Statistical Analysis Plan

NCT Number: NCT05027308

Title: A Phase 3, Open-label Safety Study of Teduglutide in Japanese Pediatric Patients With Short Bowel Syndrome Who are Dependent on Parenteral Support, Aged 4 Months of Corrected Gestational Age or Older, and Requiring the Dosing of 1.25 mg Formulation

Study Number: TAK-633-3008

Document Version and Date: Version 2.0 / 31-Oct-2023

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STATISTICAL ANALYSIS PLAN

Study Number: *TAK-633-3008*

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Phase: *3*

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Date: *31-Oct-2023*

Prepared by:

[redacted]

Based on:

Protocol Version: *Amendment 2*

Protocol Date: *19-May-2022*

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LIST OF IN-TEXT TABLES

ABBREVIATIONS

AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ASMA	anti-smooth muscle antibody
AST	aspartate aminotransferase
CI	confidence interval
CL/F	apparent clearance (clearance [CL] divided by bioavailability [F])
COVID-19	coronavirus disease 2019
ECG	Electrocardiogram
eCRF	electronic case report form
EA	early antigen
EOT	end of treatment
ET	early termination
FAS	full analysis set
INR	International normalized ratio
ITT	intention-to-treat
LLN	lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
NTT	no-teduglutide treatment
OC	observed cases
PN/IV	Parenteral nutrition/intravenous fluid
PS	Parenteral support
PT	Preferred Term (MedDRA)
Q1	25th percentile
Q3	75th percentile
RD	risk difference
RR	risk ratio
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SBS	short bowel syndrome
SC	subcutaneous
SD	standard deviation
SOC	System Organ Class
TEAE	treatment-emergent adverse event]

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

To evaluate the safety of the 1.25 mg formulation of teduglutide in Japanese pediatric patients with SBS who are dependent on PS, aged 4 months (corrected gestational age) or older, and requiring the dosing of 1.25 mg formulation.

1.1.2 Secondary Objective(s)

To evaluate the efficacy of the 1.25 mg formulation of teduglutide in Japanese pediatric patients with SBS who are dependent on PS, aged 4 months (corrected gestational age) or older, and requiring the dosing of 1.25 mg formulation.

1.1.3 Additional Objective(s)

Not Applicable.

1.2 Endpoints

1.2.1 Safety Endpoints

The following safety endpoints will be analyzed:

- *Incidence of TEAEs, serious adverse events (SAEs), and adverse events of special interest (AESIs).*
- *Physical examinations.*
- *Vital signs, including body temperature, respiratory rate, blood pressure, and pulse.*
- *Body weight, height (or length), head circumference and weight-for-length Z-scores (corrected for gestational age).*
- *Laboratory safety data (biochemistry, hematology, and urinalysis).*
- *Urine output.*
- *Fecal output.*

1.2.2 Efficacy Endpoints

The following efficacy endpoints will be analyzed:

- *Change from baseline in PS volume by each visit and EOT.*
- *Percent change from baseline in PS volume by each visit and EOT.*
- *Number and percent of subjects achieving at least 20% reduction in PS volume from baseline by each visit and EOT.*

- *Number and percent of subjects achieving enteral autonomy, defined as complete weaning off PS by each visit and EOT.*
- *Change from baseline in days per week of PS by each visit and EOT.*

1.3 Estimand(s)

Not Applicable.

2.0 STUDY DESIGN

This study is designed [redacted] *This is a phase 3, open-label study to evaluate the safety of teduglutide in Japanese pediatric patients with SBS who are dependent on PS, aged 4 months (corrected gestational age) or older, and <10 kg of body weight (or <20 kg of body weight if a subject has moderate or greater renal impairment). A 2 to 4-week screening period will be used to verify eligibility. Subjects who fail screening may be re-screened with prior sponsor approval. After screening, subjects, who meet the inclusion criteria and meet none of the exclusion criteria, will start a 28-week treatment cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg (0.025 mg/kg for patients with moderate or greater renal impairment) SC once daily, followed by a 4-week follow-up (no treatment) period. Each subject will visit the site at baseline, weekly for the first 2 weeks (Week 1 and Week 2), and every 4 weeks after Week 4 (Weeks 4, 8, 12, 16, 20, 24, and 28).*

Telephone contacts will be made as needed during the treatment period. At all site visits and during all telephone contacts, safety will be evaluated, and nutritional support will be reviewed and adjusted, as needed. A subject may "escape" the follow-up period between Week 24 and Week 28 and proceed immediately to another screening visit if the subject meets at least 1 of the follow-up period escape criteria (Section 6.2.5). Otherwise, following completion of the 28-week treatment cycle, the subject will proceed to a no-teduglutide treatment (NTT) period. The subject who escapes the follow-up period and immediately proceeds to another screening visit will start a next cycle of teduglutide treatment if at least 1 of the treatment eligibility criteria and none of the exclusion criteria are met. The subject in the NTT period may proceed to another screening visit at any time if at least 1 of the treatment eligibility criteria are met, and may start a next cycle of teduglutide treatment if at least 1 of the treatment eligibility criteria and none of the exclusion criteria are met. A subject may participate in multiple treatment cycles and NTT periods depending on his or her clinical trajectory.

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not Applicable.

3.2 Statistical Decision Rules

Not Applicable.

3.3 Multiplicity Adjustment

Not Applicable.

4.0 SAMPLE-SIZE DETERMINATION

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

5.0 ANALYSIS SETS

The full analysis set (FAS) and safety analysis set (SAS) are defined for this trial.

5.1 All Screened Subjects Analysis Set

The All Screened Subjects Analysis Set will consist of all subjects who provide informed consent for this study, to be used for reporting disposition and screening failures.

