STATISTICAL ANALYSIS PLAN

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Study Title: A Prospective, Open-label, Long-term Safety and Efficacy Study of Teduglutide in Japanese Pediatric Subjects with Short Bowel Syndrome Who Completed SHP633-302

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STATISTICAL ANALYSIS PLAN

SHP633-305

A PROSPECTIVE, OPEN-LABEL, LONG-TERM SAFETY AND EFFICACY STUDY OF TEDUGLUTIDE IN JAPANESE PEDIATRIC SUBJECTS WITH SHORT BOWEL SYNDROME WHO COMPLETED SHP633-302

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan Final 1.0 (Dated 25Jul2019) for Protocol SHP633-305.

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

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CTMS	Clinical Trial Management System
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOS	End of Study
EOT	End of Treatment
GI	Gastrointestinal
HLGT	Higher Level Group Term
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
MOS	Months
NA	Not Applicable
NTT	No-Teduglutide Treatment
PS	Parenteral Support
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBS	Short Bowel Syndrome
SC	Subcutaneous
SE	Standard Error
SI	Standard International
SOC	Standard of Care
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
ULN	Upper Limit of Normal
WHO	World Health Organization
YRS	Years

2. INTRODUCTION AND BACKGROUND INFORMATION

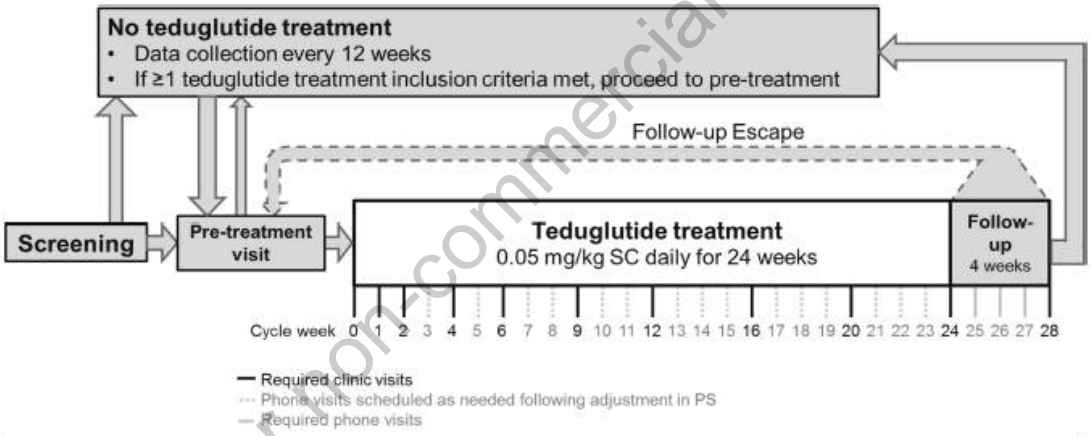
This document describes the rules and conventions to be used in the presentation and analysis of efficacy and safety data for Protocol SHP633-305. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on protocol amendment 3, dated 20 July 2018.

2.1. STUDY DESIGN

This is a Phase 3, prospective, open-label, long-term extension study to evaluate the safety and efficacy of teduglutide in Japanese pediatric subjects who completed Study SHP633-302 (core study). The study population will include 2 cohorts based on age of subjects at the time of entry in the core study: infants 4-<12 months corrected gestational age and children 1-15 years of age. A schematic representation of the study design is presented in Figure 1. The study schedule of events can be found in Table 1, 2 and 3 of the protocol.

Figure 1 Study Diagram



PS = parenteral support; SC = subcutaneous
Figure legend: Safety and efficacy data for subjects not receiving teduglutide treatment are captured approximately every 12 weeks, but subjects may proceed to the pretreatment visit at any time in order to assess eligibility for teduglutide therapy. Subjects eligible for teduglutide will enter a 28-week cycle. During this cycle, subjects will return to the site for safety and efficacy assessments at Day 1 (Week 0) and Weeks 1, 2, 4, 6, 9, 12, 16, 20, 24, and 28 (**solid black lines**). Phone visits are required approximately 1 week after adjustments in PS during the intervening weeks between Weeks 2 and 24 (**dashed grey lines**). At Week 24, subjects enter a 4-week follow-up period, where teduglutide is not received, during which phone visits will be performed weekly (**solid grey lines**). If at least 1 escape criterion is met at Week 24 or during the follow-up period, subjects may proceed directly to another pretreatment visit.

