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NAME, POSITION	ROLE	DATE TIME STAMP
[redacted] Principal Statistician [redacted]	originator	[redacted]
[redacted] Group Leader Biostatistics [redacted]	reviewer	[redacted]
[redacted] Lead Project Manager [redacted]	reviewer	[redacted]
[redacted] Project Statistician [redacted]	approver	[redacted]
[redacted] VP Head of Clinical Science [redacted]	approver	[redacted]

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VectivBio AG

STATISTICAL ANALYSIS PLAN

PROTOCOL TA799-013

A multicenter, open-label, metabolic balance study to evaluate the effects of apraglutide on intestinal absorption in adult subjects with short bowel syndrome, intestinal failure (SBS-IF), and colon-in-continuity (CIC)

Protocol Code:	TA799-013
SAP Version:	FINAL v3.0
SAP Date:	12DEC2022
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DOCUMENT HISTORY

VERSION HISTORY

Version #	Version Date
v1.0	23JUN2022
V2.0	22JUL2022
V3.0	12DEC2022

REVISION HISTORY

Version #	Chapter	Revision Summary	Reason(s) for Revision
V1.0	N/A	New	N/A
V2.0	Section 6 Interim Analysis	Removed the plan/scope of preliminary data analysis and added the scope of interim analysis (IA).	The Sponsor has decided a change in the analysis plan due to the timing of preliminary data analysis and the first protocol-defined interim analysis.
	Section 9.2 Definition of Baseline, Trial Visits, and Visit Windows	Clarified analysis timepoints for citrulline and apraglutide plasma concentration data analysis.	This is to provide clarity for analysis.
	Section 9.8.3 Laboratory Data	Added the derivation rule for the safety lab results with > or < prefix.	This is to provide clarity for analysis.
	Section 9.8.6 PK/PD	Removed the derivation rule for apraglutide plasma concentrations below the lower limit of quantification (LLOQ) in case of being taken before the first dose of trial treatment since such a sample timepoint is not applicable according to the schedule of assessment.	This is to provide clarity for analysis.
V3.0	throughout	Added Appendix 4 Addendum to Statistical Analysis Plan (SAP) to refer Note to File (NTF) issued by Sponsor throughout this document for the changes of SAP for the second interim analysis and final analysis.	To incorporate Sponsor issued NTF into this SAP.
	Section 10	Documented the change of analysis plan for Adverse Event of Special Interest (AESI) due to the NTF	To document the change from the protocol-defined

Version #	Chapter	Revision Summary	Reason(s) for Revision
		issued by Sponsor.	planned analysis.
	Approval signature page	VectivBio Approver changed from [redacted]	Change in Biostatistician

APPROVAL SIGNATURES

STUDY TITLE: A multicenter, open-label, metabolic balance study to evaluate the effects of apraglutide on intestinal absorption in adult subjects with short bowel syndrome, intestinal failure (SBS-IF), and colon-in-continuity (CIC)

PROTOCOL NUMBER: TA799-013

SAP FINAL v3.0, 12DEC2022

PSI

AUTHOR:	[redacted] Principal Statistician	Electronically signed & dated
REVIEWED BY:	[redacted] Group Leader Biostatistics	Electronically signed & dated
REVIEWED BY:	[redacted] Lead Project Manager	Electronically signed & dated

VectivBio

APPROVED BY:	[redacted] Director, Program Statistician	Electronically signed & dated
APPROVED BY:	[redacted] VP, Head of Clinical Development	Electronically signed & dated

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1. List of Abbreviations

ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BSFS	Bristol Stool Form Scale
CI	Confidence Interval
CIC	Colon-in-Continuity
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough plasma concentration
D/BHQ	Dietary/Bowel Habit Questionnaire
DEXA	Dual-Energy X-ray Absorptiometry
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOT	End of Trial
FAS	Full Analysis Set
GI	Gastrointestinal
GLP-2	Glucagon-like Peptide 2
GMT	Good Morning Time
GNT	Good Night Time
IA	Interim Analysis
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
LLOQ	Lower Limit of Quantification
LTE	Long-term Safety and Clinical Outcomes Extension Trial
MB	Metabolic Balance
MedDRA	Medical Dictionary for Regulatory Activities
MQ	Medical Questionnaire
MRI	Magnetic Resonance Imaging
nAb	Neutralizing Antibody
PD	Pharmacodynamic
PGIC	Patient Global Impression of Change
PGI-PSI	Patient Global Impression of Parenteral Support Impact
PGI-SPS	Patient Global Impression of Satisfaction with Parenteral Support
PGIS	Patient Global Impression of Severity
PGI-TS	Patient Global Impression of Treatment Satisfaction
PK	Pharmacokinetic

PN	Parenteral Nutrition
PopPK	Population Pharmacokinetic
PRO	Patient Reported Outcomes
PS	Parenteral Support
[redacted]	[redacted]
PT	Preferred Term
QOL	Quality of Life
QTcF	QT Interval corrected according to Fridericia's formula
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SBS	Short Bowel Syndrome
SBS-IF	Short Bowel Syndrome with Intestinal Failure
SBS-IF-CIC-QOL	Short Bowel Syndrome with Intestinal Failure and Colon-in-Continuity Quality of Life questionnaire
SBS-IF-TI-QOL	Short Bowel Syndrome with Intestinal Failure - Treatment Impacts - Quality of Life questionnaire
SC	Subcutaneous
SCFA	Short Chain Fatty Acid
SoA	Schedule of Assessments
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
TESAE	Treatment-Emergent Serious Adverse Events
TFL	Tables, Figures, and Listings
VRS	Verbal Response Scale
WHODD	World Health Organization Drug Dictionary

2. Introduction

This statistical analysis plan (SAP) describes the planned statistical analysis for the TA799-013 trial based on the protocol version 4.0 (dated February 7, 2022), titled "A multicenter, open-label, metabolic balance study to evaluate the effects of apraglutide on intestinal absorption in adult subjects with short bowel syndrome, intestinal failure (SBS-IF), and colon-in-continuity (CIC)", and based on the latest electronic case report forms (eCRF) prior to approval of this document.

After the SAP version 2.0 was finalized on 22 July 2022, Sponsor decided to make changes to analysis plans for the upcoming second interim analysis (IA) and final analysis and issued Note to File (NTF; Topic: TA799-013 Statistical Analysis Plan) on December 6, 2022, rather than updating SAP itself considering the scope of changes. It was agreed between Sponsor and PSI to attach the NTF as addendum to this SAP (See Appendix 4: Addendum to Statistical Analysis Plan). These changes stated in the NTF supersede any other sections in this SAP and Mock-Up Tables, Figures, and Listings (TFL) document.

Two (2) sites have enrolled subjects in this trial; a French site (2 subjects enrolled) and a Belgian site (7 subjects enrolled). Recruitment in this trial is now closed. On February 7, 2022 VectivBio issued protocol version 4 which was approved by the Belgian Ethics Committee, but rejected by the French Ethics Committee. The French site continues to operate under protocol version 3 (dated September 3, 2021).

This SAP describes differences in the endpoints and objectives between the two protocol amendments (protocol versions 3 and 4). The analysis itself will be performed as per protocol amendment 4 for all subjects.

3. Trial Objectives

3.1 Primary Objective

- To evaluate the safety and tolerability of apraglutide (applicable to the protocol version 4)
- To evaluate the efficacy of apraglutide in increasing intestinal energy absorption assessed by bomb calorimetry in relation to metabolic balance (MB) assessments (applicable to the protocol version 3)

3.2 Secondary Objectives

- To evaluate fluid, electrolytes, calories, and macronutrient absorption indicative of clinical efficacy (applicable to the protocol version 4)
- To evaluate fluid, electrolytes, and macronutrient absorption indicative of clinical efficacy (applicable to the protocol version 3)
- To evaluate the efficacy of apraglutide in reducing the administered volume per week of parenteral support (PS) from baseline
- To evaluate the safety and tolerability of apraglutide (applicable to the protocol version 3)
- To assess apraglutide plasma concentrations to inform the population pharmacokinetic (PopPK) model
- To evaluate citrulline plasma concentrations to inform the PopPK/Pharmacodynamic (PD) analysis

3.3 EXPLORATORY OBJECTIVES

- To evaluate other selected parameters indicative of clinical efficacy

3.4 EXPERIMENTAL OBJECTIVES

- To investigate predictors and underlying mechanisms on the effect of apraglutide by studying intestinal permeability, gastrointestinal (GI) motility, mucosal gene expression and mucosa-associated and luminal microbiota

4. Trial DESCRIPTION

4.1 TRIAL DESIGN

This is a repeated-dose, open-label trial investigating the efficacy, safety, PD, and pharmacokinetics (PK) of apraglutide in subjects with SBS-IF and CIC. The subjects will receive a subcutaneous (SC) dose of 2.5 mg or 5 mg apraglutide once weekly for 52 weeks. Safety follow-up assessments will be performed 4 weeks (± 1 week) after the last dose.

Subjects will undergo three 72-hour MB evaluations at baseline, Week 4, and Week 48. For the first 4 weeks, up to the completion of the second MB study, the PS should not be changed. PS volume can be reduced for safety reasons but all possible attempts should be made to return to the baseline PS prescription for the second MB period.

Subjects that do not complete the baseline and 4-week MB evaluation and/or do not receive all 4 doses of Investigational Medicinal Product (IMP), per protocol, may be replaced. Subjects that withdraw after the 4-week MB evaluation may not be replaced.

At each visit, starting after Week 4, the PS volume will be reviewed and adjusted by the investigator taking into account the protocol-defined algorithm for PS volume reduction, based on changes in urine output of 10% or greater.