5.2 Safety Analysis Set

The SAS will include all subjects who received at least 1 dose of study teduglutide. Safety analyses will be conducted using the SAS.

5.3 Full Analysis Set

The FAS will include all enrolled patients, who are not screen failures. Subjects will be in FAS regardless of whether they took any dose of teduglutide in the study. The FAS will be used for all the efficacy analyses.

5.4 Per-Protocol Analysis Set

Not Applicable.

5.5 Pharmacokinetic Analysis Set

Not Applicable.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Baseline values are defined as the last observed value before the first dose of study medication.

Due to the limited size of the study population descriptive statistics will be used with a goal of summarizing the sample which discourages the use of inferential statistics. Accordingly, no claims of significance will be made for any of the data.

Where applicable, variables will be summarized descriptively by study visit. For the categorical variables, the counts and proportions of each possible value will be tabulated. The denominator for the proportion will be based on the number of subjects who provided non-missing responses to the categorical variable. For continuous variables, the number of subjects with non-missing values, mean, median, SD, minimum, and maximum values will be tabulated. Standard errors (SE) will be displayed for the efficacy tables, and body weight, height (or length), BMI, head circumference and weight for length.

Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. CIs intervals will be presented using the same number of decimal places as the parameter estimate.

Scheduled visits will be summarized as provided in the electronic case report forms (eCRFs). An End of Treatment (EOT) time point, defined as the last determination of endpoint or last available measurement after the date of first dose during the 24-week treatment period will be analyzed in addition to the scheduled visits by each cycle. Last NTx will be defined as last determination of endpoint or last available measurement during any NTT period. Unscheduled measurements will not be included in by-visit summaries for treatment periods but can contribute to the EOT value where applicable.

Study Day will be calculated as follows:

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

  Study Day = (date of the evaluation – first day of study medication) + 1.

- If the date of the evaluation is prior to the first day of study medication then:

  Study Day = (date of the evaluation – first day of study medication).

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

6.1.1 Handling of Treatment Misallocations

Not Applicable.

6.2 Disposition of Subjects

The number of subjects in the Full analysis set and Safety analysis set will be presented for the All Screened Subjects Analysis Set.

Number of subjects included and excluded from each analysis set (including reason for exclusion) will be summarized based on the All Screened Subjects Analysis Set. A listing showing inclusion and exclusion of each subject from each analysis set, including reason for exclusion, will be provided.

The number and percentage of subjects who received teduglutide during the study as well as number and percentage of subjects who completed all treatment periods or prematurely

discontinued from any of the treatment period will be presented. Reasons for premature permanent treatment discontinuation as recorded on the end of treatment page of the eCRF will be summarized (number and percentage).

The number and percentage of subjects who completed the study or discontinued early will be presented. Reasons for early study discontinuation based on the end of study page of the eCRF will be summarized (number and percentage).

All percentages will be calculated based on the Safety Analysis Set.

A subject data listing will present subject disposition for the All Screened Subjects Analysis Set. A subject data listing will present subject disposition by teduglutide-treatment cycle and NTT visit for the All Screened Subjects Analysis Set. Inclusion criteria violations, if any, will be presented in a listing for the All Screened Subjects Analysis Set. In addition, treatment eligibility criteria and follow-up period escape criteria will be listed for the Safety analysis set.

Number and percentage of subjects with protocol deviations will be provided based on the Safety Analysis Set for each category specified in the Protocol Deviations Management Plan.

A listing of protocol deviations by subject will be presented in the data listings.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics

Demographic data and other baseline characteristics will be presented for the Safety Analysis Set.

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

- Age (years) at informed consent date for the cohort of children 1 year or more than 1 year of age.
- Chronological (actual) age (months) at informed consent date for the infant subjects.
- Corrected gestational age (months) at informed consent date for the infant subjects.
- Sex.
- Race.
- Ethnicity.
- Height or length for age Z-score and percentile at Baseline.
- Weight for age Z-score and percentile at Baseline.
- Head Circumference for age Z-score and percentile at Baseline (only for subjects who are <=36 months of age at Baseline).
- Weight for length Z-score and percentile at Baseline only for the infant subjects at Baseline.

Age will be rounded to 1 decimal place for reporting. Z-score of weight, height or length and head circumference for age as well as weight for length Z-score will be calculated based on the method described in Section 6.6.2.2. Z-scores will be rounded and presented to 2 decimal places. Percentiles will be calculated as the corresponding probability of Z-scores from the standard normal distribution. Percentiles will be rounded and presented to 1 decimal places.

Continuous demographic and other baseline characteristics will be summarized using descriptive statistics. Categorical demographic and other baseline characteristics using number and percentages of patients in each category. No statistical testing will be carried out for demographic or other baseline characteristics.

6.3.2 Medical History and Concurrent Medical Conditions

6.3.2.1 Short Bowel Syndrome History

SBS history will be presented for the Safety Analysis Set.

The following SBS history will be reported for this study:

- Duration of SBS at baseline.
- Primary reason for the diagnosis of SBS (necrotizing enterocolitis, midgut volvulus, intestinal atresia, gastroschisis, trauma, cancer, Crohn's disease, long-segment Hirschsprung disease, other).
- Secondary reason for the diagnosis of SBS (Yes/No), secondary reason (necrotizing enterocolitis, midgut volvulus, intestinal atresia, gastroschisis, trauma, cancer, Crohn's disease, long-segment Hirschsprung disease, other).
- Stoma (Yes/No), stoma type (jejunostomy, ileostomy, colostomy, other).
- Remaining colon (Yes/No), estimated percent of colon remaining, and colon in continuity (Yes/No).
- Colonoscopy in the last 12 months (Yes/No/NA [Not Applicable]).
- Total estimated remaining small intestinal length (cm).
- Presence of the distal/terminal ileum (Yes/No) and ileocecal valve (Yes/No).
- Method to determine remaining anatomy length (surgery, radiology, other).