Subjects not receiving teduglutide treatment, i.e., in a no-teduglutide treatment (NTT) period, will be seen approximately every 12 weeks to collect safety and parenteral support (PS) requirements. At any point after screening, including during an NTT period, subjects who meet

at least one teduglutide treatment inclusion criteria may proceed directly to a pretreatment visit if the investigator and the subject (and/or parent/guardian, as applicable), agree to proceed with teduglutide therapy.

At the pretreatment visit, subjects who meet at least one of the teduglutide treatment inclusion criteria and none of the teduglutide treatment exclusion criteria will start a 28-week cycle, consisting of 24 weeks of teduglutide treatment at 0.05 mg/kg subcutaneous (SC) once daily, followed by a 4-week follow-up period, during which no teduglutide is administered.

A subject may "escape" the follow-up period between cycle Week 24 and Week 28 and proceed directly to another pretreatment visit if the subject meets at least one follow-up period escape criteria. Otherwise, following completion of the 28-week treatment cycle, the subject will proceed to an NTT visit (or another pretreatment visit, if needed) within 12 weeks. A subject may participate in multiple treatment cycles and NTT periods depending on his or her clinical trajectory.

2.2. OBJECTIVES

The primary objective of the study is to evaluate the long-term safety and tolerability of teduglutide treatment in Japanese pediatric subjects with Short Bowel Syndrome (SBS) who completed Study SHP633-302.

The secondary objective of this study is to evaluate the long-term efficacy of teduglutide treatment in Japanese pediatric subjects with SBS who completed Study SHP633-302.

2.2.1. EFFICACY ASSESSMENTS

The following efficacy endpoints will be analyzed at the end of each teduglutide treatment cycle , Week 24 or End of Treatment (EOT), and at each study visit, relative to the baseline of the core study (SHP633-302):

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

2.2.2. SAFETY ASSESSMENTS

The following safety endpoints will be analyzed:

- Adverse events

- Vital signs, including temperature, heart rate, blood pressure
- Laboratory safety data (i.e., biochemistry, hematology, and urinalysis)
- Urine output
- Stool output
- Antibodies to teduglutide
- Gastrointestinal-specific testing, including fecal occult blood testing and colonoscopy or sigmoidoscopy
- Z-scores for weight, height (or length), head circumference (up to 36 months of age), and Body Mass Index (BMI)

3. DETERMINATION OF SAMPLE SIZE

The number of subjects in this study is not based on statistical power considerations as this is an extension study of the core study SHP633-302. The maximum number of subjects will be determined by the completion of Study SHP633-302.

4. UNBLINDING PROCEDURES

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

5. DATA MANAGEMENT

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

6. STATISTICAL/ANALYTICAL ISSUES

6.1. GENERAL METHODOLOGY

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

Due to the limited size of the study population descriptive statistics will be used with a goal of

summarizing the sample which discourages the use of inferential statistics. Accordingly, no claims of significance will be made for any of the data.

Continuous variables, including those assessed on a discrete scale, will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For efficacy parameters, as well as body weight, height (or length), BMI, head circumference and weight for length, standard errors (SE) will be presented in the corresponding tables. For categorical variables, descriptive statistical summaries will include number of subjects and percentages.

Subjects will be classified in cohorts based on age of subjects at the time of entry in the SHP633-302 core study as recorded on the demographics page of the SHP633-305 eCRF:

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

Unless otherwise specified, analyses will be done for all subjects, and subset of subjects who were enrolled after SHP633-305 protocol amendment 2.0. Main conclusions will be based on subjects who were enrolled after implementation of protocol amendment 2.0.

