repeated at the end of the main treatment period

(Stage 2) and at the end of the extension treatment period (Stage 3 and 4). For all subjects with a history of Crohn's disease, an upper GI contrast series with small bowel follow-through will be performed during the stabilization period, prior to the baseline visit.

2 DETERMINATION OF SAMPLE SIZE

The sample size is determined based on the small patient population and the feasibility of the study, rather than power calculation.

3 UNBLINDING PROCEDURES

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

4 DATA MANAGEMENT

Clinical data are collected using eCRF and data are processed by a clinical research organization (CRO).

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

5 STATISTICAL/ANALYTICAL ISSUES

6.1 General Methodology

All statistical procedures will be completed using SAS version 9.2 or later.

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

For summary purposes, the baseline value will be defined as the last available pre-dose value. Scheduled visits will be summarized as provided in the electronic case report forms (eCRFs). An End of Treatment (EOT) time point, defined as the last determination of endpoint or last available measurement from the date of first dose, will be analyzed in addition to the scheduled visits.

Study Day will be calculated as the date of the evaluation minus the date of the first day of study medication for study days before the first day of study medication, and the date of the evaluation minus the date of the first day of study medication plus one otherwise.

All summaries will be presented by one group, unless otherwise specified. Subjects in the eCRF database who were not treated with study medication will be included in the disposition table as "Enrolled". For subject data listings, these subjects will be listed in a treatment group specified as 'Not Treated'.

6.2 Adjustments for Covariates/Prognostic Variables

No adjustments for covariates are planned in the statistical analyses.

6.3 Handling of Dropouts or Missing Data

All subjects in the analysis population defined in Sections 7.1, 7.2 and 7.3 will be included in the associated analyses.

Missing safety parameters will not be imputed.

Details on how to handle partial dates for adverse events and prior/concomitant medications will be discussed under Safety Evaluation.

6.4 Interim Analyses and Data Monitoring

There was one interim analysis of study. A final analysis of study data will be done at the end of the study.

6.5 Multicenter Studies

Because a small number of subjects are expected at each center, data from all centers will be pooled (i.e., no center effect will be included in statistical models).

6.6 Multiple Comparisons/Multiplicity

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

6.7 Active-Control Studies Intended to Show Equivalence

This study was not an active control study intended to show equivalence.

6.8 Examination of Subgroups

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

6 ANALYSIS POPULATIONS AND VISITS

7.1 Efficacy/PD Analysis Populations

The intention-to-treat (ITT) population will consist of all subjects who are enrolled and eligible to enter Stage 2. The ITT population will be the primary analysis population analyzed for efficacy/PD endpoints.

The Per Protocol population will consist of all subjects in the ITT population who completed Stage 2 without any major protocol violations that could potentially affect the efficacy conclusions of the study. The major protocol violations will be determined with the following conditions, but not limited to:

1. Subjects with no detectable TED level in blood as part of PK assessment or no PK assessment.
2. Absence of Week 20 and Week 24 visits
3. Non-compliance to study medication for the treatment group

   Compliance is defined in Section 9.
4. Discrepancies between planned and actual treatment

The Per Protocol (PP) population will be the secondary analysis population analyzed for efficacy endpoints.

7.2 Safety Analysis Population

The Safety Population will consist of all subjects in the ITT population who receive at least one dose of study medication. All safety analyses will be conducted on this population, unless otherwise specified.

All data will be included in the listings.

7.3 PK Analysis Population (Stage 2 Only)

The PK Analysis Population is defined as all subjects, at Stage 2, in the Safety Analysis Population for whom the primary PK data are considered sufficient and interpretable.

7.4 Windowing Visits

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 early termination visit falls into the window of a scheduled visit as defined in the protocol, the early termination visit is also summarized for that scheduled visit, unless the scheduled visit already took place.

7 STUDY SUBJECTS

8.1 Subjects Screened and Enrolled

The number of subjects enrolled, and the number of subjects treated will be presented.

8.2 Study Analysis Populations

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

8.3 Protocol Deviations

A listing of subjects with protocol deviations will be presented in the data listings. The number and percent of subjects with protocol deviations will be summarized. The unique type of protocol deviations will be summarized for the ITT population.

8.4 Disposition of Subjects

For the ITT and Safety populations, study enrollment and completion will be summarized by the number and percent of subjects who complete Stages 2, Stage 3, Stage 3 V7and Stage 4. The number and percent of subjects by the reason for discontinuing each stage early will also be presented.