6.3.2.2 Other Medical History and Concurrent Medical Conditions

- Medical history is defined as any medical conditions/diseases that started and stopped prior to signing of informed consent.
- Concurrent medical conditions are defined as any medical conditions that started prior to signing of informed consent AND were ongoing at the time of signing of informed consent or ended on the day of signing of informed consent.

Medical history and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 24.0 or later, and will be summarized by System Organ Class (SOC) and Preferred Term (PT) based on the Safety Analysis Set. A subject having more than one medical condition within the same SOC/PT will be counted only once for that SOC or PT.

All medical history and concurrent medical conditions will be listed.

When the number of subject is less than three, no table will be provided (only listing will be provided).

6.3.3 PS and EN History

The following Parenteral Nutrition/Intravenous History and Enteral Nutrition (EN) History information collected at the Baseline visit will be summarized with descriptive statistics for the Full Analysis Set:

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

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

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

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

6.4 Medication History and Concomitant Medications

6.4.1 Prior Medications

- Prior medications are defined as any medication that started and stopped prior to the first dose of study intervention.

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

Prior medications use will be summarized by preferred name using the number and percentage of subjects. Medications will be sorted alphabetically by preferred name. Subjects with multiple occurrences of a medication in preferred name will only be counted once within each preferred name.

A listing of all medications will be presented. The listing will be sorted by subject identifier and will include reported name, dose, route of administration, start date, end date and indication.

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

When the number of subject is less than three, no table will be provided (only listing will be provided).

6.4.2 Concomitant Medications

- Concomitant medications are defined as:
  - Any medication that started before the first dose of study intervention AND was ongoing at the time of the first dose of study intervention or ended on the date of first dose of study intervention;
  - Any medication that started on or after the day of first dose of study intervention.

Concomitant medications will be coded to indication-specific preferred name using the WHO Drug Dictionary. Investigator verbatim as well as coded terms will be included in the listings.

Concomitant medication use will be summarized by preferred name using the number and percentage of subjects. Medications will be sorted alphabetically by preferred name. Subjects with multiple occurrences of a medication in preferred name will only be counted once within each preferred name.

A listing of all medications will be presented. The listing will be sorted by subject identifier and will include reported name, dose, route of administration, start date, end date and indication.

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

When the number of subject is less than three, no table will be provided (only listing will be provided).

6.5 Efficacy Analysis

6.5.1 Primary Endpoint(s) Analysis

Not Applicable.

6.5.2 Secondary Endpoint(s) Analysis

6.5.2.1 Key Secondary Endpoint(s) Analysis (if applicable)

- Change from baseline in PS volume by each visit and EOT.
- Percent change from baseline in PS volume by each visit and EOT.

- Number and percent of subjects achieving at least 20% reduction in PS volume from baseline by each visit and EOT.
- Number and percent of subjects achieving enteral autonomy, defined as complete weaning off PS by each visit and EOT.
- Change from baseline in days per week of PS by each visit and EOT.

6.5.2.2 Derivation of Endpoint(s)

Analyses will be conducted using the FAS.

Parenteral support will be reported in both subject diary data and the investigator-prescribed data in the eCRF. Diary and prescribed PS volume/calories will be normalized to weight in order to facilitate comparability of results across patients in this pediatric population.

Data will be summarized separately for treatment periods and NTT periods. For treatment periods, PS data will be presented by cycle and by scheduled visit within each cycle (Week 0 to Week 28). An EOT time point and a last NTx time point will also be presented as defined in Section 9.2.3.

For prescribed data, the most recent PS prescription prior to or on the date of visit will be used.

Average daily values normalized to weight will be calculated for PS volume and calories as follows:

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

Calculation of diary PS parameters (including hours per day and days per week of PS) will be based on the daily support recorded in subjects' diaries within 7 days prior to the date of each scheduled visit.

Average daily values normalized to weight will be calculated for PS volume and calories as follows:

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

If more than 2 days' values in a week are missing, the average daily value will not be calculated and will be assigned as missing. This missing data handling rule will be used to calculate all other diary average diary parameters, including PS hours per day and PS days per week.

Baseline diary PS values (volume, calories, hours per day and days per week) will be calculated using the most recent 14 days of diary data collected prior to the first dose. If more than 5 days' values are missing in two weeks before the first dose, the baseline values are missing. If the most recent days of diary data collected prior to the first dose is less than 14 days, baseline diary PS values (volume, calories, hours per day and days per week) will be calculated using the most recent 7 days of diary data collected prior to the first dose. If more than 2 days' value are missing in one week before the first dose, the baseline values are missing.

Percent reduction in weight-normalized diary and prescribed PS values from baseline at the scheduled visit will be calculated using the formula below:

- Percent reduction in PS value at the visit = [(average daily value at the scheduled visit - average daily value at baseline) / average daily value at baseline] * 100.

Percent reduction calculation will be performed on both diary and prescribed PS data.

For prescribed PS data, Tables and Figures will not be provided (only listings will be provided) when almost all of patients were hospitalized.

6.5.2.3 Main Analytical Approach

6.5.2.3.1 Change and percent change from baseline in PS volume and calories

The absolute and percent change from baseline in average daily values for PS volume and calories to each scheduled visit, separately for NTT (including last NTx) and each treatment cycle (including EOT), will be presented using descriptive statistics.

Mean ± standard error (SE) plots of percent change in PS volume and caloric intake will be generated by scheduled visit for each treatment cycle.

Plots of PS volume and caloric intake by scheduled visit in each treatment cycle will be presented for each individual subject in the FAS.