For subjects with change in urine output not higher than 10%, cases will be adjudicated by the participating investigators who will review the clinical status of participants to assess if PS volume reduction is warranted. The three investigators will make recommendations for the safety of subjects and with the objective to standardize and harmonize decisions on PS volume reduction and weaning across the three sites.

The safety follow-up is planned at the end of trial (EOT) visit, 4 weeks after the last IMP dose. If trial treatment is discontinued permanently, assessments will be performed at EOT visit, 4 weeks after the last dose. If the subject enters the long-term Safety and Clinical Outcomes extension trial (LTE, TA799-012), no EOT assessments will occur.

In case a subject discontinues or withdraws prematurely from the trial treatment for any reason after receiving at least one dose of IMP, subjects will be asked to continue to participate in the trial beyond the EOT visit according to the schedule of assessments (with the exception of IMP administration).

The schedule of assessments are found in Appendix 1: Schedule of Assessments.

4.2 TRIAL TREATMENT

A single 2.5 mg dose (for subjects with body weight less than 50 kg at most recent trial visit) or 5 mg dose (for subjects with body weight 50 kg or more at most recent trial visit) of apraglutide will be administered by SC injection once weekly during a treatment period of 52 weeks.

IMP should be administered on the same day of the week based on the first administration at Week 0 (Visit 3), with a window of ±24 hours, i.e., the administration could be done up to

24hours earlier or later than per schedule. On days when the subject will be at the site, the IMP must be administered at the site. Change of dosing is only allowed at each clinic visit. Between visits, IMP can be either self-administered at home or by a family member/caregiver, or administered at the clinic.

4.2.1 CONSIDERATIONS ON IMP DOSE REDUCTION AND TEMPORARY DISCONTINUATION OF IMP

If the Investigator reduces the IMP dose due to safety reasons, documentation as an adverse event (AE) is required. If the Investigator reduces or temporarily discontinues the IMP, resumption of the IMP or return to the prescribed dose must be based on the medical condition of the subject and the Investigator's clinical judgment.

Reduction of the IMP can be from 5.0 mg to 2.5 mg or from 2.5 mg to 0 mg. No other dose adjustments are allowed. The Investigator should attempt to return to the per protocol dose as soon as the medical condition of the subject allows. If the subject does not continue to tolerate the per protocol dose, the Investigator may choose to resume IMP administration at the lower dose of 2.5 mg weekly.

There is no limit to the number of dose reductions for an individual subject during the trial. However, the Investigator should discuss with the subject and use their clinical judgment to determine if it is safe and appropriate for the subject to continue if numerous IMP discontinuations and/or reductions have been required.

Changes and discontinuations must be discussed with the Medical Monitor. If the subject's medical condition allows, this discussion may occur prior to changes but may occur afterwards if this is not possible (e.g., an AE necessitating an immediate halt). The final decision to reduce or discontinue the IMP will be that of the Investigator.

Dose changes and the rationale will be documented in the medical records, in the subject diary (for IMP administration at the subject's home) and in the eCRF. Missed doses will not be made up for, i.e., the treatment period will not be prolonged due to temporary discontinuation. Reporting as a protocol deviation is required.

5. SAMPLE SIZE AND POWER CALCULATION

No formal sample size calculation has been performed for this trial. This trial is to enroll approximately 10 subjects. This is considered sufficient to provide adequate information about the general safety, tolerability, efficacy, PD and PK of the compound at this stage of development.

6. INTERIM ANALYSIS

Interim analyses will be performed after the last subject completes Week 4 and another after the last subject completes Week 24.

All data except for Anti-Drug Antibodies (ADA) data will be included in the first IA, hence excluding ADA, it is planned to produce all planned tables and listings (except for figures) for the first IA.

For IA, all available data points by the data snapshot will be included in the analysis while some may remain missing at the time of IA snapshot. The additional changes to this plan can be found in Appendix 4: Addendum to Statistical Analysis Plan.

Additional interim analyses may be performed by the sponsor at any time.

6.1 DATA MONITORING COMMITTEE

Ongoing safety surveillance will be performed by the Data Monitoring Committee (DMC) that is performing safety surveillance for the TA799-007 and TA799-012 trials, which is using the same IMP. The data from these 3 studies will be used to perform an overall safety evaluation for apraglutide.

Details on the composition and conduct with regards to open and closed sessions, tasks and responsibilities of the DMC will be described in a separate DMC charter.

7. ENDPOINTS

7.1 PRIMARY ENDPOINT

The following primary endpoints are applicable to the protocol version 4:

- Adverse events (system organ class, frequency, and severity)
- Adverse events of special interest (AESIs)
    - Injection site reaction
    - Gastrointestinal obstruction
    - Gallbladder, biliary and pancreatic disease
    - Fluid overload
    - Colorectal polyps
    - Malignancies
- Clinical chemistry, hematology, hemostasis, ADA, and urine analysis

The following primary endpoint is applicable to the protocol version 3:

- Absolute change in absorption of energy over MB periods from baseline to Week 48

7.2 SECONDARY ENDPOINTS

<u>Efficacy endpoints related to PS volume</u>

- Relative change from baseline in actual weekly PS volume at Weeks 4, 24 and 52
- Absolute change from baseline in actual weekly PS volume at Weeks 24 and 52
- Subjects who achieve a reduction of at least 1 day per week of PS from baseline at Weeks 24 and 52
- Clinical responders (20% reduction of PS volume from baseline) at Weeks 24 and 52
- Subjects reaching enteral autonomy at Weeks 24 and 52
- Energy reduction in the Parenteral Nutrition (PN) from baseline at Weeks 24 and 52

<u>Efficacy endpoint related to nutritional, fluid (wet weight) and electrolyte absorption</u>

- Absolute change in absorption of energy over MB periods from baseline to Week 48 (applicable to the protocol version 4)
- Relative change in absorption of energy over MB periods from baseline at Week 48
- Change in absorption of macronutrients over MB periods from baseline at Week 48

- Absolute change in absorption of energy over MB periods from baseline at Week 4
- Change in absorption of macronutrients over MB periods from baseline at Week 4
- Changes in urine output and urinary electrolytes (sodium, potassium, calcium and magnesium) over MB periods from baseline at Week 4 and at Week 48

Patient reported outcomes (PRO)

- Changes from baseline in [redacted] at Weeks 24 and 52
- Patient Global Impression of Change (PGIC) at Weeks 24 and 52
- Changes from baseline in Patient Global Impression of Treatment Satisfaction (PGI-TS) at Weeks 24 and 52
- Changes from baseline in Patient Global Impression of Satisfaction with PS (PGI-SPS) at Week 24 and 52
- Changes from baseline in Patient Global Impression of PS Impact (PGI-PSI) at Week 24 and 52.

PK/PD related endpoints

- Trough plasma concentration
- Plasma citrulline levels

Safety endpoints (applicable to the protocol version 3)

- AESI
- Clinical chemistry, hematology, hemostasis, ADAs, and urine analysis
- AEs

7.3 EXPLORATORY ENDPOINTS

Endpoints related to nutritional status

- Changes from baseline in lean body mass, bone mineral content and fat mass by Dual-Energy X-ray Absorptiometry (DEXA) scan from baseline at Weeks 4, 24, and 48
- Change in body weight from baseline at Weeks 4, 24, and 48 (applicable to the protocol version 4)
- Change in body weight from baseline at Weeks 24 and 48 (applicable to the protocol version 3)
- Change in dietary intake of wet weight (oral solid food, oral fluid), energy, macronutrients, and electrolytes (sodium, potassium, calcium and magnesium) from baseline at Weeks 4 and 48
- Change in fecal excretion of wet weight (feces), energy, macronutrients, and electrolytes (sodium, potassium, calcium and magnesium) from baseline at Weeks 4 and 48

Endpoints related to efficacy

- Change from baseline in the total time per day that subjects infuse PS at Weeks 24 and 52
- Change from baseline in the total time per week that subjects infuse PS at Weeks 24

and 52

- Change in electrolytes, minerals, macronutrients and other contents of the PS from baseline at Weeks 24 and 52

Patient Reported Outcomes

- Short Bowel Syndrome with Intestinal Failure and Colon-in-Continuity - Changes from baseline in Quality of Life Questionnaire (SBS-IF-CIC-QOL) at Weeks 24 and 52
- Short Bowel Syndrome with Intestinal Failure - Observed scores in Treatment Impacts - Quality of Life Questionnaire (SBS-IF-TI-QOL) at Weeks 24 and 52

[redacted]

8. ANALYSIS POPULATIONS

Analyses of efficacy and PRO will be based on the Full Analysis Set (FAS; See definition below), whereas all the rest of analyses will be based on the Safety Analysis Set (SAS; See the definition below), except for the summary table for all screened subjects and for the disposition table, which will be based on SAS as well as FAS.

To help characterize the FAS, tables for demographics & other baseline characteristics, concomitant diseases and medications, and treatment exposure & compliance will be repeated by FAS. The additional changes to this plan can be found in Appendix 4: Addendum to Statistical Analysis Plan.

8.1 FULL ANALYSIS SET

FAS will comprise all subjects who have received at least one dose of trial treatment and contributed at least one valid post-baseline efficacy point.

8.2 SAFETY ANALYSIS SET

SAS will comprise all subjects exposed to trial medication.

9. Analytical Plan and Statistical Methods

9.1 General Conventions and Statistical Considerations

The statistical evaluation of the trial will include descriptive statistics of the primary and secondary endpoints reflecting the exploratory nature of the trial. In addition, simple analyses will be provided for efficacy endpoints and PRO.

Descriptive statistics for continuous variables will include the number of subjects, mean and standard deviation, median, first and third quartiles (Q1-Q3), and minimum and maximum values. All raw data will be presented to the original number of decimal places. Where appropriate, means, medians, and confidence intervals will be presented to 1 more decimal place than in the raw data. Likewise, standard deviations will be presented to 2 more decimal places than in the raw data.