6.2. BASELINE

For summary purposes, the baseline value will be defined as the last available pre-dose value in the core study SHP633-302.

6.3. VISIT SUMMARIES

Scheduled visits will be summarized as provided in the eCRFs.

Visits will be summarized within the associated pre-treatment period or treatment cycle or NTT period. For teduglutide treatment cycles, Cycle x Day 1, Cycle x Week 1, …, Cycle x Week 24, Cycle x Week 25 Follow-up, Cycle x Week 26 Follow-up, Cycle x Week 27 Follow-up and Cycle x Week 28 Follow-up data will be collected according to the schedule of events.

If the first pre-treatment visit is indicated in the eCRF to have been combined with the SHP633-302 core study's End of Study (EOS) visit, data from the SHP633-302 EOS visit will be presented for the SHP633-305 first pre-treatment visit. For subsequent treatment cycles, if the pre-treatment visit is indicated to be combined with Week 24 or Week 28 of the previous treatment cycle, that pre-treatment visit will not be in the tables. All data will be in the listings.

For NTT periods, NTx data will be collected approximately every 12 weeks. Data for teduglutide treatment periods and NTT periods will be presented in separate tables.

For each treatment cycle, an EOT time point, defined as the last determination of endpoint or last available measurement after the date of first dose during that 24-week treatment period

will be analyzed in addition to the scheduled visits. An EOT endpoint will also be presented for the last treatment cycle, defined as the last determination of endpoint or last available measurement on treatment.

Similarly, a last NTx endpoint, defined as the last determination of endpoint or last available measurement during any NTT period, will be presented.

Unscheduled measurements will not be included in by-visit summaries, but can contribute to the EOT value where applicable. Datasets and listings will include data collected at both scheduled and unscheduled visits.

6.4. 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 study day will be done for data obtained at the scheduled visits.

The end of treatment visit within a teduglutide treatment cycle will be mapped to a scheduled visit within that treatment cycle if it falls into the appropriate visit window as defined in the protocol and if that scheduled visit did not occur.

For subjects who withdraw from the study prematurely, if the early termination visit falls into the window of a scheduled visit as defined in the protocol, the early termination visit is also summarized for that scheduled visit, unless the scheduled visit already took place.

6.5. REFERENCE START DAY AND STUDY DAY

Reference start date is defined as the date of first study drug administration in SHP633-302 core study.

Study Day will be calculated as follows:

- If the date of the evaluation is on or after the reference start date then:
  Study Day = (date of the evaluation – reference start date) + 1.
- If the date of the evaluation is prior to the reference start date then:
  Study Day = (date of the evaluation – reference start date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day will be missing.

6.6. ADJUSTMENTS FOR COVARIATES/PROGNOSTIC VARIABLES

No adjustments for covariates are planned in the statistical analyses.

6.7. HANDLING OF DROPOUTS OR MISSING DATA

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

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

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.**

6.8. INTERIM ANALYSES AND DATA MONITORING

Interim analyses may be conducted during the study, as needed. Analyses will be descriptive in nature. No formal comparisons are planned and no hypotheses will be formally tested.

A Data Monitoring Committee (DMC) will be involved in the management of this study. The DMC members will review the data approximately every 3 months during the study treatment periods (date of the first subject's first dose to date of the last subject's last dose). The DMC review will include cumulative safety data (ie, AEs, laboratory assessments, physical examinations, etc.) through each cutoff period.

6.9. MULTICENTER STUDIES

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

6.10. MULTIPLE COMPARISONS/MULTIPLICITY

Not Applicable.

6.11. ACTIVE-CONTROL STUDIES INTENDED TO SHOW EQUIVALENCE

Not applicable.

6.12. EXAMINATION OF SUBGROUPS

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

7. ANALYSIS POPULATIONS

7.1. SCREENED POPULATION

All subjects who provided signed informed consent/assent will be included in the Screened population.