8 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

9.1 Analysis of Demographic and Other Baseline Characteristics

The baseline and demographic characteristics will be summarized with descriptive statistics defined in Section 6.1 for the ITT and Safety Population. 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.

- gender
- race
- ethnicity
- height (cm) at the Baseline visit
- weight (kg) at the Baseline visit
- body mass index (BMI) (kg/m^2) at the Baseline visit

BMI is calculated as body weight (kg)/body height^2 (m).

The following Short Bowel Syndrome History information collected at the Screening visit (i.e., Visit 1.0) will be summarized with descriptive statistics defined in Section 6.1 for the ITT and Safety Populations:

- Duration of SBS (years)
- reason for major intestinal resection (Crohn's disease, vascular disease, injury, volvulus, cancer, and other)
- stoma (Y/N), stoma type (jejunostomy, ileostromy, colostomy, other)
- Remaining colon (Y/N), estimated percent colon remaining, and colon in continuity (Y/N)
- Colonoscopy in the last 6 months (Y/N/NA)
- 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, other)

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

The following Parenteral Nutrition History information collected at the Screening visit (i.e., Visit 1.0) will be summarized with descriptive statistics defined in Section 6.1 for the ITT and Safety Populations:

- years since start of PN dependency
- prescribed weekly PN/IV volume
- actual weekly PN/IV volume
- prescribed weekly PN calorie
- actual weekly PN calorie
- prescribed weekly number of days of PN/IV
- actual weekly number of days of PN/IV

The following Crohn's Disease Evaluation information collected at the Screening visit (i.e., Visit 1.0) will be summarized with descriptive statistics defined in Section 6.1 for the ITT and Safety Population:

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

The following Gastrointestinal–specific Testing information collected during the stabilization period will be summarized with descriptive statistics defined in Section 6.1 for the ITT and Safety Population:

- For subjects with Crohn's disease, upper gastrointestinal 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)

Colonoscopy and sigmoidoscopy will also be collected at the end of Stage 2 and Stage 3.

Partial dates for the start date of PN dependency and date of last surgical resection 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.

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

9 MEASUREMENTS OF TREATMENT COMPLIANCE

Percent compliance will be calculated as 100 times the doses administered divided by the number of days on treatment. Doses administered will be calculated as the total number of vials dispensed minus the total number of vials returned unused during the study period. Number of days on treatment is calculated as (last dose date – first dose date +1). Drug accountability information, first dose date, last dose date, and study medication interruptions are reported in the eCRF. Subjects will be considered compliant overall for study medication if the calculated compliance is > =80%. Overall treatment compliance will be presented for both percent compliance calculations using descriptive statistics and the number and percentage of subjects who are >= 80% compliant for both the ITT and Safety Populations. Treatment compliance by visit will not be calculated. Compliance for Stage 2 Only will also be calculated.

Information about interruptions of study medication (start date of interruption, date study medication resumed, and reason for interruption) is included in data listings.

10 EFFICACY/PHARMACODYNAMIC EVALUATION

11.1 Analysis of Efficacy and Pharmacodynamic Variables

All efficacy/pharmacodynamic analyses will be conducted on the ITT and PP populations. Analyses on weekly PN/IV support are based on two data sources: the subject diary data(also referred to as actual data) and the investigator prescribed data.

Investigator prescribed data is captured in the PN history and adjustments eCRFs. The actual weekly PN 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 value = (sum of daily values in the diary/number of days with values) *7

Missing daily PN volumes will not be imputed. If there are more than 5 days of missing diary data within an interval, the interval will be classified as missing actual volume information. An exception to this rule is the Baseline visit, which case traced back beyond 14 days prior to

first dose until 9 data points were obtained. Data will be summarized at all scheduled visits. An End of Treatment (EOT) time point will also be added. Therefore,

- PN/IV volume/ calories and days per week of PN/IV support will be summarized at Baseline, Stage 2 Weeks 2, 4, 8, 12, 16, 20, 24, and nominal visits in Stage 3 and Stage 4 will be summarized.

- Plasma citrulline will be summarized at Baseline, Stage 2 Weeks 4, 8, 16, 24, and nominal visits in Stage 3 and Stage 4 will be summarized.

Data collected at unscheduled time points will be included in the listings but will not be summarized at those unscheduled time points.

Change in weekly PN/IV volume from baseline

The absolute and percent change in weekly PN/IV volume from baseline to each scheduled visit, as well as at EOT, will be presented using descriptive statistics defined in Section 6.1. The 95% confidence intervals will be presented for Week 24 and End of Stage 2.

Response to Teduglutide

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 (Visit 2) in weekly PN/I.V. volume.