6.5.2.3.2 >= 20% Reduction in PS volume at each study visit

PS volume reduction at each scheduled visit compared to baseline will be calculated using average daily values. The number and percentage of subjects who achieve at least a 20% reduction in PS volume will be presented at each scheduled visit separately for NTT (including last NTx) and each treatment cycle (including EOT).

6.5.2.3.3 Enteral autonomy (completely weaned off PS)

Enteral autonomy (completely weaned off PS) is defined as the first visit where there is no use of PS for the 7 days prior to the visit and there is no prescribed PS at that visit.

The enteral autonomy (completely weaned off PS) will be summarized by visits.

For each treatment cycle, a listing will present the study week when enteral autonomy was achieved for these subjects who achieved enteral autonomy during the teduglutide treatment cycles.

6.5.2.3.4 Change and percent change from baseline in hours per day and days per week of PS

Change and percent change from baseline in hours per day and days per week of PS to each scheduled visit, separately for NTT (including last NTx) and each treatment cycle (including EOT), will be presented using descriptive statistics.

Hours per day of diary PS for all visits except the baseline visit will be calculated as follows:

- Hours per day of diary PS = (sum of hours per day for each day that PS intake data is recorded within the 7 days prior to the visit / number of days that PS hours per day data is recorded within the 7 days prior to the visit)

Days per week of diary PS for all visits except the baseline visit will be calculated as follows:

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

Prescribed PS hours per day and days per week for each visit will be taken from the most recent prescription data prior to or at that visit.

In addition, the number and percentages of subject will be tabulated for the reduction in number of days per week of PS usage from baseline at Week 24 and Week 28 categorized into days: >=1, >=2, >=3, >=4, >=5, >=6 and =7 days.

6.5.3 Other Secondary Endpoints Analysis (if applicable)

Not Applicable.

6.5.4 Subgroup Analyses (if applicable)

Not Applicable.

6.6 Safety Analysis

All safety evaluations will be conducted on the Safety analysis set. By-visit summaries will be presented separately for treatment periods and NTT periods. For each treatment cycle, all protocol scheduled visits during the 24-week treatment period and Week 28 visit will be presented. An EOT time point and a last NTx time point will also be presented as defined in Section 9.2.3.

The primary safety endpoints are:

- Incidence of TEAEs, serious adverse events (SAEs), and adverse events of special interest (AESIs).
- Physical examinations.
- Vital signs, including body temperature, respiratory rate, blood pressure, and pulse.
- Body weight, height (or length), head circumference and weight-for-length Z-scores (corrected for gestational age).
- Laboratory safety data (biochemistry, hematology, and urinalysis).
- Urine output.
- Fecal output.

6.6.1 Adverse Events

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

Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases during or after receiving the study medication. AEs with an unknown date of onset and a stop date after the start of the study period or unknown will be included as treatment emergent AEs. Any AE with a start date equal to the date of first dose, where the time of the AE cannot definitively place the start of the AE prior to the first dose, will be considered treatment emergent. If any AE records contain only partial dates, these will be handled by imputation, as described in Section 9.2.1. AEs which are not treatment emergent will be flagged in listings.

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

Treatment emergent AEs will be summarized using number and percentage of subjects. Subject incidence for AEs within each SOC and PT will be presented, unless otherwise specified. The number of events will also be summarized. Categories summarized will be the same as those summarized in the overview tabulations, except that no summary table will be provided for TEAEs leading to death. Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending incidence.

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

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

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

- Growth of pre-existing polyps of the colon.
- Benign neoplasia of the GI tract including the hepatobiliary system.
- Tumor-promoting ability (e.g., benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system).

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

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

6.6.2 Other Safety Analysis

6.6.2.1 CLINICAL LABORATORY EVALUATION

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

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

Table 6.a Lists the Clinical Safety Laboratory Tests

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

The laboratory summaries will be based on central lab results only and be presented separately for treatment periods and NTT periods. For treatment periods, laboratory data will be presented

by cycle and by scheduled visit within each cycle, i.e., weeks 0, 1, 2, 4, 8, 12, 16, 20, 24 and 28. In addition, laboratory results will also be presented at EOT and at last NTx time points.

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

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

6.6.2.2 VITAL SIGNS

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

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

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

- Weight for length ratio (kg/cm) for infants 4-<12 months corrected gestational age.
- Height or length for age Z-score and percentile.
- Weight for age Z-score and percentile.
- Weight for length Z-score and percentile for infants 4-<12 months corrected gestational age.
- Head circumference for age Z-score and percentile for subjects ≤36 months of age.

The vital sign summaries will be presented separately for treatment periods and NTT periods. For treatment periods, vital signs will be presented by cycle and by scheduled visit within each cycle. In addition, vital sign results will also be presented at EOT and at last NTx time points.

Descriptive statistics will be used to summarize the vital signs at each scheduled study visit. Both observed value and change from baseline will be summarized with descriptive statistics. Mean ±

SE plots of body weight, height or length and head circumference for age Z-scores and weight for length Z-score will be generated by scheduled visit for each treatment cycle.

The following specific derivations will be used:

- Weight for length ratio = Body weight (kg)/length (cm), where both body weight and length data are available at the same scheduled visit. Weight for length ratio will only be presented for the subjects in the subjects <2 years corrected gestational age.

Height or length, Weight, Head Circumference for age Z-scores and weight for length Z-score. A z-score is the deviation of the value for an individual from the mean value of the reference population divided by the standard deviation for the reference population.

Z-scores are calculated using the formula below:

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

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

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

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

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

[3] Weight for length is only calculated for the cohort of infants <2 years corrected gestational age.

NA = Not applicable; mos = Months; yrs = Years; child = children; WHO = World Health Organization

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

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

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

Percentiles will be calculated as the corresponding probability of Z-scores from the standard normal distribution. Percentiles will be rounded and presented to 1 decimal places.