Summary statistics for categorical variables will contain count and percentage. Percentages will be presented to one decimal, except for one hundred percent, which will be presented as 100%. Unless otherwise specified, percentages for baseline summaries will be based on the total number of subjects in the respective analysis set, whereas percentages for post-baseline summaries will be based on the total number of subjects assessed (i.e. with non-missing values) in the respective analysis set as specified in Section 8.

Confidence intervals for means and percentages will be calculated when appropriate and will be 2-sided at the 95% level unless otherwise specified. *p*-values will be reported to 3 decimal places where applicable; p-values less than 0.001 will be reported as p<0.001.

All data will be listed individually by subject, sorted by Subject Identifier (ID) and date of assessment or start date as applicable. In general, listings will be based on SAS except for eligibility and enrollment information including inclusion/exclusion criteria and informed consent, visit/telephone contact information, demographics, adverse events, and death, which will be based on screened subjects. Listings may include age, sex, indication of whether the subject has qualified for analysis set (e.g., SAS or FAS), or analysis record (e.g. Yes if used in analysis), where applicable. In case of indication for analysis set, listings will be generally sorted by subjects qualifying for SAS first before those not qualifying for SAS amongst screened subjects.

For efficacy parameters, the absolute and relative change from baseline will be derived as follows:

- Absolute change from baseline = X_i-X_0
- Relative change from baseline = 100*(X_i-X_0)/ X_0

Where X_i = observed/assessed value at a given analysis timepoint, whereas X_0 = observed/assessed value at baseline.

All analyses will be performed using [redacted]

9.2 Definition of Baseline, Trial Visits, and Visit Windows

The baseline is the last available assessment/observation prior to first trial treatment (i.e. first administration of apraglutide). For assessments done on the same day as the first trial treatment, the time of assessment should be used to recognize whether or not the assessment was done prior to the first trial treatment. Otherwise, when the time of assessment is not available, last available assessments on or prior to the date of first trial treatment will be

considered as baseline since assessments are to be performed prior to dosing on the day of the first IMP administration according to the schedule of assessments in the protocol.

For evaluation of MB parameters, all relevant data measured over the MB period at the scheduled visit will be considered as the analysis timepoint. This applies to baseline, Week 4, and Week 48. The detailed derivation of baseline MB period data can be found in Section 9.7.Except for EOT visit data for efficacy analyses, by-visit efficacy data will be analyzed based on eCRF visits.

For all efficacy analyses, the EOT visit data will be mapped to a visit as defined below and will be only used to replace any missing by-visit efficacy data:

Table 9.2.1: Data Mapping Scheme

Visit	Analysis timepoint	Target day*	[redacted]
4	Week 2	Day 15	
5	Week 4	Day 29	
6	Week 8	Day 57	
7	Week 12	Day 85	
8	Week 16	Day 113	
9	Week 20	Day 141	
10	Week 24	Day 169	
11	Week 28	Day 197	
12	Week 32	Day 225	
13	Week 36	Day 253	
14	Week 40	Day 281	
15	Week 44	Day 309	
16	Week 48	Day 337	
17	Week 52	Day 365	

*based on the relative days from the first trial treatment where the relative days from the first trial treatment = date of assessment or event – date of first trial treatment + 1, when both dates are known for assessments or events started on or after the day of the first trial treatment. (e.g., Relative Study Day 1 = the first study dosing day)

For safety data analysis, by-visit data will be analyzed based on the assigned analysis visit based on the data mapping scheme above. If more than one assessment falls into allowed time window the closest to the target date will be used. If two values are equidistant from the planned visit/assessment date, the first value will be used.

The citrulline and apraglutide plasma concentration data will be analyzed by scheduled visit based on eCRF visit (including EOT where applicable).

9.3 HANDLING OF MISSING DATA

In general, missing values will not be replaced, and observed values will be used for analyses unless specified in the sections below.

For the calculation of duration of SBS disease history, if there are any partial dates of SBS disease history, the first day and/or month of the year will be assumed for a missing day and/or month for the purpose of duration calculation based on the worst case scenario approach.

For medication or therapeutic interventions with imprecise/partial date(s), the first day/month of the year will be assumed for unknown day/month of the start date, and the last day/month of the

year will be assumed for unknown day/month of the stop date to categorize medications or therapeutic interventions as concomitant for the worst case scenario.

For events with imprecise/partial date(s), unless the start or end date of the known month or year is before the date of the first trial treatment, all events will be deemed as treatment-emergent adverse events (TEAEs) as opposed to pre-existing AEs.

For analyses of safety, missing data about AE relationship to trial treatment, intensity, seriousness, and outcome will be assumed to be 'related to the trial treatment', 'severe', 'serious', and 'not recovered/not resolved', respectively, based on the worst case scenario.

For analyses of efficacy, weekly PS data from diary may be missing in case of PS being 'weaned off'. In this case, missing weekly PS diary data (e.g. volume, frequency, total time of infusion etc.) will be imputed to 0 for analyses based on 'weaned off' information according to the PS prescription eCRF. Once 'weaned off' is recorded in eCRF at a visit, sites are not asked to repeat this data in the next visit. Hence, for analysis, 'weaned off' data will be carried forward to the next analysis timepoint(s) where applicable based on subjects' visit information until indicated otherwise (i.e. no longer reported as 'weaned off').

9.4 SUBJECT DISPOSITION

Number of subjects who were screened and screen-failures (along with reasons) will be summarized for all screened subjects. The percentages will be calculated based on the total number of subjects screened.

This table will also document the number and percentages of subjects enrolled, enrolled but not treated, in the SAS, and in the FAS. The percentages will be calculated based on the number of subjects screened. The enrolled subjects will be identified as subjects who signed the informed consent form (ICF) and have met all eligibility criteria. The number (%) of subjects screened and enrolled will be also summarized by country.

The number (%) of subjects who completed the trial treatment and prematurely discontinued from trial treatment will be tabulated, along with reasons for discontinuation. The number (%) of subjects who entered and did not enter 4-week safety follow-up will be presented, along with reasons for not entering follow-up. The 4-week safety follow-up completion status will be summarized with counts and percentages, along with the reason for not completing for subjects who have not completed the safety follow-up. The number (%) of subjects continuing with trial visits after withdrawal and subjects who agreed to provide PS administration details to the investigator will also be tabulated in the same table. For such subjects, the extended follow-up (observation) completion status will also be summarized with counts and percentages, along with the reason for not completing trial visits or PS data collection after permanent withdrawal of trial treatment.

The above tabulations will be produced for the SAS and FAS separately.

All disposition data will be listed.

A listing of eligibility and enrollment will be prepared for all screened subjects. A separate listing will be prepared to document subjects excluded from efficacy analysis.

9.5 PROTOCOL DEVIATIONS

Deviations will be collected by the clinical team during the trial conduct and reviewed by the sponsor as outlined in the most current Protocol Deviations Management Plan. The deviations will be classified as major or minor.

Protocol deviations will be tabulated for the SAS. Summaries will include number and

percentage of subjects with at least one major deviation, with at least one minor deviation, and at least one major deviation of each category.

A separate summary of protocol deviations related to COVID-19 will be presented for the SAS.

A listing of all protocol deviations will be produced.

9.6 SUBJECT CHARACTERISTICS

9.6.1 BASELINE AND DEMOGRAPHIC CHARACTERISTICS

Summary tables will include age (in years), sex (including child-bearing potential and reason, if applicable e.g., surgically sterile, post-menopausal, other), race, ethnicity, and country. Weight (kg) and height (cm) will also be tabulated together with body mass index (BMI) (kg/m^2). The BMI will be calculated using weight in kg, divided by height in m^2.

Listings of all baseline and demographic characteristics will be produced.

9.6.2 MEDICAL AND SURGICAL HISTORY

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 24.0 or higher). The number and percentage of subjects having at least one medical and/or surgical history record will be presented, along with summaries by System Organ Class (SOC) and preferred term (PT).

All medical and surgical history data collected in the eCRF will be listed.

A summary of SBS disease history will be presented, and this will include the cause of SBS, time from SBS diagnosis, time from PS initiation, length of remnant small bowel (cm), length of remnant colon in percentage (%) according to Cummings classification, time from major intestinal surgery which led to SBS, time from last continuity surgery, and whether ileocecal valve has been preserved. The durations will be derived as follows:

- Time from SBS diagnosis (months) = (date of ICF signed – date of SBS diagnosis +1)/30.4375. Refer to Section 9.3 for handling of the imprecise date of SBS diagnosis.
- Time from PS initiation (months) = (date of ICF signed – date of PS initiation +1)/30.4375. Refer to Section 9.3 for handling of the imprecise date of PS initiation.
- Time from major intestinal surgery which led to SBS (months) = (date of ICF signed – date of major intestinal surgery which led to SBS +1)/30.4375. Refer to Section 9.3 for handling of the imprecise date of major intestinal surgery which led to SBS.
- Time from last continuity surgery (months) = (date of ICF signed – date of last continuity surgery +1)/30.4375. Refer to Section 9.3 for handling of the imprecise date of last continuity surgery.

All SBS disease and gastrointestinal (GI) health history data will also be listed.

9.6.3 PRIOR AND CONCOMITANT MEDICATION AND INTERVENTIONS

All medication records will be categorized as either prior or concomitant medications for analyses. Concomitant medications are any ongoing medications at the time of the first trial treatment or any medications started on or after the date of the first trial treatment. Prior medications are any medications that ended prior to the date of the first trial treatment.

Prior and concomitant medications will be coded by World Health Organization Drug Dictionary (WHODD; version March 2021 Format B3 or higher) and summarized in separate tables by

Anatomical Therapeutic Chemical (ATC) classification 2, ATC classification 4, and PT.