Binary response to Teduglutide

The number and percentage of subjects who demonstrate a response at each visit will be presented. A response is defined as the achievement of at least a 20% reduction from baseline (Visit 2) in weekly PN/I.V. volume.

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

The absolute change in days per week of PN/IV support from baseline to each scheduled visit, as well as at EOT, will be presented using descriptive statistics defined in Section 6.1.

Changes in plasma citrulline from baseline

The absolute and percent change in plasma citrulline from baseline to each scheduled visit, as well as at EOT, will be presented using descriptive statistics defined in Section 6.1.

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) if the investigator prescribes no PN and there is no use of PN recorded in the subject diary at the last dosing visit.

The number and percentage of subjects who completely wean off PN/IV support up to Week 24 in Stage 2 will be presented. Also, similar analysis will be done for those completely wean off PN/IV support at end of Stage 3 and end of study.

11 PHARMACOKINETIC EVALUATION

Details of pharmacokinetic evaluation are included in the Pharmacokinetic Analysis Plan.

12 SAFETY EVALUATION

All safety evaluations will be conducted on the Safety population at the following time points.

- Concomitant medication will be summarized for the study period for all enrolled subjects.
- AEs will be summarized for the study period for all enrolled subjects.
- Vital signs will be summarized at Baseline, Stage 2 Weeks 2, 4, 8, 12, 16, 20, 24, and nominal visits in Stage 3 and Stage 4 will be summarized.
- Electrocardiograms will be summarized at Baseline, Stage 2 Weeks 4, 24, and nominal visits in Stage 3 and Stage 4 will be summarized.
- Lab tests will be summarized at Baseline, Stage 2 Weeks 2, 4, 8, 12, 16, 20, 24, and nominal visits in Stage 3 and Stage 4 will be summarized.
- Antibodies to teduglutide and ECP will be summarized at Baseline, Stage 2 Weeks 12, 24, and nominal visits in Stage 3 and Stage 4 will be summarized.
- 48-hour oral fluid intake and 48-hour urine output will be summarized at Baseline, Stage 2 Weeks 2, 4, 8, 12, 16, 20, 24, and nominal visits in Stage 3 and Stage 4 will be summarized.
- Body weight and BMI will be summarized at Baseline, Stage 2 Weeks 2, 4, 8, 12, 16, 20, 24, and nominal visits in Stage 3 and Stage 4 will be summarized.

Complete dates will be imputed from partial dates of adverse events and medications solely for the purpose of defining treatment emergence for adverse events and prior/concomitant status for medications. Dates will be defined using the hierarchy of derivations below.

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

1. If year and month are known, and it is the month and year of the first dose date, use the first dose date.

2. If year and month are known, and it is 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.

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

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

6. Should any of the previous start dates created be after a complete stop date provided, use the stop date instead of the date that would otherwise be created.

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

Medication stop date (references to month are the month of the stop date):

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 year and month are known and study medication stopped after the date of informed consent and not in the month that medication stopped, use the last day of the month.

4. If year and month are known and are prior to the month of informed consent, use the first day of the month.

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

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

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

8. Should any of the previous 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.

9. Otherwise, if stop date is unknown leave as missing.

13.1 Extent of Exposure

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

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

The first dose date, last dose date, and interruptions of study medication will be based on the eCRF. The extent of exposure, the number of days that the dose was administered will be summarized. The number and percentages of subject will be tabulated for extent of exposure categorized into months (<6 months, 6 – <12 months, 12 – <24 months, 24 – <30 months, >=30 months). Exposure summaries will be presented for the ITT and Safety Population.

13.2 Adverse Events

Adverse events will be summarized in three categories: 1) Overall TEAEs that happened in the study, 2) TEAEs that happened in Stage 2, and 3) TEAEs that happened in Stage 3 and 4. AEs will be coded using the MedDRA. Investigator verbatim as well as preferred terms and body systems will be included in the listings, and the corresponding list of body systems, preferred terms and the verbatim terms that code to each preferred term will be presented as a preface to the listings of the AEs.

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 period or unknown will be included as treatment emergent AEs. Any AE with a start date equal to the date of first dose, where the time of the AE can't definitively place the start of the AE prior to the first dose, will be considered treatment emergent. If any AE records contain only partial dates, these will be handled by imputation, as described in Section 6.3. AEs which are not treatment emergent will be flagged in listings.

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

Treatment emergent AEs will be summarized using number and percentage of subjects. Subject incidence for AEs within each SOC and PT will be presented, unless otherwise specified. TEAEs will be summarized by Severity. The number of events will also be summarized except for summaries by highest category. TEAEs will be summarized by relationship to the drug, whether it is related or not related. TESAEs will be summarized. TESAE will also be summarized based on Severity as well as Relationship. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending incidence.