For more information on the LMS method, see

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

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

6.6.2.2.1 Z-SCORES OF HEIGHT FOR AGE AND WEIGHT FOR AGE FOR CHILDREN 1YEAR OR MORE THAN 1 YEAR OF AGE

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

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

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

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

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

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

Corrected gestational age will be used for infants and the actual (chronological) age for children.

6.6.2.2.2 Z-SCORES OF LENGTH FOR AGE AND WEIGHT FOR AGE FOR SUBJECTS <2 YEARS CORRECTED GESTATIONAL AGE

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

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

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

The L, M and S values of head circumference for age for Japanese population as given in Kato et al. (2014) will be used. These values are also given in Table 3 of APPENDIX 2.

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

For ages (in months) that fall between two age categories given in Table 3, a similar interpolation as described in Section 6.6.2.2.1 will be used to calculate the L, M, S values.

6.6.2.2.4 Z-SCORES OF WEIGHT FOR LENGTH FOR INFANTS

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

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

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

6.6.2.3 PHYSICAL EXAMINATION

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

6.6.2.4 GASTROINTESTINAL-SPECIFIC TESTING

The results of GI-specific testing including fecal occult blood testing and colonoscopy/ sigmoidoscopy will be reported in the listings only for the Safety analysis set.

6.6.2.5 FECAL AND URINE OUTPUT

Output diary data is recorded over a 48 hour period of PS stability before every scheduled visit and, for subjects that are in a teduglutide treatment cycle, within 1 week of implementing any PS prescription adjustment. For the analysis, the latest 48-hour period of output diary data entered prior to each visit will be used (The 48-hour period does not need to be within 48 hours of the

visit). Any additional output diary data collected out of this 48-hour window will only be presented in the listings.

The output diary summaries will be presented separately for treatment periods and NTT periods. For treatment periods, output diary data will be presented by cycle and by scheduled visit within each cycle. In addition, results will also be presented at EOT and at last NTx time points.

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

- (Total urine output over 48 hours / 2) / most recent body weight (kg) prior to or on the scheduled visit

where total urine output is calculated as the sum of the urine output in mL and the urine-only diaper weights in g (1g = 1mL) for the subject collected on the output diary form of eCRF over 48 hours. Values will not be calculated if the urine output is not available at the visit.

The average daily fecal output will be summarized separately by the number of stools per day, the typical stool form score using Bristol Stool Form Scale, the total daily stool/mixed stool diaper weight (g/kg/day) and the total ostomy output per day (mL/kg/day). The number of stools per day and the average typical stool form score will be calculated as (sum of the daily data in a 48-hour period / 2). The body weight will be used to calculate the daily stool/mixed stool diaper weight (g/kg/day) and the total ostomy output per day (mL/kg/day) using a formula analogous to that used to calculate the average daily urine output.

The change and the percent change in average daily output for urine and fecal from baseline to each scheduled visit will be presented using descriptive statistics.

6.6.3 Extent of Exposure and Compliance

6.6.3.1 Extent of Exposure, Extent of Observation and Gap in Treatment

The extent of exposure will be presented both overall and by treatment cycle for the Safety analysis set.

The extent of exposure in days for Cycle X will be calculated as (last exposure date on or before Cycle X EOT – Cycle X Week 0 + 1).

The overall extent of exposure in weeks will be calculated as [the sum of extents of exposure across all cycles] / 7.

Overall and by-cycle extent of exposure will be presented using descriptive statistics. In addition, the number and percentages of subject will be tabulated for the overall extent of exposure categorized into weeks: 0-<12, 12-<24, 24-<48, 48-<72, 72-<96, 96-<120, 120-<144, 144-<168 and >=168 weeks.

The overall extent of observation will be presented for the Safety analysis set using descriptive statistics. The overall extent of observation in weeks will be calculated as (last date of follow-up – inform consent date + 1) / 7. The last date of follow-up is defined as the date of the last available visit.

The overall time to start cycle 1 will be presented for the Safety analysis set using descriptive statistics. The overall time to start cycle 1 in weeks will be calculated as (Cycle 1 Week 0 – inform consent day + 1) / 7.

The gap in treatment between each treatment cycle will be presented for the Safety analysis set using descriptive statistics. The gap in treatment in weeks for Cycle X will be calculated as [Cycle X Week 0 – last exposure date of Cycle (X-1) + 1] / 7. The gap in treatment in weeks for Cycle 1 will not be presented.

The overall number of cycles on teduglutide will also be summarized as a numeric variable.

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

6.6.3.2 Study Treatment Compliance

Treatment compliance will be presented both overall and by treatment cycle.

Percent compliance for Cycle X will be calculated as 100 times the number of days the study treatment was administered per instructions between Cycle X Week 0 and Cycle X EOT divided by the number of days on treatment in Cycle X. Number of days on treatment in Cycle X is calculated as (last exposure date on or before Cycle X EOT – Cycle X Week 0 + 1).

Overall compliance will be calculated as 100 times the total number of days the study treatment was administered per instructions across all cycles divided by the total number of days on treatment across all cycles.

The information whether the study treatment was administered per instructions is captured on the study drug administration daily diary. Administration of the study treatment at site will be considered per instructions.

Subjects will be considered compliant for study medication if the calculated compliance is >= 80%. Overall and by-cycle treatment compliance will be presented for both percent compliance calculations using descriptive statistics and the number and percentage of subjects who are >= 80% compliant for the Safety Analysis Set.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

6.7.1 Pharmacokinetic Analysis

Not Applicable.

6.7.2 Pharmacodynamic Analysis

Not Applicable.

6.7.3 Biomarker Analysis

Not Applicable.

6.8 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

6.8.1 PRO Analysis

Not Applicable.