Moreover, there will be a separate summary for concomitant antibiotic and non-antibiotic medications. The antibiotics will be identified by ATC codes starting with J01 or J04.

A subject data listing will be prepared to document all medications, and there will be a flag to identify prior vs. concomitant medications.

Similarly, there will be a subject data listing to document all therapeutic interventions reported.

9.7 EFFICACY ENDPOINTS AND ANALYSIS

In addition to the efficacy analyses defined below, for all continuous efficacy endpoints for the protocol defined analysis timepoints, mean change from baseline to the respective analysis timepoint will be presented with a *p*-value based on the paired t-test and 95% confidence interval (CI) for the mean change from baseline based on t-distribution. The 95% confidence interval (CI) for the mean change from baseline will be done for both absolute and relative change from baseline. Due to the relatively small sample size, one-sample (paired) Hodges-Lehmann median estimator for non-parametric estimate of change from baseline to the respective analysis timepoint, will be computed with the corresponding 95% CI.

Subject data listings will be prepared to document efficacy data, such as results from MB parameters, wet weight during the MB period, and DEXA scan. This will be supplemented by listings based on data from the MB period summary, including hospital admission information and drinking menu.

All data from the PS diary or PS infusion will also be listed to document efficacy data. This will be supplemented by listings using data from PS prescription, PS evening diary, urine sample for sodium analysis, change in eating/appetite, drinking diary, stool assessment, Bristol stool form scale diary, and stool frequency diary.

There will be separate subject data listings for PRO data from questionnaires, such as the [redacted], SBS-IF-TI-QOL, SBS-IF-CIC-QOL, Patient Global Impression of Severity (PGI-S), PGIC, PGI-TS, PGI-SPS, and PGI-PSI.

9.7.1 ANALYSIS OF PRIMARY ENDPOINT

There is no primary efficacy endpoint for this study.

9.7.2 ANALYSIS OF SECONDARY ENDPOINTS

9.7.2.1 ANALYSIS OF SECONDARY ENDPOINTS RELATED TO PS VOLUME

Subject diary data will be used to obtain PS volume information for analyses. Subjects are to complete diary prior to a scheduled visit. If a subject's e-dairy data is not available, PS data recorded at the site will be used for analyses. If a subject has issues/difficulties using the e-diary, PS volume data will be captured in the paper diary and will be entered into the electronic data capture (EDC) system at a trial visit.

The relative as well as absolute change in actual weekly PS volume from baseline to every 4 weeks until Week 52 will be summarized by descriptive statistics. *p*-values and Hodges-Lehmann median estimator along with 95% CI will be produced for Week 24 and Week 52 as defined in the introduction of Section 9.7. The sum of daily PS volume (including extra fluids) from weekly PS diary data recorded for the corresponding analysis timepoint will be used for analysis.

The proportion (%) of subjects who have achieved a reduction of at least 1 day per week of PS from baseline at every 4 weeks until Week 52 will be produced. Subjects will be considered to

have a reduction of at least one day per week of PS from baseline (incl. extra fluids) if the number of days with PS from weekly PS diary data recorded for the corresponding analysis timepoint is smaller compared to the number of days with PS from weekly PS diary data for the baseline.

In addition, the proportion (%) of clinical responders (20% reduction of PS volume from baseline) at every 4 weeks until Week 52 will be produced. Subjects will be considered to be a clinical responder if the relative change from baseline in weekly PS volume is ≤ -20% for the corresponding visit.

For above analyses, missing weekly PS data from diary (e.g. volume, frequency, etc) will be imputed to 0 in case of PS being weaned off (Refer to Section 9.3.).

Moreover, the proportion (%) of subjects with enteral autonomy at every 4 weeks until Week 52 will be produced using eCRF data. Once 'weaned off' is recorded in eCRF at a visit, sites are not asked to repeat this data in the next visit. Hence, for analysis, 'weaned off' data will be carried forward to the next analysis timepoint(s) where applicable based on subjects' visit information until indicated otherwise (i.e. no longer reported as 'weaned off') and enteral autonomy will be identified when there are at least two consecutive wean off records for analysis timepoints (after considering carried forward wean-off records) except for Week 52. For Week 52, enteral autonomy will be identified by 'weaned off' data reported at Week 52 since there is no subsequent/further analysis timepoint.

For PS compliance measure, the percent change in actual weekly PS volume from the prescribed weekly PS volume and the difference in actual days per week of PS from prescribed days per week of PS will be assessed for each post-baseline timepoint as well as for overall using the average per subject. The percent change in actual weekly PS volume from the prescribed weekly PS volume is calculated as (actual weekly PS volume minus prescribed weekly PS volume) x 100, divided by prescribed weekly PS volume for the corresponding timepoint. The difference in actual days per week of PS from prescribed days per week of PS (day) is calculated as actual days per week of PS minus prescribed days per week of PS.

The energy reduction in the PN from baseline at every 4 weeks until Week 52 will be assessed by descriptive statistics of the absolute and relative change in the total energy prescription data from baseline to analysis timepoints. *p*-values and Hodges-Lehmann median estimator along with 95% CI will be produced for Week 24 and Week 52 as defined in the introduction of Section 9.7. If it is reported that PS is weaned off at the given analysis timepoint, the total energy prescription data will be considered as 0 for analysis.

9.7.2.2 Analysis of Secondary Endpoints related to Nutritional, Fluid (Wet Weight) and Electrolyte Absorption

The absolute change in absorption of energy, over MB periods from baseline to Week 48 will be summarized by descriptive statistics.

The absorption will be defined as dietary intake minus output from fecal excretion over a 72-hour MB period at a given analysis timepoint. Hence, the absorption of energy will be calculated as energy intake minus energy output data (as collected on MB Results eCRF). Since dietary intake and fecal excretion are to be measured daily, i.e. up to 3 measurements may contribute to absorption calculations, the average over all available daily absorption measurements over the 72-hour period will be used for analysis. In other words, absorption data will be derived by average of all available intake minus average of all available excretion, regardless of whether there is a case in which either energy intake or energy output data are missing in a daily measurement.

Similar derivations will be applied for absorption of each of the other MB parameters, such as macronutrients (fat, carbohydrate, nitrogen, and protein).

Similarly, the wet weight absorption will be calculated as average of all wet weight input (oral solid + drinks) minus average of all wet weight output (only using feces) under assumption of 1mL = 1g for oral fluids.

Descriptive statistics will be produced for analyses of the following endpoints using absolute and relative change from baseline:

- Relative change in absorption of energy and wet weight over the MB period from baseline to Week 48.
- Absolute change in absorption of energy and wet weight over the MB period from baseline to Week 4 (See above for the derivation of absorption of energy).
- Change in absorption of macronutrients (fat, carbohydrate, and protein) over the MB period from baseline to Week 4 and to Week 48 (See above for the derivation of absorption of macronutrients).
- Change in urinary electrolytes (calcium, magnesium, sodium, potassium, urea, and creatinine) over the MB periods from baseline to Week 4 and Week 48. Since urinary electrolytes data are expected to be measured over the 72-hour MB period, the average of all available results will be used for analyses for each MB parameter at a given analysis timepoint.
- Change in urine volume over the MB periods from baseline to Week 4 and Week 48. This analysis will be based on average daily urine volume data derived as per Balance Period Calculations eCRF since the average daily urine volume should be calculated based on investigator's decision on which 48 hours of the 72 hour metabolic balance study collection to be used.

p-values and Hodges-Lehmann median estimator along with 95% CI will be produced for absolute and relative change from baseline where applicable as defined in the introduction of Section 9.7 for the above analysis timepoints. If a measurement of absorption yields a negative value, such a measurement result will be regarded as invalid and treated as non-evaluable for the relative change analysis. In the analysis dataset, such cases will not be flagged as analysis records since it is considered non-evaluable for the relative change analysis.

The following figures will be provided for energy absorption:

- Line graph using individual observations by timepoint
- Line graph using individual relative change from baseline by timepoint
- Cumulative distribution of change from baseline
- Change from baseline – mean (95%CI) by timepoint
- Relative change from baseline (%) – mean (95%CI) by timepoint

Figures will be repeated for other MB parameters, absorption of wet weight, fat, carbohydrate, and protein.

In addition, the absolute and relative change from baseline in average daily urine volume (derived as per Balance Period Calculations eCRF) will be also summarized for other timepoints. The number of subjects with an increase or decrease from baseline of more than 10% will be tabulated by analysis visit up to Week 52.

Furthermore, the change from baseline in urine sodium will be summarized by descriptive statistics for scheduled time points.

9.7.2.3 Analysis of Secondary Endpoints related to PRO

The change in [redacted] total score and other component scores from baseline to scheduled time point(s) will be summarized by descriptive statistics. The number (%) of subjects with [redacted] total score =<5 and >5 will be also summarized by scheduled timepoint. *p*-values and Hodges-Lehmann median estimator along with 95% CI will be produced for change in [redacted] total score at Week 24 and Week 52 as defined in the introduction of Section 9.7. The [redacted] total score and other component scores will be derived as defined in Appendix 2: Scoring Method FOR [redacted].

Since PGIC, PGI-TS, PGI-SPS, and PGI-PSI responses have seven or fewer ordered categories, the average or total will not be derived from these measures while treating them as ordinal variables. Hence, PGIC, PGI-TS, PGI-SPS, and PGI-PSI will be described by frequency (%) of each response.

There will be a separate table to summarize the observed and change in PGI-TS, PGI-SPS, and PGI-PSI from baseline to scheduled timepoint(s) by descriptive statistics using mean, SD, …etc.

Similarly, the observed PGIC v2.0 at scheduled timepoint(s) will be also by descriptive statistics using mean, SD, …etc.