Summaries of TEAEs, related TEAEs, and TESAEs will also be presented by PT. These presentations will be sorted 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 gender, age, SOC, PT, reported term, start date/time, end date/time, frequency, severity, relationship, action taken, and outcome.

Pre-Treatment AEs will be summarized. These AEs will be summarized using number and percentage of subjects. Subject incidence for AEs within each SOC and PT will be presented. The number of events will also be summarized. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending incidence.

TEAEs will summarized by time to onset (<6 months, 6 – <12 months, 12 – <24 months, 24 – <30 months, >=30 months). These AEs will be summarized using number and percentage of subjects. Subject incidence for AEs within each SOC and PT will be presented. The number of events will also be summarized. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending incidence.

One of the benefits of Teduglutide's ability to reduce PN assumption is to reduce or eliminate the risk of systemic catheter-related infections in SBS patients who are PN dependent. Adverse events that are considered to be central line systemic infections include central line infection, catheter related infection, catheter sepsis, catheter bacteraemia,

bacteraemia, and blood culture positive. These TEAEs will be presented by PT, sorted by descending incidence.

13.3 Clinical Laboratory Evaluation

Laboratory parameters will be collected and processed via a central laboratory, SRL, and presented in standard international (SI) units. Clinical laboratory evaluations include the following:

- Chemistry
    - Alanine Aminotransferase
    - Albumin
    - Alkaline Phosphatase
    - Amylase
    - Aspartate Aminotransferase
    - Total Bilirubin
    - Direct Bilirubin
    - Indirect Bilirubin
    - Blood Urea Nitrogen
    - C Reactive Protein
    - Calcium
    - Chloride
    - Total Cholesterol
    - Creatinine
    - Creatinine Clearance
    - Gamma Glutamyl Transferase
    - Glucose
    - Lipase
    - Magnesium
    - Phosphate
    - Potassium
    - Sodium
    - Triglycerides
    - Uric Acid
- Hematology
    - Erythrocytes
    - Hematocrit
    - Hemoglobin

- Leukocytes
- Platelets

- Urinalysis
  - Urine Blood
  - Urine Glucose
  - Urine Leukocytes
  - Urine Microscopic
  - pH
  - Urine Osmolality
  - Urine Protein
  - Urine Sodium

Quantitative results will be summarized for hematology, serum chemistry, and selected urinalysis parameters at each visit collected and at endpoint. Both actual values and change from baseline will be summarized with descriptive statistics defined in Section 6.1. Additionally, shift tables will be presented for parameters provided by the central laboratory, summarizing cross tabulations of low, normal, and high based on the parameter normal range, from baseline to Week 24, End of Stage 3 and End of Stage 4. Percentages for shift tables will be based on the number of subjects with a value at baseline and at least one post-baseline visit.

Markedly abnormal laboratory values are defined 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 results qualifying as markedly abnormal as defined in this table will be summarized by parameter. A listing will present all values for a subject and laboratory parameter if at least one post-baseline value for that subject and parameter is markedly abnormal.

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

Laboratory results will be presented in an appendix data listing for each lab panel (chemistry, hematology, 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 appendix data listings only.

13.4 Vital Signs

Descriptive statistics (e.g., mean, standard deviation, median, minimum and maximum values, the number and percent of subjects in specified categories) will be used to summarize the vital signs (i.e., sitting systolic blood pressure, sitting diastolic blood pressure, seated pulse rates, body temperature, weight, height, and BMI) by visit and at EOT. Both actual value and change from baseline will be summarized with descriptive statistics defined in Section 6.1.

13.5 ECG Variables

The number and percentage of subjects with each type of ECG finding (Normal/Abnormal, Not Clinically Significant/Abnormal, Clinically Significant) will be presented at Baseline, Week 4, 24, and nominal visits in Stage 3 and Stage 4 will be summarized.

13.6 Physical Examination

Physical examination results will be presented in appendix data listings only. Any clinically significant findings for physical examinations were to be recorded as medical history at screening or as adverse events for all other visits.

13.7 Antibodies to Teduglutide and Escherichia coli Protein (ECP)

A summary table will provide the number of subjects with a sample analyzed for Baseline, Weeks 12, 24, and nominal visits in Stage 3 and Stage 4 will be summarized. The summary table will also provide the number of subjects with an antibody finding at each of those visits.