6.8.2 Health Care Utilization Analysis

Not Applicable.

6.9 Other Analyses

Not Applicable.

6.10 Interim Analyses

No interim analysis is planned.

6.11 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not Applicable.

7.0 REFERENCES

1. Isojima, T., Kato, N., Ito, Y., Kanzaki, S., and Murata, M. (2016). Growth standard charts for Japanese children with mean and standard deviation (SD) values based on the year 2000 national survey. Clin Pediatr Endocrinol 2016; 25(2), 71–76.
2. Kato, N., Takimoto, H., Yokoyama, T., Yokoya, S., Tanaka, T., and Tada, H. (2014). Updated Japanese growth references for infants and preschool children, based on historical, ethnic and environmental characteristics. Acta Paediatrica 2014; 103, e251-e261.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

For efficacy endpoints, 95% CI was supposed to be provided in Protocol but they will not be done because of the few number of subjects.

9.0 APPENDIX

9.1 Changes From the Previous Version of the SAP

From the SAP version 1.0, the following parts were updated.

Section 6.1 General Considerations

Before the change

Similarly, an End of Study (EOS) time point will be defined as the last determination of endpoint or last available measurement. Unscheduled measurements will not be included in by-visit summaries, but can contribute to the EOT/EOS value where applicable.

After the change

Last NTx will be defined as last determination of endpoint or last available measurement during any NTT period. Unscheduled measurements will not be included in by-visit summaries for treatment periods but can contribute to the EOT value where applicable.

Reason for the change

EOS visit is not available in this study.

Section 6.2 Disposition of Subjects

Before the change

The number of subjects in the Enrolled population and Safety analysis set will be presented for the All Screened Subjects Analysis Set.

…

Number and percentage of subjects with important protocol deviations, as identified by the study team as being major or critical, will be provided based on the Safety Analysis Set for each category specified in the Protocol Deviations Management Plan.

After the change

The number of subjects in the Full analysis set and Safety analysis set will be presented for the All Screened Subjects Analysis Set.

…

Number and percentage of subjects with protocol deviations will be provided based on the Safety Analysis Set for each category specified in the Protocol Deviations Management Plan.

Reason for the change

Error correction.

Section 6.4.1 Prior Medications, Section 6.4.2 Concomitant Medications

Before the change

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

After the change

A listing of all medications will be presented. The listing will be sorted by subject identifier and will include reported name, dose, route of administration, start date, end date and indication.

Reason for the change

Error correction.

Section 6.5.2.2 Deviation of Endpoint(s)

Before the change

Data will be summarized separately for treatment periods and NTT periods. For treatment periods, PS data will be presented by cycle and by scheduled visit within each cycle (Day 1 to Week 28). An EOT time point and a last NTx time point will also be presented as defined in Section 9.2.3. Data collected at unscheduled time points will be included in the listings but will not be summarized at those unscheduled time points.

Pre-treatment visits will not be analyzed for efficacy.

…

Baseline diary PS values (volume, calories, hours per day and days per week) will be calculated using the most recent 14 days of diary data collected prior to the first dose. If more than 5 days' values are missing in two weeks before the first dose, the baseline values are missing.

After the change

Data will be summarized separately for treatment periods and NTT periods. For treatment periods, PS data will be presented by cycle and by scheduled visit within each cycle (Week 0 to Week 28). An EOT time point and a last NTx time point will also be presented as defined in Section 9.2.3.

…

Baseline diary PS values (volume, calories, hours per day and days per week) will be calculated using the most recent 14 days of diary data collected prior to the first dose. If more than 5 days' values are missing in two weeks before the first dose, the baseline values are missing. If the most recent days of diary data collected prior to the first dose is less than 14 days, baseline diary PS values (volume, calories, hours per day and days per week) will be calculated using the most recent 7 days of diary data collected prior to the first dose. If more than 2 days' value are missing in one week before the first dose, the baseline values are missing.

Reason for the change

For the definition of cycle, it's updated due to error correction. For the handling of unscheduled visit, visit window is not applicable for PS diary data. For the handling of missing PS diary data, there was a subject with only 7-day PS diary data (it was determined as a protocol deviation). Considering the inclusion criteria 6 and small sample size, handling rule was changed to use as many subject data as possible. Also, it was considered that 7-day PS diary data for baseline will not have a big influence on the efficacy evaluation.

Section 6.5.2.2 Deviation of Endpoint(s)

Before the change

Not Applicable.

After the change

For prescribed PS data, Tables and Figures will not be provided (only listings will be provided) when almost all of patients were hospitalized.

Reason for the change

For hospitalized patients, no prescribed data other than screening data were recorded as PS was not prescribed at each visit but administered appropriate volume at each day by investigators.

Section 6.5.2.3.3 Enteral autonomy (completely weaned off PS)

Before the change

Enteral autonomy (completely weaned off PS) is defined as the first visit where there is no use of PS for the 7 days prior to the visit and there is no prescribed PS at that visit, and the patient remains off PS for the remainder of the treatment period of that cycle.

After the change

Enteral autonomy (completely weaned off PS) is defined as the first visit where there is no use of PS for the 7 days prior to the visit and there is no prescribed PS at that visit.

Reason for the change

In order to compare it with 305 study results, the definition of Enteral autonomy was changed to be consistent with the one in the previous study.

Section 6.6.1 Adverse Events

Before the change

The MedDRA terms corresponding to each grouping of events of special interest are included in the external data source provided to Bios team.

After the change

Delete the description.

Reason for the change

Error correction.

Section 6.6.2.1 CLINICAL LABORATORY EVALUATION

Before the change

Laboratory evaluations that are done at study site visits will be collected and processed via a central laboratory, and presented in standard international (SI) units. Laboratory evaluations that are required at intervals that do not coincide with study site visits may be obtained by a local laboratory. The local laboratory data will be collected on the local laboratory tests form of eCRF.