7.2. ENROLLED POPULATION

The enrolled population will include all enrolled subjects. A subject will be considered enrolled in the study once the informed consent/assent has been obtained and the subject meets all of the study inclusion criteria at screening.

7.3. SAFETY POPULATION

The safety population will include all enrolled subjects in the study and who received at least one dose of teduglutide (in study SHP633-302 or SHP633-305). Safety population will be used for both safety and efficacy analyses.

8. STUDY SUBJECTS

8.1. SUBJECTS SCREENED

The number of subjects screened will be presented.

8.2. STUDY ANALYSIS POPULATIONS

The number of subjects in the Enrolled population and Safety population will be presented for the Screened population.

8.3. PROTOCOL DEVIATIONS

Protocol deviations as obtained from a clinical trial management system (CTMS) will be assessed throughout the study. All identified deviations will be reported in the CTMS. Protocol deviations from the CTMS will be coded to severity categories ("minor", "important" and "priority") and provided as part of the CTMS transfer to Biostatistics. Protocol deviations will be summarized for the Safety population. A listing of protocol deviations by subject will be presented in the data listings.

8.4. DISPOSITION OF SUBJECTS

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 population.

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

9. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

9.1. ANALYSIS OF DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

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

- Age (years) at informed consent/assent date of SHP633-302 study for the cohort of children 1-15 years of age.
- Chronological (actual) age (months) at informed consent/assent date of SHP633-302 study for the infant cohort.

  Corrected gestational age (months) at informed consent/assent date of SHP633-302 study for the infant cohort.
- Sex
- Race
- Ethnicity
- Height or length for age Z-score and percentile at Baseline of SHP633-302 study
- Weight for age Z-score and percentile at Baseline of SHP633-302 study
- Head Circumference for age Z-score and percentile at Baseline of SHP633-302 study (only for subjects who are <= 36 months of age at Baseline of SHP633-302 study)
- BMI for age Z-score and percentile at Baseline of SHP633-302 study only for children 2-15 years of age at Baseline of SHP633-302 study
- Weight for length Z-score and percentile at Baseline of SHP633-302 study only for the infant cohort

Age will be rounded to 1 decimal place for reporting. BMI, Z-score of weight, height or length, BMI and head circumference for age as well as weight for length Z-score will be calculated based on the method described in Section 12.4. 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.

Any update in SBS history since SHP633-302 core study's screening visit will be collected and summarized. If there is no update in the SBS history from the core study, the data from SHP633-302 screening visit will be used in the SBS history summary below.

The following SBS history will be summarized with descriptive statistics defined in Section 6.1 for the Safety population:

- Duration of SBS at baseline of the core study
- Primary reason for the diagnosis of SBS (necrotizing enterocolitis, midgut volvulus, intestinal atresia, gastroschisis, trauma, cancer, Crohn's disease, long-segment Hirschprung disease, other)
- Secondary reason for the diagnosis of SBS (Yes/No), secondary reason (necrotizing enterocolitis, midgut volvulus, intestinal atresia, gastroschisis, trauma, cancer, Crohn's disease, long-segment Hirschprung disease, other)
- Stoma (Yes/No), stoma type (jejunostomy, ileostromy, 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]) as collected at the screening visit of SHP633-302 core study
- 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)

For the cohort of children 1-15 years of age, duration of SBS in years will be calculated as (Date of informed consent/assent form signed for SHP633-302 study – Date of diagnosis of SBS +1) / 365.25 and rounded to 1 decimal place for reporting.

For the cohort of infants, duration of SBS in months will be calculated as (Date of informed consent/assent form signed for SHP633-302 study – Date of diagnosis of SBS +1) / (365.25/12) and rounded to 1 decimal place for reporting.

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

Medical and surgical history will supplement the medical history information collected at the start of the SHP633-302 core study and will consist of the following:

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

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Type of medical or surgical history, severity for ongoing AEs from the core study, investigator verbatim as well as preferred terms and system organ class will be included in the listings. The medical and surgical history will be summarized by system organ class (SOC) and preferred term (PT) within system organ class for the Safety population, with

SOC sorted alphabetically and PT within SOC by descending incidence.