13.8 Prior and Concomitant Medications

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

Prior medications are defined as medications taken prior to the first dose of study medication. 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. The subject's PN and any components of their PN should not be recorded as a prior or concomitant medication. Partial date imputation for medications is described in Section 6.3.

Prior and concomitant medication use will be summarized by preferred name using the number and percentage of subjects. Medications will be sorted alphabetically by ATC and preferred name within ATC. Subjects with multiple occurrences of a medication in ATC and preferred name will only be counted once within each ATC and preferred name. Since medications are coded to ATC by indication, preferred names may appear under multiple ATCs.

A listing of all medications, both prior and concomitant, will be presented. Any abbreviations and codes will be clearly explained on each page of the listing. The listing will be sorted by subject identifier and will include fourth level ATC code, reported name, dose, route of administration, dosing frequency, start date, end date, indication, and period of medication (prior only, concomitant only, prior and concomitant).

13 CHANGES TO THE STATISTICAL METHODOLOGY PRESENTED IN THE PROTOCOL

There are some changes in SAP plan from the protocol as follows;

- PN/IV volume/ calories based on Investigator Prescribed Data will be summarized.
- Binary response to Teduglutide at each visit will be summarized.
- The comparisons with the results of Phase 3 Study CL0600 020, defined in the protocol, will not be performed, and thus will not be included in the clinical study report.

14 GENERAL PROGRAMMING INFORMATION

15.1 General

All programmed table, figure and listing outputs, unless specified otherwise, will be generated using the SAS version 9.2 or later. The programmed outputs will be similar to the format/appearance of the table and listing shells. However, space/formatting limitations may dictate changes in the programmed output. The footnotes specified in the table and listing shells may be changed as necessary for clarifying table entries or the explanation of algorithms or methods used for producing the entries. Significant changes in footnotes will be discussed prior to their implementation.

15.2 Format of Tables/Listings

Tables and listings should be produced in landscape mode and centered horizontally. Required margins are 1 inch for the top, left, right and bottom margins. All output should have a 3-line header at the upper left margin:

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All output should have a 1-linefooter 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 will have the report listings for the data analyses presented in the table identified at the lower left margin, and listings will have the source eCRF identified.

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

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

A number should identify each table/listing, and the table designation (e.g., Table 1) should be centered above the title. A decimal system (e.g., x, x.y, x.y.z) should be used to identify tables/listings with related contents. The title should be centered and in mixed-case characters. The title and table/listing designation should be single-spaced but are separated from the content of the table/listing by a space and a solid underline. The study population and/or subgroup (e.g., ITT Population) should be identified on the line immediately following the title.

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

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

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

For summarizations of categorical data, an Unknown or Missing category should be added to any variable for which information is not available for all subjects. However, only the number of unknown or missing subjects will be presented, and percent will be based on non-missing data.

Individual data listings will be sorted and presented by subject number and visit date.

15.3 Data Formats

Unless otherwise specified, means 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.

Data in columns will be formatted as follows:

- Alphanumeric values will be center-justified (in mixed upper and lower-case)
- Numerical data will be decimal aligned.
- Fractional data should be presented with the zero to the left of the decimal point (e.g., 0.54).

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%).

Dates will be presented in a DDMONYY format. Dates with partial missing data will be presented with a dash (i.e., '-') for the missing data (e.g., --JAN05).