9.7.3 Analysis of Exploratory Efficacy Endpoints

9.7.3.1 Analysis of Exploratory Endpoints related to Nutritional Status

The following exploratory endpoints related to nutritional status will be analyzed by descriptive statistics using absolute and relative change from baseline:

- Changes from baseline in lean body mass, bone mineral content and fat mass by DEXA scan from baseline to Week 4, Week 24, and Week 48
- Change in body weight from baseline to Week 4, Week 24, and Week 48
- Change in dietary intake of wet weight (oral solid food, oral fluid), energy, macronutrients (fat, carbohydrate, nitrogen, and protein), and electrolytes (sodium, potassium, calcium and magnesium) from baseline to Weeks 4 and 48
- Change in fecal excretion of wet weight (feces), energy, macronutrients (fat, carbohydrate, nitrogen, and protein), and electrolytes (sodium, potassium, calcium and magnesium) from baseline at Weeks 4 and 48

For each MB parameter, it is expected that there will be up to 3 measurements at a given analysis timepoint based on dietary intake and fecal excretion data; hence, the average of all available results over the 72-hour MB period will be used for analysis for each MB parameter at a given analysis timepoint.

p-values and Hodges-Lehmann median estimator along with 95% CI will be produced for change from baseline as defined in the introduction of Section 9.7 for the above specified analysis timepoints.

The body weight will be summarized by descriptive statistics for scheduled visits. If there are multiple body weight results available over MB period, the last available result taken on or prior to the scheduled visit will be used for the corresponding analysis timepoint (Week 4 or Week 48).

9.7.3.2 Analysis of Exploratory Endpoints related to Efficacy

The following exploratory endpoints related to efficacy will be analyzed by descriptive statistics using the absolute change from baseline.

- Change in the total time per day that subjects infuse PS from baseline to every 4 weeks until Week 52 (to be derived based on the total time of PS infusion (including extra fluid) from weekly PS diary data recorded for the corresponding analysis timepoint, divided by 7). *p*-values and Hodges-Lehmann median estimator along with 95% CI will be produced for Week 24 and Week 52 as defined in the introduction of Section 9.7; Note: For handling of missing weekly PS data from diary in case of PS being weaned off, refer to Section 9.3.
- Change in the total time per week that subjects infuse PS from baseline to every 4 weeks until Week 52 (to be derived based on the total time of PS infusion (including extra fluid) from weekly PS diary data recorded for the corresponding analysis timepoint). *p*-values and Hodges-Lehmann median estimator along with 95% CI will be produced for Week 24 and Week 52 as defined in the introduction of Section 9.7; Note: For handling of missing weekly PS data from diary in case of PS being weaned off, refer to Section 9.3.
- Change in electrolytes, minerals, macronutrients and other contents of the PS from baseline to every 4 weeks until Week 52. This is to be derived using each of the following prescription data at the given analysis timepoint. If it is reported that PS is weaned off at a given analysis timepoint, the data will be considered as 0 for analysis.
    - Total energy lipid
    - Total energy glucose
    - Total energy amino acids
    - Magnesium concentration
    - Potassium concentration
    - Sodium concentration

p-values and Hodges-Lehmann median estimator along with 95% CI will be produced for Week 24 and Week 52 as defined in the introduction of Section 9.7.

In addition, for analysis of change in in electrolytes, minerals, macronutrients and other contents of the PS, the relative change from baseline will be also summarized.

9.7.3.3 Analysis of Exploratory Endpoints related to PRO

For analyses of PRO using SBS-IF-CIC-QOL, the change in scores from baseline to scheduled visit will be summarized by descriptive statistics. *p*-values and Hodges-Lehmann median estimator along with 95% CI will be produced for Week 24 and Week 52 as defined in the introduction of Section 9.7.

For analyses of PRO using SBS-IF-TI-QOL, PS impact subscale and GLP-2 impact subscale scores will be summarized by scheduled visit using descriptive statistics along with the descriptive statistics of two item values in Part 2 regarding GLP-2 impact.

For SBS-IF-CIC-QOL, it is assumed that the score will be calculated by taking the mean of the 14 items. For SBS-IF-TI-QOL, it is assumed that two subscale scores will be calculated, PS impact, and GLP-2 impact. The PS impact subscale will be calculated for the subjects with CIC by taking the mean of items 1 to 10 in Part 1. The GLP-2 impact subscale will be calculated by taking the mean of items 1 and 2 in Part 2.

In case at least one item is missing (i.e. not reported), the mean will not be calculated with the

following exceptions: In case of SBS-IF-TI-QOL item(s) 1 or 9 being reported as N/A, the PS impact subscale will be calculated by taking mean of the relevant item responses. In case of SBS-IF-TI-QOL item 2 response being not reported or N/A in Part 2, the GLP-2 impact subscale will be calculated only based on item 1 response since item 2 may not be relevant for subjects who do not prepare GLP-2 injection themselves

[redacted]

9.7.4 Sensitivity Analysis to the Efficacy analyses

The analyses of the following endpoints related to nutritional status and nutritional absorption will be repeated for sensitivity analyses using a subgroup of subjects in the FAS excluding subjects missing more than 20% of the planned injections prior to the respective visit. Hence, the number of injections leading to exclusion will be 1 at Week 4, 5 at Week 24, and 10 at Week 48. In other words, the subgroup for Week 4 analysis will be composed of subjects in the FAS with at least 4 injections prior to the visit date of Week 4 assuming 4 planned injections prior to Week 4. Similarly, the subgroup for Week 24 analysis will be composed of subjects in the FAS with at least 20 injections prior to the visit date of Week 24, whereas the subgroup for Week 48 analysis will be composed of subjects in the FAS with at least 39 injections prior to the visit date of Week 48.

- Change in absorption of energy and wet weight over the MB period from baseline to Week 4 and Week 48
- Relative change in absorption of energy and wet weight over the MB period from baseline to Week 48
- Change in absorption of macronutrients (fat, carbohydrate, and protein) over the MB period from baseline to Week 4 and to Week 48
- Change in urine output and urinary electrolytes (calcium, magnesium, sodium, potassium, urea, and creatinine) over the MB periods from baseline to Week 4 and Week 48
- Changes from baseline in lean body mass, bone mineral content and fat mass by DEXA scan from baseline to Week 4, Week 24, and Week 48
- Change in body weight from baseline to Week 4, Week 24 and Week 48
- Change in dietary intake of wet weight (oral solid food, oral fluid), energy, macronutrients (fat, carbohydrate, nitrogen, and protein), and electrolytes (sodium, potassium, calcium and magnesium) from baseline to Weeks 4 and 48
- Change in fecal excretion of wet weight (feces), energy, macronutrients (fat, carbohydrate, nitrogen, and protein), and electrolytes (sodium, potassium, calcium and magnesium) from baseline at Weeks 4 and 48

9.8 Safety Endpoints and Analysis

The primary endpoints of this study are the safety endpoints as specified in Section 7.1.

9.8.1 Exposure to Trial Treatment

The extent of trial treatment exposure will be summarized descriptively by the following:

- Trial treatment duration (weeks). To be derived as follows: (date of last trial treatment – date of first trial treatment +1)/7, when both dates are known.
- Cumulative treatment exposure (mg). To be based on the total amount of trial medication taken by a subject as determined using diary and information provided by sites.
- Compliance (%). To be calculated as follows: [total amount of drug taken by a subject (based on diary and site information)/ ((number of weeks when a subject was assigned a dose of 2.5 mg)*2.5 + (number of weeks when a subject was assigned a dose of 5 mg)*5)]*100, where the number of weeks for the assigned dose will be calculated as follows: (stop date of the respective dose – start date of the respective dose +1)/7, rounded up to the next higher integer to represent the planned number of weeks for the assigned dose.

The compliance will be also summarized categorically by >=80% and <80%.

The frequency (%) of dose reductions and trial treatment discontinuation will be summarized as a part of safety analyses (See Section 9.8.2)

All IMP administration data will be listed.

9.8.2 Adverse Events

AEs that started on or after the first trial treatment will be categorized as TEAEs; whereas AEs that started on or after signing ICF but prior to first trial treatment will be categorized as pre-treatment AEs.

TEAEs reported as definitely, probably, or possibly related to the trial treatment will be deemed as trial treatment-related TEAEs for the purpose of reporting.

On-treatment AEs will be defined as any AE recorded in the trial database, started on or after the first trial treatment until 4 weeks from the last trial treatment (i.e., date of last trial treatment +28 days inclusive).

AESI will be programmatically derived based on Appendix 3: Sponsor-Defined List of Preferred Terms. As ongoing pharmacovigilance could reveal new relevant Standardize MedDRA Queries (SMQs) or Customer Queries (CQs), the final selection will be determined at the data review meeting prior to database lock. The additional changes to this plan can be found in Appendix 4: Addendum to Statistical Analysis Plan.

All AEs will be coded using MedDRA version 24.0 or higher.

An overall summary of AEs will be presented, which will include the incidence (%) of subjects with at least one pre-treatment AE, TEAE, treatment-emergent serious adverse event (TESAE), treatment-emergent AESI (programmatically derived as described above), trial treatment-related TEAE, trial treatment-related TESAE, TEAE leading to trial treatment dose increased, dose reduction of trial treatment, dose interruption of trial treatment, permanent discontinuation of trial treatment, not entering 4 weeks of safety follow-up, follow-up discontinuation, AE leading to death, and on-treatment AE along with the number of events.