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

…

Table 6.a Lists the Clinical Safety Laboratory Tests

Blood Chemistry

…

The laboratory summaries will be based on central lab results only and be presented separately for treatment periods and NTT periods. For treatment periods, laboratory data will be presented by cycle and by scheduled visit within each cycle, i.e., day 1, weeks 1, 2, 4, 6, 9, 12, 16, 20, 24 and 28. In addition, laboratory results will also be presented at EOT and at last NTx time points.

…

Laboratory results will be presented in an appendix data listing for each lab panel (chemistry, hematology, urinalysis) by subject, parameter, and date of collection.

After the change

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

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

…

Table 6.a Lists the Clinical Safety Laboratory Tests

BioChemistry

Coagulation

Prothrombin time

International normalized ratio

…

The laboratory summaries will be based on central lab results only and be presented separately for treatment periods and NTT periods. For treatment periods, laboratory data will be presented by cycle and by scheduled visit within each cycle, i.e., weeks 0, 1, 2, 4, 8, 12, 16, 20, 24 and 28. In addition, laboratory results will also be presented at EOT and at last NTx time points.

…

Laboratory results will be presented in an appendix data listing for each lab panel (chemistry, hematology, urinalysis, coagulation) by subject, parameter, and date of collection.

Reason for the change

Error correction.

Section 6.6.2.2 VITAL SIGNS

Before the change

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

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

After the change

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

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

Reason for the change

Error correction.

Section 6.6.3 Extent of Exposure and Compliance

Before the change

The extent of exposure in days for Cycle X will be calculated as (last visit date on or before Cycle X Week 24 (EOT) – Cycle X Day 1 + 1).

The overall extent of exposure in weeks will be calculated as [the sum of extents of exposure across all cycles in the extension study] / 7.

…

The overall extent of observation will be presented for the Safety analysis set using descriptive statistics. The overall extent of observation in weeks will be calculated as (last date of follow-up – inform consent date + 1) / 7. The last date of follow-up is defined as the date of the last available follow-up visit.

The overall time to start cycle 1 will be presented for the Safety analysis set using descriptive statistics. The overall time to start cycle 1 in weeks will be calculated as (Cycle 1 Day 1 – inform consent day + 1) / 7.

The gap in treatment between each treatment cycle will be presented for the Safety analysis set using descriptive statistics. The gap in treatment in weeks for Cycle X will be calculated as [Cycle X Day 1 – EOT of Cycle (X-1) + 1] / 7. The gap in treatment in weeks for Cycle 1 will not be presented.

The overall number of cycles on teduglutide will also be summarized as a numeric variable.

The information related to the study drug accountability, study drug interruption and study drug training provided by the study physician will be listed for all subjects in the Safety analysis set.

…

Treatment compliance will be presented both overall and by treatment cycle.

Percent compliance for Cycle X will be calculated as 100 times the number of days the study treatment was administered per instructions between Cycle X Day 1 and Cycle X Week 24 (EOT) divided by the number of days on treatment in Cycle X. Number of days on treatment in Cycle X is calculated as (last visit date on or before Cycle X Week 24 (EOT) – Cycle X Day 1 + 1).

Overall compliance will be calculated as 100 times the total number of days the study treatment was administered per instructions across all cycles divided by the total number of days on treatment across all cycles.

The information whether the study treatment was administered per instructions is captured on the study drug administration daily diary. Administration of the study treatment by the investigator will be considered per instructions.

After the change

The extent of exposure in days for Cycle X will be calculated as (last exposure date on or before Cycle X EOT – Cycle X Week 0 + 1).

The overall extent of exposure in weeks will be calculated as [the sum of extents of exposure across all cycles] / 7.

The overall extent of observation will be presented for the Safety analysis set using descriptive statistics. The overall extent of observation in weeks will be calculated as (last date of follow-up – inform consent date + 1) / 7. The last date of follow-up is defined as the date of the last available visit.

The overall time to start cycle 1 will be presented for the Safety analysis set using descriptive statistics. The overall time to start cycle 1 in weeks will be calculated as (Cycle 1 Week 0 – inform consent day + 1) / 7.

The gap in treatment between each treatment cycle will be presented for the Safety analysis set using descriptive statistics. The gap in treatment in weeks for Cycle X will be calculated as [Cycle X Week 0 – last exposure date of Cycle (X-1) + 1] / 7. The gap in treatment in weeks for Cycle 1 will not be presented.

The overall number of cycles on teduglutide will also be summarized as a numeric variable.

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

…

Treatment compliance will be presented both overall and by treatment cycle.

Percent compliance for Cycle X will be calculated as 100 times the number of days the study treatment was administered per instructions between Cycle X Week 0 and Cycle X EOT divided by the number of days on treatment in Cycle X. Number of days on treatment in Cycle X is calculated as (last exposure date on or before Cycle X EOT – Cycle X Week 0 + 1).

Overall compliance will be calculated as 100 times the total number of days the study treatment was administered per instructions across all cycles divided by the total number of days on treatment across all cycles.

The information whether the study treatment was administered per instructions is captured on the study drug administration daily diary. Administration of the study treatment at site will be considered per instructions.

Reason for the change

Error correction.

Section 8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Before the change

Not Applicable.

After the change

For efficacy endpoints, 95% CI was supposed to be provided in Protocol but they will not be done because of the few number of subjects.

Reason for the change

They should have been described in the 1st version because 95%CI of efficacy endpoint has already been deleted in the 1st version of the SAP.