15 LISTINGS OF TABLE, FIGURE AND DATA LISTINGS

16.1 List of Tables

Table 14.1.1	Study Analysis Populations	All Enrolled Subjects
Table 14.1.1.1	Protocol Deviations	Intention-to-Treat Population
Table 14.1.2.1	Subject Disposition	Intention-to-Treat Population
Table 14.1.2.2	Subject Disposition	Safety Population
Table 14.1.3.1	Demographics and Baseline Characteristics	Intention-to-Treat Population
Table 14.1.3.2	Demographics and Baseline Characteristics	Safety Population
Table 14.1.4.1	Short Bowel Syndrome History	Intention-to-Treat Population
Table 14.1.4.2	Short Bowel Syndrome History	Safety Population
Table 14.1.5.1	Parenteral Nutrition History	Intention-to-Treat Population
Table 14.1.5.2	Parenteral Nutrition History	Safety Population
Table 14.1.6.1	Crohn`s Disease Evaluation	Intention-to-Treat Population
Table 14.1.6.2	Crohn`s Disease Evaluation	Safety Population
Table 14.1.7.1	Gastrointestinal-specific Testing	Intention-to-Treat Population
Table 14.1.7.2	Gastrointestinal-specific Testing	Safety Population
Table 14.1.8	Medical and Surgical History	Safety Population
Table 14.1.9.1	Prior Medications	Safety Population
Table 14.1.9.2	Concomitant Medications	Safety Population
Table 14.1.10.1	Study Medication Compliance	Intention-to-Treat Population
Table 14.1.10.1.1	Study Medication Compliance - Stage 2 Only	Intention-to-Treat Population
Table 14.1.10.2	Study Medication Compliance	Safety Population
Table 14.2.1.1	Summary of Response to Teduglutide Based on Subject Diary Data	Intention-to-Treat Population
Table 14.2.1.2	Summary of Response to Teduglutide Based on Subject Diary Data	Per-Protocol Population
Table 14.2.1.3	Summary of Response to Teduglutide Based on Investigator Prescribed Data	Intention-to-Treat Population
Table 14.2.1.4	Summary of Response to Teduglutide Based on Investigator Prescribed Data	Per-Protocol Population
Table 14.2.2.1	Binary Response Status by Visit Based on Subject Diary Data	Intention-to-Treat Population
Table 14.2.2.2	Binary Response Status by Visit Based on Subject Diary Data	Per-Protocol Population
Table 14.2.2.3	Binary Response Status by Visit Based on Investigator Prescribed Data	Intention-to-Treat Population
Table 14.2.2.4	Binary Response Status by Visit Based on Investigator Prescribed Data	Per-Protocol Population
Table 14.2.3.1	Change and Percent Change in PN Volume from	Intention-to-Treat Population

	Baseline by Visit Based on Subject Diary Data	
Table 14.2.3.2	Change and Percent Change in PN Volume from Baseline by Visit Based on Subject Diary Data	Per-Protocol Population
Table 14.2.3.3	Change and Percent Change in PN Volume from Baseline by Visit Based on Investigator Prescribed Data	Intention-to-Treat Population
Table 14.2.3.4	Change and Percent Change in PN Volume from Baseline by Visit Based on Investigator Prescribed Data	Per-Protocol Population
Table 14.2.4.1	Change and Percent Change in Number of Days of PN Usage from Baseline by Visit Based on Investigator Prescribed Data	Intention-to-Treat Population
Table 14.2.4.2	Change and Percent Change in Number of Days of PN Usage from Baseline by Visit Based on Investigator Prescribed Data	Per-Protocol Population
Table 14.2.5	Number (%) of Subjects Who Stop PN Usage Based on Prescribed and Subject Diary Data	Intention-to-Treat Population
Table 14.2.6	Change and Percent Change in PN Kilocalories from Baseline by Visit	Intention-to-Treat Population
Table 14.2.7	Change and Percent Change in Citrulline from Baseline by Visit	Intention-to-Treat Population
Table 14.3.1.1	Extent of Exposure	Intention-to-Treat Population
Table 14.3.1.2	Extent of Exposure	Safety Population
Table 14.3.2.1	Overall Summary of Treatment Emergent Adverse Events	Safety Population
Table 14.3.2.1.1	Overall Summary of Treatment Emergent Adverse Events - Stage 2 Only	Safety Population
Table 14.3.2.1.2	Overall Summary of Treatment Emergent Adverse Events - Stage 3 and 4 Only	Safety Population
Table 14.3.2.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.2.1	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term - Stage 2 Only	Safety Population
Table 14.3.2.2.2	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term - Stage 3 and 4 Only	Safety Population
Table 14.3.2.2.3	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term - Stage 3 Only	Safety Population
Table 14.3.2.2.4	Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term - Stage 4 Only	Safety Population
Table 14.3.2.3	Summary of Treatment Emergent Adverse Events by Preferred Term	Safety Population
Table 14.3.2.3.1	Summary of Treatment Emergent Adverse Events by Preferred Term - Stage 2 Only	Safety Population
Table 14.3.2.3.2	Summary of Treatment Emergent Adverse Events by Preferred Term - Stage 3 and 4 Only	Safety Population
Table 14.3.2.4	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity	Safety Population
Table 14.3.2.4.1	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity - Stage 2 Only	Safety Population
Table 14.3.2.4.2	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Severity - Stage 3 and 4 Only	Safety Population
Table 14.3.2.5	Summary of Related Treatment Emergent Adverse	Safety Population