The incidence (%) of subjects experiencing AEs for the following categories will be further summarized by SOC and PT in separate tables:

- TEAE

- Treatment-emergent AESI (programmatically derived)
- Trial treatment-related TEAE
- TEAE by severity
- On-treatment AE
- TESAE
- Non-serious TEAE
- Trial treatment-related TESAE

Subjects may report more than one event per coded term. For incidence (%) of subjects, subjects will be counted only once per given SOC or per given PT within SOC. This will also apply to the analysis of TEAEs by severity based on the highest severity. Note: For the summary of treatment-emergent AESI, AESI categories will be used for analysis instead of SOC. The additional changes to this plan can be found in Appendix 4: Addendum to Statistical Analysis Plan.

All AEs will be listed. There will be separate listings for AESIs, SAEs and for AEs leading to permanent discontinuation of trial treatment. All AE listings will include a flag to indicate pre-treatment AE vs. TEAE.

9.8.3 Laboratory Data

For laboratory panels (hematology, chemistry, and hemostasis), summary statistics of observed and change from baseline values will be produced by analysis visit up to Week 52 for all continuous variables. For laboratory results reported with a prefix, for example "<" or ">", the value derived from the reported results without a prefix will be analyzed.

Shift tables will display the cross tabulation of Common Terminology Criteria for Adverse Events (CTCAE) grades (based on version 5.0 or higher) from the baseline to worst post-baseline based on the maximum post-baseline grade during the treatment and safety follow-up periods considering both scheduled and unscheduled post-baseline values. The percentages will be calculated based on the number of subjects assessed who have both baseline and post-baseline results.

All laboratory data for hematology & hemostasis, chemistry, urinalysis, endocrinology, and serology will be listed.

There will be separate listings for hematology & hemostasis, and chemistry data with clinically significant results.

9.8.4 Vital Signs and Other Safety Parameters

For vital signs (systolic and diastolic blood pressure, heart rate, and temperature) and weight, summary statistics of observed and changes from baseline values will be presented by analysis visit up to Week 52.

All height, weight, and vital signs data will be listed.

Similarly, for each electrocardiogram (ECG) parameter (RR interval, PR interval, QRS interval, QT interval, QTcF interval), summary statistics of observed and changes from baseline values will be presented by analysis visit. In addition, ECG interpretation results will be summarized by frequency (%) for each analysis visit up to Week 52.

All ECG data will be listed.

All physical examination data will be listed.

The relative change from baseline in urine volume (%) will be summarized by analysis visit up to Week 52. The change from baseline and percent change from baseline will be calculated using the average daily urine volume data as per the Balance Period Calculations eCRF.

Subject data listings will be prepared to document data from the 48-hour urine collection diary, 24-hour urine collection diary, balance period calculations, post-PS volume reduction safety evaluation, and PS adjudication.

There will be a separate listing to document PS volume details upon withdraw from trial visits for subjects who have permanently discontinued from trial treatment.

The investigator narratives data will be listed.

Colonoscopy/colonography data will be listed.

9.8.5 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will be analyzed descriptively using the following categories based on SAS:

- Number (%) of subjects with an ADA-positive sample at baseline and at post-baseline. Percentages will be calculated based on the number of subjects assessed with a determinant baseline ADA sample or at least one determinant post-baseline ADA sample, respectively.
- Number (%) of subjects with an ADA-positive sample cross-reactive to endogenous GLP-2 at baseline and at post-baseline. Percentages will be calculated based on the number of subjects assessed with a determinant baseline ADA sample or at least one determinant post-baseline ADA sample, respectively.
- Number (%) of subjects with a neutralizing antibody (nAb)-positive sample at baseline or at post-baseline. Percentages will be calculated based on the number of subjects assessed with a determinant baseline nAb sample or at least one determinant post-baseline nAb sample, respectively.
- Number (%) of subjects with a nAb-positive sample cross-reactive to endogenous GLP-2 at baseline and post-baseline. Percentages will be calculated based on the number of subjects assessed with a determinant baseline nAb sample or at least one determinant post-baseline nAb sample, respectively.

The above analyses will be performed based on availability of immunogenicity assessment data.

All immunogenicity assessment data will be listed.

9.8.6 PK/PD

Descriptive statistics will be used to summarize the predose and post-dose apraglutide plasma concentrations and plasma citrulline levels by scheduled visit. All apraglutide plasma concentrations and plasma citrulline levels data will be listed.

Any exploratory PK analysis and PK/PD modelling will be described in a separate document.

10. DEVIATIONS FROM ANALYSIS DESCRIBED IN THE PROTOCOL

The following update has been made from the planned analysis defined in the protocol to align the safety analysis plan as defined in the TA799-007 study.

- In the protocol, TEAE is defined as all AEs occurring after first dose of trial medication and up to the 4 weeks follow-up visit. However, for the safety analysis, TEAE will be defined as any adverse events that started on or after the first dose of trial medication (i.e. no longer depends on 4 weeks follow-up visit).

There is one deviation from the planned analysis described in the protocol. According to the protocol, the primary endpoint AESIs are to be derived based on SMQ or CQs. Sponsor issued NTF (See Appendix 4: Addendum to Statistical Analysis Plan), to clarify that AESI will be identified by using the investigator's assessment, reported in eCRF for analysis.

In addition, the following list contains typographical error (typo) corrections from the protocol that have been made to this SAP for clarity:

- The protocol refers to 'change in absolute absorption'. It is clarified in SAP that this refers to 'absolute change from baseline' in comparison to 'relative change in absorption'. Note: This SAP uses 'absolute change from baseline' and 'change from baseline' interchangeably.
- One of the secondary efficacy endpoints defined in the protocol is 'clinical responder at Week 52' but unlike the protocol synopsis and Section 1.5.2.2 of the protocol, Section 7.1.2 of the protocol indicated Week 48 instead of Week 52. This typo has been corrected to Week 52 in this SAP.
- One of the efficacy endpoints defined in the protocol is 'change in dietary intake of wet weight, energy, macronutrients, fluid, electrolytes (sodium, potassium, calcium, and magnesium) from baseline at Week 4 and Week 48', but this 'fluid' is a part of weight as oral fluid; hence, this text, 'fluid', is omitted in this SAP.
- One of the efficacy endpoints defined in the protocol is "change in fecal excretion of wet weight, energy, macronutrients, fluid and electrolytes (sodium, potassium, calcium, and magnesium) from baseline at Week 4 and Week 48", but this "fluid" is a part of wet weight (urine), which has already been covered by urine output as a part of the secondary efficacy endpoint; hence, the text, 'fluid', is omitted in this SAP.
- The protocol states the sensitivity analysis excluding subjects missing more than 20% of the planned injections prior to the time of analysis, and the number of injections leading to exclusion are to be 1 at Week 4, 6 at Week 24, and 11 at Week 52, but this text has been corrected to "…. 1 at Week 4, 5 at Week 24, and 10 at Week 48", respectively, in order to exclude subjects missing more than 20% of the planned injections prior to the corresponding analysis timepoint.
- One of the exploratory endpoints defined in the protocol stated "change in body weight from baseline at Week 24 and Week 52", but the protocol synopsis refers to "Week 48". This has been consistently referred to as Week 48 in the SAP for the efficacy endpoint, although the change in body weight from baseline to Week 52 will be also summarized for safety analyses.
- One of secondary endpoints related to PRO is 'PGIC at Week 24 and Week 52 ' but unlike the protocol synopsis and Section 7.1.2, Section 1.5.2.2 of the protocol indicated as 'change in PGIC' where it should only be referred as 'PGIC'. This typo has been corrected in this SAP.
- SBS-IF-TI-QOL data collection has been removed from baseline according to the protocol amendment version 3 dated 03SEP2021, hence the change from baseline analysis defined as the endpoint has been updated to 'observed'.

11. PROGRAMMING SPECIFICATIONS

All outputs will be produced using SAS version 9.4 or a later version.

The margins should be at least 1.50 inches for the binding edge and 1.0 inches for all others.

In the top left portion of each table/listing, the *protocol number* will be presented. On the next line, a *table/listing number* followed by the *title* of the table/listing and *analysis population* information will be displayed. Horizontal lines will appear after the column heading of the table/listing. *Footnotes* will be put under the main body of text at the bottom of the page. The source listing number will be displayed for all tables. The *SAS program name* will appear in the bottom left corner in a string, and the *page number* will appear in the top right corner of each table/listing. The *date and time of creation* of the table/listing will appear in the bottom left corner under to the SAS program name line.

Courier New 8-point font will be used for all tables and listings. Usually, a landscape layout is suggested for both tables and listings, but it is not mandatory. Any date information in the listing will use the date9. format, for example, 07MAY2002.

Shells for tables and listings are provided in a separate Mock-Up TFL document.