10. MEASUREMENTS OF TREATMENT COMPLIANCE

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.

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 population.

11. EFFICACY/PHARMACODYNAMIC EVALUATION

11.1. ANALYSIS OF EFFICACY AND PHARMACODYNAMIC VARIABLES

Primary efficacy analyses will be conducted on the Safety population.

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 (Day 1 to Week 28). An EOT time point and a last NTx time point will also be presented as defined in Section 6.3. The baseline value of the SHP633-302 core study will also be presented as applicable. 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.

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

Baseline prescribed PS values (volume, calories, hours per day and days per week) will be obtained from the analysis datasets of the SHP633-302 core study.

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 of the SHP633-302 core study. If more than 5 days' values are missing in two weeks before the first dose of the core study, 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:

% reduction in PS value at the visit = [(average daily value at the scheduled visit - average daily value at baseline of the core study) / average daily value at baseline of the core study] * 100

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

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 defined in Section 6.1.

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 Safety population.

≥ 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).

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, and the patient remains off PS for the remainder of the treatment period of that cycle.

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.

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 defined in Section 6.1.

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.

12. SAFETY EVALUATION

All safety evaluations will be conducted on the Safety population. 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 6.3. The baseline value of the SHP633-302 core study will also be presented as applicable.

12.1. EXTENT OF EXPOSURE

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

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 include the extent of exposure in both the SHP633-302 core study and the extension study. It will be calculated as [the exposure in days in the core study (date of last dose - date of first dose + 1) + the sum of extents of exposure across all cycles in the extension study] / 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 population using descriptive statistics. The overall extent of observation in weeks will be calculated as (last date of follow-up or interim analysis cut-off date – SHP633-305 inform consent/assent 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 population using descriptive statistics. The overall time to start cycle 1 in weeks will be calculated as (Cycle 1 Day 1 – SHP633-305 inform consent/assent day + 1) / 7.

The gap in treatment between each treatment cycle will be presented for the Safety population 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 be calculated as (Cycle 1 Day 1 – last dose date in SHP633-302 study + 1) / 7.

The overall number of cycles on teduglutide during the extension study 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 population.

12.2. ADVERSE EVENTS

Adverse Events will be coded using MedDRA. Investigator verbatim as well as preferred term and system organ class will be included in the listings. Only AEs recorded in the SHP633-305 eCRF will be used for the analysis.

Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases on or after the date of first study drug administration in SHP633-302 core study. AEs with an unknown date of onset and a stop date on or after the date of first study drug administration in SHP633-302 core study or unknown will be included as treatment emergent AEs. If any AE records contain only partial dates, these will be handled by imputation, as described in Section 6.7. AEs which are not treatment emergent, if any, will be flagged in listings.

An overview summary of AEs for the categories below will be provided using descriptive statistics (e.g., number and percent of subjects). The number of events will also be presented. Categories summarized will include any TEAE (Yes/No), 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 gastrointestinal (GI) tract including the hepatobiliary system
- Tumor-promoting ability (e.g., benign and/or malignant neoplasia of any kind, not limited to those of the GI or hepatobiliary system)

The MedDRA terms corresponding to each grouping of events of special interest are included

in APPENDIX 3.

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

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

TEAEs will be summarized by AE onset time in 3 month increments (i.e., 6<-9 months, 9<-12 months, 12<-15 months, etc.). The denominator for each interval will be the number of subjects who reached same interval of observation duration. It will be displayed where data available.

AE onset time in months will be calculated as (AE start date – Date of first dose in SHP633-302 Study + 1) / 30.4375. The observation duration in months, used for the denominators, will be calculated as (Last date of follow-up or interim analysis cut-off date – Date of first dose in SHP633-302 Study + 1) / 30.4375. The last date of follow-up is defined as the date of the last available follow-up visit.