	Events by System Organ Class and Preferred Term	
Table 14.3.2.5.1	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship - Stage 2 Only	Safety Population
Table 14.3.2.5.2	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship - Stage 3 and 4 Only	Safety Population
Table 14.3.2.5.3	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship - Stage 3 Only	Safety Population
Table 14.3.2.5.4	Summary of Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship - Stage 4 Only	Safety Population
Table 14.3.2.6	Summary of Related Treatment Emergent Adverse Events by Preferred Term	Safety Population
Table 14.3.2.6.1	Summary of Treatment Emergent Adverse Events by Preferred Term and Relationship - Stage 2 Only	Safety Population
Table 14.3.2.6.2	Summary of Treatment Emergent Adverse Events by Preferred Term and Relationship - Stage 3 and 4 Only	Safety Population
Table 14.3.2.7	Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.7.1	Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term - Stage 2 Only	Safety Population
Table 14.3.2.7.2	Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term - Stage 3 and 4 Only	Safety Population
Table 14.3.2.8	Summary of Treatment Emergent Serious Adverse Events by Preferred Term	Safety Population
Table 14.3.2.8.1	Summary of Treatment Emergent Serious Adverse Events by Preferred Term - Stage 2 Only	Safety Population
Table 14.3.2.8.2	Summary of Treatment Emergent Serious Adverse Events by Preferred Term - Stage 3 and 4 Only	Safety Population
Table 14.3.2.9	Summary of Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Severity	Safety Population
Table 14.3.2.9.1	Summary of Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Severity - Stage 2 Only	Safety Population
Table 14.3.2.9.2	Summary of Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Severity - Stage 3 and 4 Only	Safety Population
Table 14.3.2.10	Summary of Related Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.10.1	Summary of Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Relationship - Stage 2 Only	Safety Population
Table 14.3.2.10.2	Summary of Treatment Emergent Serious Adverse Events by System Organ Class, Preferred Term, and Relationship - Stage 3 and 4 Only	Safety Population
Table 14.3.2.11	Details of Serious Adverse Events	Safety Population
Table 14.3.2.11.1	Details of Serious Adverse Events - Stage 2 Only	Safety Population
Table 14.3.2.11.2	Details of Serious Adverse Events - Stage 3 and 4 Only	Safety Population

Table 14.3.2.12	Summary of Treatment Emergent Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.12.1	Summary of Treatment Emergent Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term - Stage 2 Only	Safety Population
Table 14.3.2.12.2	Summary of Treatment Emergent Adverse Events Leading to Discontinuation by System Organ Class and Preferred Term - Stage 3 and 4 Only	Safety Population
Table 14.3.2.13	Details of Adverse Events Leading to Discontinuation	Safety Population
Table 14.3.2.13.1	Details of Adverse Events Leading to Discontinuation - Stage 2 Only	Safety Population
Table 14.3.2.13.2	Details of Adverse Events Leading to Discontinuation - Stage 3 and 4 Only	Safety Population
Table 14.3.2.14	Details of Adverse Events Leading to Death	Safety Population
Table 14.3.2.14.1	Details of Adverse Events Leading to Death - Stage 2	Safety Population
Table 14.3.2.14.2	Details of Adverse Events Leading to Death - Stage 3 and 4 Only	Safety Population
Table 14.3.2.15	Summary to Treatment Emergent Adverse Events by Time to Onset, System Organ Class, and Preferred Term	Safety Population
Table 14.3.2.16	Summary of Pre-treatment Adverse Events by System Organ Class and Preferred Term	Safety Population
Table 14.3.2.17	Summary of Treatment Emergent Central Line Systemic Infections by Preferred Term	Safety Population
Table 14.3.2.17.1	Summary of Treatment Emergent Central Line Systemic Infections by Preferred Term - Stage 2 Only	Safety Population
Table 14.3.2.17.2	Summary of Treatment Emergent Central Line Systemic Infections by Preferred Term - Stage 3 and 4 Only	Safety Population
Table 14.3.3.1	Summary of Laboratory Values and Change from Baseline by Visit - Chemistry	Safety Population
Table 14.3.3.2	Summary of Laboratory Values and Change from Baseline by Visit - Hematology	Safety Population
Table 14.3.3.3	Summary of Laboratory Values and Change from Baseline by Visit - Urinalysis	Safety Population
Table 14.3.3.4	Summary of Antibody Results by Visit	Safety Population
Table 14.3.3.5	Shift from Baseline to Post-baseline in Clinical Laboratory Parameters by Visit - Chemistry	Safety Population
Table 14.3.3.6	Shift from Baseline to Post-baseline in Clinical Laboratory Parameters by Visit - Hematology	Safety Population
Table 14.3.3.7	Shift from Baseline to Post-baseline in Clinical Laboratory Parameters by Visit - Urinalysis	Safety Population
Table 14.3.3.8	Summary of Post-Baseline Markedly Abnormal Laboratory Values – Chemistry	Safety Population
Table 14.3.3.9	Summary of Post-Baseline Markedly Abnormal Laboratory Values – Hematology	Safety Population
Table 14.3.4.1	Change and Percent Change in 48-hour Fluid Intake from Baseline by Visit	Safety Population
Table 14.3.4.2	Change and Percent Change in 48-hour Urine Output from Baseline by Visit	Safety Population
Table 14.3.5.1	Summary of Vital Sign Values and Change from Baseline by Visit	Safety Population