12. REFERENCE

APPENDIX 1: SCHEDULE OF ASSESSMENTS

Table 1: Schedule of Assessments (SoA)

	Screening	Baseline	Treatment Period															End of trial
Visit No.[1]	**1**	**2[3]**	**3**	**4**	**5[3]**	**6**	**7**	**8**	**9**	**10[26]**	**11**	**12**	**13**	**14**	**15**	**16[3]**	**17**	**18**
Week (weeks unless indicated)	**-4 to -2 (Day -28 to -14)**	**-1 (Day-7 to -3)**	**0 (Day 0)**	**2 (+1)**	**4**	**8[4] (±1)**	**12 (±2)**	**16 (±2)**	**20 (±2)**	**24 (±2)**	**28 (±2)**	**32 (±2)**	**36 (±2)**	**40 (±2)**	**44 (±2)**	**48 (±1)**	**52 (±2)**	**4 weeks after last dose** ±1 week
General																		
Informed consent	X																	
Inclusion and Exclusion criteria	X	X																
Demographics	X																	
Medical history	X																	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
GI health history	X	X	X															
Metabolic balance evaluation (see Table 2 for detailed schedule)		X			X											X		
Safety																		
Colonoscopy or colonography[5,7]	X									X[6]						X[23]		
Physical examination[8]	X	X			X					X						X	X	X
12-lead ECG[8]	X	X			X					X						X	X	X

	Screening	Baseline	Treatment Period															End of trial
Visit No.[1]	**1**	**2[3]**	**3**	**4**	**5[3]**	**6**	**7**	**8**	**9**	**10[26]**	**11**	**12**	**13**	**14**	**15**	**16[3]**	**17**	**18**
Week (weeks unless indicated)	**-4 to -2 (Day -28 to -14)**	**-1 (Day-7 to -3)**	**0 (Day 0)**	**2 (+1)**	**4**	**8[4] (±1)**	**12 (±2)**	**16 (±2)**	**20 (±2)**	**24 (±2)**	**28 (±2)**	**32 (±2)**	**36 (±2)**	**40 (±2)**	**44 (±2)**	**48 (±1)**	**52 (±2)**	**4 weeks after last dose** ±1 week
Vital signs (blood pressure, heart rate, axillary temperature)[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body weight and height[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigator narrative		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Telephone contact[11]	X		X															
Laboratory																		
Clinical chemistry incl. liver enzymes, hematology, hemostasis, urinalysis (dipstick)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum pregnancy test premenopausal women	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for PK[12]				X	X		X			X		X		X		X	X	X
Blood sample for citrulline[12]		X		X	X		X			X		X		X		X	X	X
Blood sample for ADA[12]		X		X	X		X			X				X		X		X[13]

	Screening	Baseline	Treatment Period															End of trial
Visit No.[1]	**1**	**2[3]**	**3**	**4**	**5[3]**	**6**	**7**	**8**	**9**	**10[26]**	**11**	**12**	**13**	**14**	**15**	**16[3]**	**17**	**18**
Week (weeks unless indicated)	**-4 to -2 (Day -28 to -14)**	**-1 (Day-7 to -3)**	**0 (Day 0)**	**2 (+1)**	**4**	**8[4] (±1)**	**12 (±2)**	**16 (±2)**	**20 (±2)**	**24 (±2)**	**28 (±2)**	**32 (±2)**	**36 (±2)**	**40 (±2)**	**44 (±2)**	**48 (±1)**	**52 (±2)**	**4 weeks after last dose** ±1 week
HIV and hepatitis test	X																	
Post-PS volume reduction safety evaluations[14]					X	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy																		
Prescribed PS volume, composition, days per week	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[15]
Define and confirm drinking menu[16]	X	X																
Patient Reported Outcome (PRO) questionnaires[2]		X			X		X			X			X				X	X
Change in Eating/Appetite		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for sodium analysis (from sample taken during 48-hour urine collection, balance period) [16]		X[17]		X	X[17]	X	X	X	X	X	X	X	X	X	X	X[17]	X	
DEXA Scan		X			X					X						X		
Gastroduodenoscopy	X									X[6]						X[23]		
Trial Medication and																		

	Screening	Baseline	Treatment Period															End of trial
Visit No.[1]	**1**	**2[3]**	**3**	**4**	**5[3]**	**6**	**7**	**8**	**9**	**10[26]**	**11**	**12**	**13**	**14**	**15**	**16[3]**	**17**	**18**
Week (weeks unless indicated)	**-4 to -2 (Day -28 to -14)**	**-1 (Day-7 to -3)**	**0 (Day 0)**	**2 (+1)**	**4**	**8[4] (±1)**	**12 (±2)**	**16 (±2)**	**20 (±2)**	**24 (±2)**	**28 (±2)**	**32 (±2)**	**36 (±2)**	**40 (±2)**	**44 (±2)**	**48 (±1)**	**52 (±2)**	**4 weeks after last dose** ±1 week
Diary																		
Hand out subject e-diary	X																	
Subjects complete diary prior to the visit		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review all subject diary information since last visit		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SC injection of IMP at site			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Instruct subject in IMP handling at home and assess self-administration capability[18]			X															
Dispense IMP			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Return home administered IMP vials to site				X	X	X	X	X	X	X	X	X	X	X	X	X	X	
[redacted]																		
[redacted]		[redacted]																

	Screening	Baseline	Treatment Period														End of trial
Visit No.[1]	1	2[3]	3	4	5[3]	6	7	8	9	10[26]	11	12	13	14	15	16[3]	17	18
Week (weeks unless indicated)	-4 to -2 (Day -28 to -14)	-1 (Day-7 to -3)	0 (Day 0)	2 (+1)	4	8[4] (±1)	12 (±2)	16 (±2)	20 (±2)	24 (±2)	28 (±2)	32 (±2)	36 (±2)	40 (±2)	44 (±2)	48 (±1)	52 (±2)	4 weeks after last dose ±1 week
[redacted]																		

ADA, anti-drug antibodies; AE, adverse event; AESI, adverse event of special interest; DEXA, dual-energy X-ray absorptiometry; ECG, electrocardiogram; EOT, end of trial; GI, Gastrointestinal; HIV, human immunodeficiency virus; IMP, investigational medicinal product; LTE, long-term safety and clinical outcomes extension trial; [redacted], PGIC, patient global impression of change; PGIS, patient global impression of severity; PGI-PSI, patient global impression of parenteral support impact; PGI-SPS, patient global impression of satisfaction with parenteral support; PGI-TS, patient global impression of treatment satisfaction; PK, pharmacokinetics; PRO, patient reported outcomes; PS, parenteral support, [redacted]; SBS-IF-CIC-QOL, Short Bowel Syndrome with Intestinal Failure and Colon-in-Continuity Quality of Life questionnaire; SBS-IF-TI-QOL, Short Bowel Syndrome with Intestinal Failure - Treatment Impacts - Quality of Life questionnaire; SC, subcutaneous; [redacted]

1. If at any visit the subject shows signs of significant fluid overload, leading to clinical decompensation, the Investigator should consider PS reduction. An AESI of fluid overload must be reported. In all cases this reduction must be discussed with the medical monitor either before or after reduction.

2. Patient reported outcomes collected as follows (with the following preferred order):
   At Baseline: SBS-IF-CIC-QOL, [redacted] PGIS, PGI-PSI, PGI-SPS, PGIC (1.0), PGIC (2.0)
   At Weeks 4, 12, and 36: SBS-IF-CIC-QOL, SBS-IF-TI-QOL, [redacted] PGIS, PGI-PSI, PGI-TS, PGI-SPS, PGIC (1.0), PGIC (2.0)
   At weeks 24, 52, and EOT visit: SBS-IF-CIC-QOL, SBS-IF-TI-QOL, [redacted] PGIS, PGI-PSI, PGI-TS, PGI-SPS, PGIC (1.0), PGIC (2.0)
   Only subjects that completed version 1.0 of the PGIC and PGIS at baseline continue to complete these during the trial.
3. See Table 2 Schedule of Assessments for metabolic balance periods
4. The visit window of ±1 week or ±2 weeks allows a shift in the visit 7 or 14 days (±1 day) from baseline calculated visits. Visits should be done at the same day of the week with a window of ±1 day. Investigational medicinal product administrations during a week with a site visit must be done at the site.
5. If biopsies are required a colonography will NOT be performed unless a full view of the colon to check for polyps was not possible during colonoscopy.
6. Optional assessments.
7. When deemed anatomically feasible by the Investigator, colonoscopy or colonography should be performed within ± 3 weeks of end of treatment.
8. ECG, physical exam and vital signs should be recorded prior to blood sampling and prior to IMP administration.
9. Subjects to be asked to measure their body weight weekly and record results in the e-diary. Body height will be measured once at screening only
10. Adverse events and Adverse events of special interest should be recorded starting after obtaining informed consent (see Section 6.1 of the protocol).
11. Telephone contact will be made every 7 days (±1 day) during screening. During each contact, AEs will be collected and changes in concomitant medications recorded. At all contacts the subject will be asked to recollect the frequency and severity of nausea, vomiting, abdominal pain in the preceding 7 days. This information will also be collected at Visit 3, pre-dose. At Week 0, Day 1 (+1 day), the subject will be contacted to assess for fluid overload and frequency of stools.
12. Pharmacokinetic, ADA and citrulline samples are to be collected pre-dose except on the metabolic balance periods (see Table 2). Unscheduled ADA sample may be collected following an injection site reaction or hypersensitivity event at the discretion of the investigator.
13. If a subject performs EOT visit, they will be requested to return for blood samples for ADA as detailed in Section 5.1.11 of the protocol.
14. If PS was reduced, an additional visit and assessments will be performed as per Section 5.2.9 of the protocol.
15. At early discontinuation, the Investigator will decide to continue documentation of PS prescription in source documents and electronic case record form until the scheduled end of trial visit for that subject, if subject consents
16. Drinking Menu defined at Screening must remain stable throughout the trial and applies to the 48-hour balance periods and the 72-hour metabolic balance periods only. This will be confirmed and agreed upon at baseline. The 48-hour balance period is defined as starting not more than 4 days before trial visit and should be completed no later than the start time of their trial visit procedure assessments (e.g. on the morning of their trial visit). For Visit 4, the 48hr balance period is defined as starting not more than 2 days before trial visit and should be completed before the start time of their trial visit procedure assessments (e.g. on the morning of their trial visit). The 48-h balance period must be conducted over 48 consecutive hours.
17. Sample from the 72-hour metabolic balance study collection.
18. To be instructed on a continuous basis, as needed.