12.3. CLINICAL LABORATORY EVALUATION

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

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

- Chemistry:
  - Albumin
  - Alkaline phosphatase
  - Alanine aminotransferase
  - Amylase
  - Aspartate aminotransferase
  - Bicarbonate
  - Bilirubin (total, direct and indirect)
  - Blood urea nitrogen
  - Calcium (total)
  - Chloride
  - Cholesterol
  - C-reactive protein
  - Creatinine
  - Estimated glomerular filtration rate (Schwartz formula)
  - Gamma-glutamyl transferase
  - Glucose
  - Lipase
  - Magnesium
  - Phosphorus
  - Potassium
  - Sodium
  - Triglycerides
  - Uric acid

- Hematology:
  - Hematocrit
  - Hemoglobin
  - Platelet count
  - Red blood cell (RBC) count
  - RBC morphology, if needed
  - White blood cell count with differential
- Coagulation:
  - Prothrombin time/International normalized ratio
- Urinalysis:
  - Blood
  - Glucose
  - Leucocytes
  - Microscopic analysis
  - pH
  - Protein
  - Specific gravity

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. The baseline value of the SHP633-302 core study will also be presented as applicable.

Quantitative results will be summarized for hematology, serum chemistry, and selected urinalysis parameters by scheduled visit. Both observed values and change from the SHP633-302 core study baseline will be summarized with descriptive statistics defined in Section 6.1. Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

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

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

urine/serum pregnancy test results will be presented in appendix data listings only.

12.4. VITAL SIGNS

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

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

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

- BMI (kg/m^2) for subjects 2-15 years of age in the children and infant cohorts
- 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
- BMI for age Z-score and percentile for subjects 2-15 years of age
- 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. The baseline value of the SHP633-302 core study will also be presented.

Descriptive statistics (e.g., mean, standard deviation, median, minimum and maximum values, the number and percent of subjects in specified categories) will be used to summarize the vital signs at each scheduled study visit. Both observed value and change from baseline of the SHP633-302 core study will be summarized with descriptive statistics defined in Section 6.1. Mean ± SE plots of body weight, height or length, BMI and head circumference for age Z-scores and weight for length Z-score will be generated by scheduled visit for each treatment cycle.

The following specific derivations will be used:

- BMI

BMI = 10000* Body weight (kg)/body height (cm)^2, where both body weight and body height data are available at the same scheduled visit. BMI will only be presented for subjects 2-15

years of age.

- Weight for length ratio

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

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

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

Z-scores are calculated using the formula below:

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

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

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

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

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

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

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

[4] 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 1-15 years of age. Note that the calculated age at each vital sign assessment date will be obtained using the date of birth as reference date for actual (chronological) age and (date of birth + difference in days between corrected gestational age and actual age at informed consent/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 BMI, weight, height, and head circumference based on the L, M, S values referred above. For more information on the CDC SAS programs, see http://www.cdc.gov/growthcharts/computer_programs.htm.

12.4.1. Z-SCORES OF HEIGHT FOR AGE AND WEIGHT FOR AGE FOR CHILDREN 1-15 YEARS OF AGE AND SUBJECTS IN THE INFANT COHORT ≥ 2 YEARS CORRECTED GESTATIONAL 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.

12.4.2. Z-SCORES OF LENGTH FOR AGE AND WEIGHT FOR AGE FOR SUBJECTS IN THE INFANT COHORT < 2 YEARS CORRECTED GESTATIONAL AGE

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

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

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

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

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

For ages (in months) that fall between two age categories given in Table 5, a similar interpolation as described in Section 12.4.1 will be used to calculate the L, M, S values.