Table 14.3.6.1	Summary of ECG Findings by Visit	Safety Population

16.2 List of Figures

Figure 14.2.1.1.1	Individual Change in Weekly PN Volume by Visit	Intention-to-Treat Population
Figure 14.2.1.1.2	Mean (SE) Change in Weekly PN Volume by Visit	Intention-to-Treat Population
Figure 14.2.1.1.3	Mean (SE) Change in Weekly PN Volume by Visit – Stage 2 Only	Intention-to-Treat Population
Figure 14.2.1.2.1	Individual Percent Change in Weekly PN Volume by Visit	Intention-to-Treat Population
Figure 14.2.1.2.2	Mean (SE) Percent Change in Weekly PN Volume by Visit	Intention-to-Treat Population
Figure 14.2.1.2.3	Mean (SE) Percent Change in Weekly PN Volume by Visit – Stage 2 Only	Intention-to-Treat Population

16.3 List of Data Listings

Listing 16.2.1	Subject Disposition and Completion/Discontinuation	All Enrolled Subjects
Listing 16.2.2.1	Inclusion and Exclusion Criteria Violations	All Enrolled Subjects
Listing 16.2.2.2	Subject Level Protocol Deviations	All Enrolled Subjects
Listing 16.2.3	Demographics	All Enrolled Subjects
Listing 16.2.4.1	SBS History	All Enrolled Subjects
Listing 16.2.4.2	Parenteral Nutrition History	All Enrolled Subjects
Listing 16.2.4.3	Crohn's Disease Evaluation	All Enrolled Subjects
Listing 16.2.4.4	Medical and Surgical History	All Enrolled Subjects
Listing 16.2.4.5	Prior and Concomitant Medications	All Enrolled Subjects
Listing 16.2.4.6	Study Medication	All Enrolled Subjects
Listing 16.2.5.1	Study Drug Administration	All Enrolled Subjects
Listing 16.2.5.2	Study Drug Accountability	All Enrolled Subjects
Listing 16.2.5.3	Study Drug Interruption	All Enrolled Subjects
Listing 16.2.6.1	PN Usage	All Enrolled Subjects
Listing 16.2.6.2	PN/IV Adjustment	All Enrolled Subjects
Listing 16.2.6.3	48 Hour Parenteral/Enteral Fluid Intake and Urine Output	All Enrolled Subjects
Listing 16.2.6.4	PN Nutrition Intake Diary	All Enrolled Subjects
Listing 16.2.6.5	Prescribed and Actual PN Support by Patient and Visit	All Enrolled Subjects
Listing 16.2.7.1	Adverse Events	All Enrolled Subjects
Listing 16.2.7.2	Serious Adverse Events Details	All Enrolled Subjects
Listing 16.2.8.1	Lab Sample Collection	All Enrolled Subjects
Listing 16.2.8.2	Lab Test Results - Chemistry	All Enrolled Subjects
Listing 16.2.8.3	Lab Test Results - Hematology	All Enrolled Subjects
Listing 16.2.8.4	Lab Test Results - Urinalysis	All Enrolled Subjects
Listing 16.2.8.5	Lab Test Results - Citrulline	All Enrolled Subjects
Listing 16.2.8.6	Lab Test Results - Antibody to Teduglutide and ECP	All Enrolled Subjects
Listing 16.2.8.7	Urine Pregnancy Test	All Enrolled Subjects
Listing 16.2.8.8	Diagnostic, Surgical, or Therapeutic Procedures during	All Enrolled Subjects

	the Study	
Listing 16.2.8.9	Gastrointestinal-specific Testing	All Enrolled Subjects
Listing 16.2.8.10	Physical Examination	All Enrolled Subjects
Listing 16.2.8.11	Vital Signs	All Enrolled Subjects
Listing 16.2.8.12	ECG Tracing Interpretation	All Enrolled Subjects

16 TABLE, FIGURE AND DATA LISTING SHELLS

17.1 Table Shells

See separate file.

17.2 Figure Shells

See separate file.

17.3 Data Listing Shells

See separate file.