Section 9.2.3 Definition of Visit Windows

Before the change

A windowing convention will be used to determine the analysis value for a given study visit for Laboratory test, Vital sign, Output diary (Fecal and Urine), and Intake diary (PS) data analyses. The window conventions are:

Table 9.a

One or more results for a particular analysis variable may be obtained in the same visit window. In such an event, the result with the date closest to the expected visit date will be used in the analysis. In the event that two observations are equidistant from the expected visit date, the later observation will be used in the analysis.

Beside the Laboratory test, Vital sign, Output diary (Fecal and Urine), and Intake diary (PS) analyses, no visit windowing will be performed for analysis of other variables in this study.

After the change

No visit windowing will be performed for analysis in this study. Nominal visit will be used for analysis for treatment periods. For NTT periods, data will be summarized in sequential order regardless of their cycle and visit.

Reason for the change

As sample size was small (only 3) and 2 subjects were hospitalized ones, we considered using nominal visit will not have a big influence on the evaluation.

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

Details on how to handle partial dates for adverse events are described below.

Complete dates will be imputed from partial dates of adverse events solely for the purpose of calculating the onset time of adverse events (Imputed dates will not be presented in the listings). Dates will be defined using the hierarchy of derivations below.

- **Adverse event start date (references to month and year are the month and year of the start date):**

1. If year and month are known, and it is the month and year of the informed consent/assent date, use the informed consent/assent date.

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

- Partial adverse event stop date will not be imputed.

9.2.2 Definition of Baseline

Unless otherwise specified, baseline is defined as the last non-missing measurement taken prior to the first dose of study intervention (including unscheduled assessments). In the case where the last non-missing measurement and the date and time of the first dose of study intervention coincide, that measurement will be considered pre-baseline, but AEs and medications commencing on the date of the first dose of study intervention will be considered post-baseline.

9.2.3 Definition of Visit Windows

No visit windowing will be performed for analysis in this study. Nominal visit will be used for analysis for treatment periods. For NTT periods, data will be summarized in sequential order regardless of their cycle and visit.

9.2.4 L, M AND S VALUES OF HEIGHT, BODY WEIGHT AND HEAD CIRCUMFERENCE FOR AGE FOR JAPANESE

Table 1 L, M and S Values of Height for Age for Japanese Children 1-15 Years of Age and Subjects in the Infant Cohort ≥2 Years Corrected Gestational Age

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

Table 2 L, M and S Values of Weight for Age for Japanese Children 1-15 Years of Age and Subjects in the Infant Cohort ≥2 Years Corrected Gestational Age

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

Table 3 L, M and S Values of Head Circumference for Age for Japanese Subjects ≤36 Months of Age

	Boys			Girls		
	LMS			LMS		
Age	*L*	*M*	*S*	*L*	*M*	*S*
Birth	3.57516	33.5340	0.041033	3.16302	33.0616	0.039349
30 days	3.51357	36.6508	0.038015	3.31746	35.8649	0.036895
1.5 months	3.47738	37.9537	0.036657	3.38432	37.0478	0.035782
2.5 months	3.39959	39.9479	0.034410	3.48864	38.8785	0.033925
3.5 months	3.31270	41.3592	0.032639	3.56084	40.2025	0.032438
4.5 months	3.21754	42.3408	0.031291	3.60300	41.1507	0.031282
5.5 months	3.11495	43.0462	0.030314	3.61724	41.8547	0.030417
6.5 months	3.00576	43.6255	0.029657	3.60581	42.4433	0.029803
7.5 months	2.89081	44.1563	0.029267	3.57827	42.9833	0.029401
8.5 months	2.77094	44.6439	0.029092	3.51326	43.4792	0.029171
9.5 months	2.64698	45.0903	0.029081	3.43670	43.9330	0.029074
10.5 months	2.51976	45.4977	0.029181	3.34267	44.3466	0.029069
11.5 months	2.39013	45.8680	0.029340	3.23327	44.7219	0.029118
12.5 months	2.25893	46.2032	0.029508	3.11059	45.0609	0.029182
13.5 months	2.12698	46.5059	0.029658	2.97674	45.3658	0.029240
14.5 months	1.99512	46.7783	0.029791	2.83380	45.6395	0.029293
15.5 months	1.86419	47.0232	0.029906	2.68386	45.8847	0.029340
16.5 months	1.73503	47.2431	0.030005	2.52903	46.1042	0.029381
17.5 months	1.60847	47.4406	0.030088	2.37140	46.3008	0.029418
18.5 months	1.48535	47.6181	0.030156	2.21305	46.4772	0.029448
19.5 months	1.36650	47.7783	0.030210	2.05609	46.6363	0.029474
20.5 months	1.25277	47.9238	0.030249	1.90261	46.7807	0.029496
21.5 months	1.14498	48.0570	0.030276	1.75470	46.9134	0.029512
22.5 months	1.04397	48.1806	0.030290	1.61446	47.0370	0.029524
23.5 months	0.95058	48.2970	0.030292	1.48399	47.1543	0.029531
27 months	0.69015	48.6746	0.030216	1.12237	47.5434	0.029525
33 months	0.45065	49.2382	0.029846	0.80613	48.1547	0.029414
39 months	0.39445	49.7113	0.029298	0.76467	48.7035	0.029206
45 months	0.43079	50.1119	0.028712	0.87148	49.1982	0.028934
51 months	0.46891	50.4577	0.028230	1.00006	49.6471	0.028633
57 months	0.41804	50.7642	0.027995	1.02390	50.0499	0.028337
63 months	0.18741	51.0444	0.028148	0.81650	50.3975	0.028081
69 months	−0.31374	51.3113	0.028831	0.25137	50.6807	0.027898
75 months	−1.17618	51.5780	0.030185	−0.79801	50.8899	0.027824

9.3 Analysis Software

All analyses will be conducted using SAS version 9.4 or higher.