12.4.4. Z-SCORES OF BMI FOR ALL STUDY SUBJECTS 2-15 YEARS OF AGE

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

12.4.5. Z-SCORES OF WEIGHT FOR LENGTH FOR INFANTS

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

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

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

12.5. PHYSICAL EXAMINATION

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

12.6. ANTIBODIES TO TEDUGLUTIDE

A summary table will provide the number of subjects with a sample analyzed for Day 1, Week 12, Week 24 and Week 28 of each treatment cycle. In addition, results will also be presented at EOT. The baseline value of the SHP633-302 core study will also be presented. The summary table will also provide the number of subjects with an antibody finding (Antibodies to teduglutide Negative/Positive and No Neutralizing Antibodies Present/Neutralizing Antibodies Present) at each of those visits. All antibody results, including those based on samples collected in NTT periods, will be presented in the listings.

Observed value, change and percentage change from baseline for selected efficacy endpoints (Diary PS Volume, Prescribed PS Volume, Diary Days per Week of PS, Prescribed Days per Week of PS) will be analysed by antibody to teduglutide result (positive/negative) for scheduled visit Day 1, Week 12, Week 24 and Week 28 of each treatment cycle and EOT, relative to the baseline of the core study (SHP633-302).

12.7. GASTROINTESTINAL-SPECIFIC TESTING

The results of GI-specific testing including fecal occult blood testing and colonoscopy/ sigmoidoscopy will be reported as 'Normal', 'Abnormal, not clinically significant', 'Abnormal, clinically significant' or 'Negative', 'Positive, not clinically significant', 'Positive, clinically significant'. The number of patients and percentage for each GI-specific testing parameter and result category will be presented by scheduled visit for each treatment cycle. GI-specific testing conducted during NTT periods will be included in the listings only.

12.8. 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 baseline value of the SHP633-302 core study will also be presented.

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 of the SHP633-302 core study to each scheduled visit will be presented using descriptive statistics defined in Section 6.1.

12.9. CONCOMITANT MEDICATIONS

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 medications are defined as any medication taken during the SHP633-305 study.

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, dosing frequency, 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.

13. CHANGES IN THE STATISTICAL METHODOLOGY PRESENTED IN THE PROTOCOL

There is no change of analysis from protocol.

14. GENERAL PROGRAMMING INFORMATION

14.1. GENERAL

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

14.2. FORMAT OF TABLES/LISTINGS

Tables will present subject cohorts, including all subjects and subset of subjects who were enrolled after protocol amendment 2.0, in the following order: “Children (1 - 15 years) After Amendment 2”, “Total Children (1 - 15 years)”, and “Infants (4 - <12 months)”, unless otherwise specified. Note that all subjects in the infant cohort will be enrolled after protocol amendment 2.0 and thus the subset of subjects who were enrolled after protocol amendment 2.0 will not be presented for the infant cohort. The following footnote will be presented in all tables/listings: "Infants are of 4 - <12 months corrected gestational age”.

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

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

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

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

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

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

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

For summarizations of categorical data, an Unknown or Missing category should be added to any variable for which information is not available for all subjects. The default denominator will be all subjects in the analysis set unless otherwise specified in the SAP. For both tables and listings where there are no observations (and hence there would be no output), the table/listing should be produced with all titles and footnotes as per its shell, but with the text showing no observations in the body of the output.

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

14.3. DATA FORMATS

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

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

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

15. TABLE, FIGURE AND DATA LISTING SHELLS

15.1. TABLE SHELLS

See separate file.

15.2. FIGURE SHELLS

See separate file.

15.3. DATA LISTING SHELLS

See separate file.

16. REFERENCES

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

APPENDIX 1. MARKEDLY ABNORMAL LABORATORY CRITERIA

Lab Parameter	Unit	Lower Limit Criteria	Upper Limit Criteria
Chemistry			
Albumin	g/L	<20	>68
Alkaline Phosphatase	U/L		>5 x ULN
Alanine Aminotransferase (ALT)	U/L		>8 x ULN
Aspartate Aminotransferase (AST)	U/L		>8 x ULN
Amylase	U/L		>3 x ULN
Lipase	U/L		>3 x ULN
Bilirubin Total	umol/L		>3 x ULN
Direct Bilirubin	umol/L		>34.208
Blood Urea Nitrogen	mmol/L		>12.495
Calcium	mmol/L	<1.5	>3
Creatinine	umol/L		>132.6 if age < 10 y; >150.28 if age 10-<13 y; >176.8 if age 13-<16 y; >221 if age 16+
C Reactive Protein	mg/L		>=100
Glucose	mmol/L	<2.22	>13.875
Magnesium	mmol/L	<0.4114	>1.2342
Phosphorus	mmol/L	<0.644	>2.254
Potassium	mmol/L	<2.5	>6.5
Sodium	mmol/L	<120	>160
Triglycerides	mmol/L		>5.65
Hematology			

Hemoglobin	g/L	<70	>200
Hematocrit	fraction of 1	<0.21	>0.60
Platelets	10^9/L	<75	>700
Leukocytes	10^9/L	<2	>30
Neutrophils, absolute	10^9/L	<0.5	

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

Table 1 L, M and S Values of Height for Age for Japanese Children 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 BMI for Age for Japanese Subjects ≥2 Years of Age (Male)

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

Table 4 L, M and S Values of BMI for Age for Japanese Subjects ≥2 Years of Age (Female)

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

Table 5 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	37.0473	0.035782
2.5 months	3.39959	39.9479	0.034410	3.48864	38.8785	0.033925
3.5 months	3.31270	41.3592	0.032639	3.56084	40.2025	0.032438
4.5 months	3.21754	42.3408	0.031291	3.60300	41.1507	0.031282
5.5 months	3.11495	43.0462	0.030314	3.61724	41.8547	0.030417
6.5 months	3.00576	43.6255	0.029657	3.60563	42.4433	0.029803
7.5 months	2.89081	44.1563	0.029267	3.57027	42.9833	0.029401
8.5 months	2.77094	44.6439	0.029092	3.51326	43.4792	0.029171
9.5 months	2.64698	45.0903	0.029081	3.43670	43.9330	0.029074
10.5 months	2.51976	45.4977	0.029181	3.34267	44.3466	0.029069
11.5 months	2.39013	45.8680	0.029340	3.23327	44.7219	0.029118
12.5 months	2.25893	46.2032	0.029508	3.11059	45.0609	0.029182
13.5 months	2.12698	46.5059	0.029658	2.97674	45.3658	0.029240
14.5 months	1.99512	46.7783	0.029791	2.83380	45.6395	0.029293
15.5 months	1.86419	47.0232	0.029906	2.68386	45.8847	0.029340
16.5 months	1.73503	47.2431	0.030005	2.52903	46.1042	0.029381
17.5 months	1.60847	47.4406	0.030088	2.37140	46.3008	0.029418
18.5 months	1.48535	47.6181	0.030156	2.21305	46.4772	0.029448
19.5 months	1.36650	47.7783	0.030210	2.05609	46.6363	0.029474
20.5 months	1.25277	47.9238	0.030249	1.90261	46.7807	0.029496
21.5 months	1.14498	48.0570	0.030276	1.75470	46.9134	0.029512
22.5 months	1.04397	48.1806	0.030290	1.61446	47.0370	0.029524
23.5 months	0.95058	48.2970	0.030292	1.48399	47.1543	0.029531
27 months	0.69015	48.6746	0.030216	1.12237	47.5434	0.029525
33 months	0.45065	49.2382	0.029846	0.80613	48.1547	0.029414
39 months	0.39445	49.7113	0.029298	0.76467	48.7035	0.029206
45 months	0.43079	50.1119	0.028712	0.87148	49.1982	0.028934
51 months	0.46891	50.4577	0.028230	1.00006	49.6471	0.028633
57 months	0.41804	50.7642	0.027995	1.02390	50.0499	0.028337
63 months	0.18741	51.0444	0.028148	0.81650	50.3975	0.028081
69 months	−0.31374	51.3113	0.028831	0.25137	50.6807	0.027898
75 months	−1.17618	51.5780	0.030185	−0.79801	50.8899	0.027824

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

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

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

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

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

Note: MedDRA terms are based on MedDRA version 20.0.