[redacted]

[redacted]

Table 2: Schedule of Assessments for Metabolic Balance Periods (Visits 2 (Baseline), 5, and 16)

	Metabolic balance period				
Procedure	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Admission to hospital	X (at least 16 h prior to MB samples collection start)				
Hospital discharge					X
Confirmation of eligibility[1]	X Baseline only				X Baseline only
Review all subject diary information since last visit	X				
Adverse events	X	X	X	X	X
Concomitant medication	X	X	X	X	X
Investigator narrative	X				
GI health history	X				
Physical examination	X				
12-lead ECG	X				
Vital signs (blood pressure, heart rate, axillary temperature)[2]	X	X	X	X	X
Clinical chemistry	X				
Hematology	X				
Hemostasis	X				
Urinalysis	X				
Pregnancy test (premenopausal women)	X				
Citrulline blood sample	X				
Blood samples for PK (Visits 5 and 16) [1]		Pre-dose (within 30 min prior to dosing)	24 h (±2 h), 30 h (±2 h),	48h (±2 h),	72 h (±2 h),
Blood sample ADA, nAb	X				

	Metabolic balance period				
Procedure	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Fasting	X (start 22:00 ±30 min)	X (until start of MB collections)			
Urinate & defecate – prior to MB collection start[1]		X (-30 min)			
Urinate & defecate – end of MB period					X (-30 min)
Body weight[2]	X	X	X	X	X
Start of MB collection[2]		X Time of IMP[3] (+15 min)			
Collection of urine		X	X	X	X
Collection of feces		X	X	X	X
Collection of duplicate food and drinks		X	X	X	X
End of MB collection					72 h from start (±1 h)
Change in appetite	X				
Confirm drinking menu	X Baseline only				
Adhere to agreed upon drinking menu		X	X	X	X
Define baseline PS type, volume, content	X Baseline only				
Fixed baseline PS type, volume and content (baseline & Visit 5)		X	X	X	X
DEXA Scan		X[4]			
Patient reported outcomes (PRO)		X (13:00-18:00)			

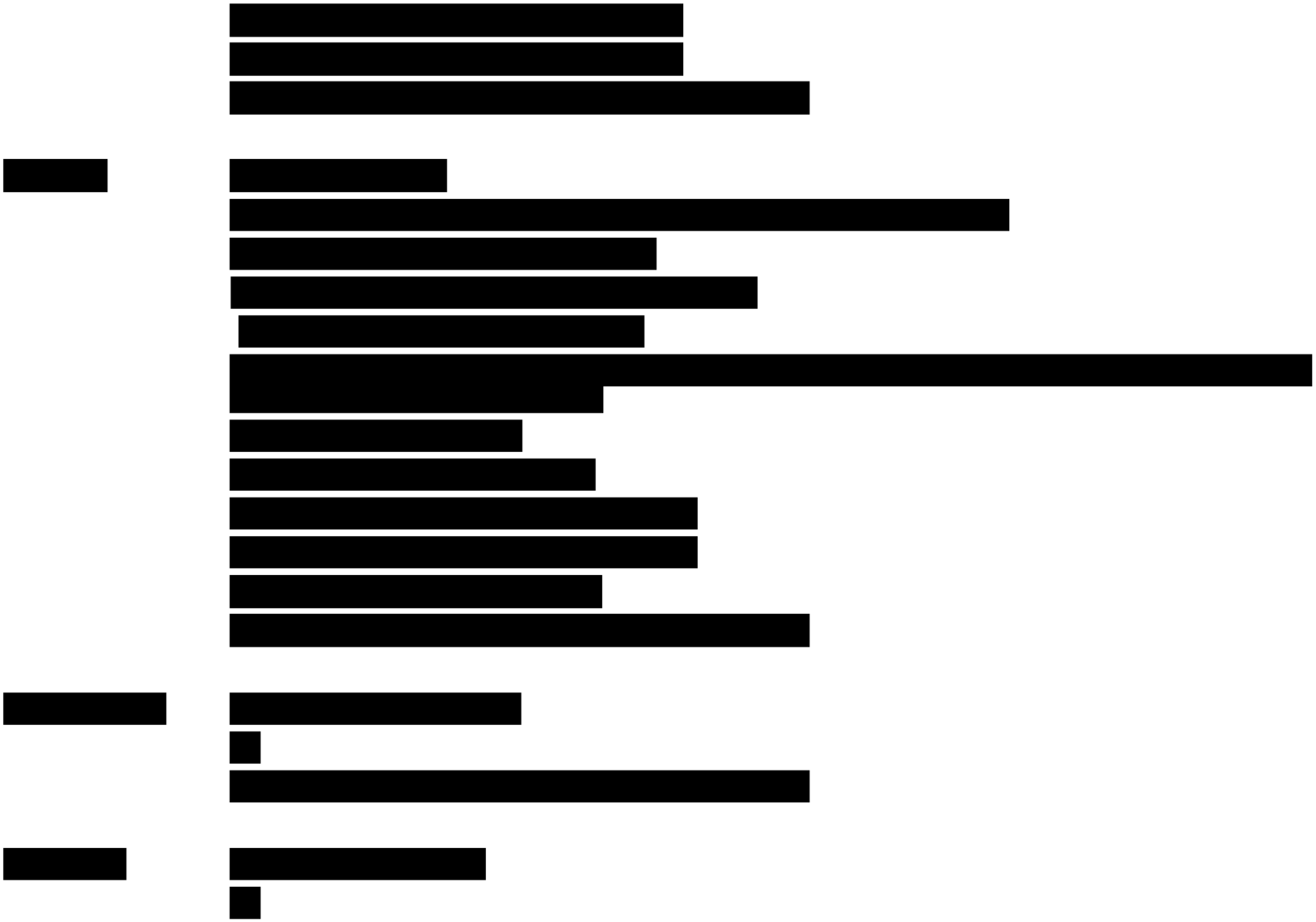
	Metabolic balance period				
Procedure	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**
Bristol Stool Form Scale and Frequency of bowel movement		X	X		
IMP administration (Visits 5 and 16)		X			
Dispense IMP (Visits 5 and 16)					X
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

ADA, anti-drug antibodies; [redacted]; DEXA, dual-energy X-ray absorptiometry; ECG, electrocardiogram; GI, gastrointestinal; IMP, investigational medicinal product; nAb, neutralizing antibody; PK, pharmacokinetics; PRO, patient reported outcomes; PS, parenteral support; MB, metabolic balance; [redacted]; [redacted]; [redacted]

1. At the first MB period only, confirmed of Screening eligibility to be confirmed on Day 1 and confirmation of inclusion criteria 12 and 13 to be confirmed on Day 5.
2. The activities should be performed in the following sequence on Days 2-5: AE collection, weight, vital signs, pre-dose PK sample (Visits 5 and 16 only), defecate/urinate, IMP administration (Visits 5 and 16 only), start of 72-hour collection of urine, feces and food. Body weight and vital signs will be measured on Day 1 at any time, on Day 2 after defecation but before IMP administration, and on subsequent days at the same time as on Day 2 ± 1 h.
3. Visits 5 and 16 MB periods only.
4. Same timing across all MB periods with regard to PS infusion and time of day based on first MB period ± 2 h (see Section 5.2 of the protocol for more details).

[redacted]

[redacted]



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APPENDIX 3: SPONSOR-DEFINED LIST OF PREFERRED TERMS

AESI Category	SMQ or CQ	SMQ Scope
Gallbladder, biliary and pancreatic disease	SMQ Biliary system related investigations, signs and symptoms	Broad+Narrow
Gallbladder, biliary and pancreatic disease	SMQ Biliary tract disorders	Narrow
Gallbladder, biliary and pancreatic disease	SMQ Gallbladder related disorders	Narrow
Gallbladder, biliary and pancreatic disease	SMQ Gallstone related disorders	Narrow
Gallbladder, biliary and pancreatic disease	PT: Pancreatic disorder	
Gallbladder, biliary and pancreatic disease	PT: Pancreatic duct dilatation	
Gallbladder, biliary and pancreatic disease	PT: Pancreatic duct obstruction	
Gallbladder, biliary and pancreatic disease	PT: Pancreatic enzyme abnormality	
Gallbladder, biliary and pancreatic disease	PT: Pancreatic toxicity	
Gallbladder, biliary and pancreatic disease	PT: Bile duct obstruction	
Gallbladder, biliary and pancreatic disease	PT: Bile duct stone	
Gallbladder, biliary and pancreatic disease	PT: Obstructive pancreatitis	
Gallbladder, biliary and pancreatic disease	PT: Sphincter of Oddi dysfunction	
Gallbladder, biliary and pancreatic disease	PT: Cholestasis	
Gallbladder, biliary and pancreatic disease	PT: Cholestasis of pregnancy	
Gallbladder, biliary and pancreatic disease	PT: Deficiency of bile secretion	
Gallbladder, biliary and pancreatic disease	PT: Hepatitis cholestatic	
Gallbladder, biliary and pancreatic disease	PT: Hyperbilirubinaemia	
Gallbladder, biliary and pancreatic disease	PT: Jaundice	
Gallbladder, biliary and pancreatic disease	PT: Jaundice acholuric	
Gallbladder, biliary and pancreatic disease	PT: Jaundice cholestatic	
Gallbladder, biliary and pancreatic disease	PT: Jaundice extrahepatic obstructive	
Gallbladder, biliary and pancreatic disease	PT: Jaundice hepatocellular	
Gallbladder, biliary and pancreatic disease	PT: Neonatal cholestasis	
Gallbladder, biliary and pancreatic disease	PT: Ocular icterus	
Gallbladder, biliary and pancreatic disease	PT: Parenteral nutrition associated liver disease	
Gallbladder, biliary and pancreatic disease	PT: Yellow skin	
Gallbladder, biliary and pancreatic disease	PT: Biliary polyp	
Gallbladder, biliary and pancreatic disease	PT: Biloma	
Gallbladder, biliary and pancreatic disease	PT: Biloma rupture	
Gallbladder, biliary and pancreatic disease	PT: Cholaemia	
Gallbladder, biliary and pancreatic disease	PT: Hepatobiliary disease	
Gallbladder, biliary and pancreatic disease	PT: Hepatobiliary infection	
Gallbladder, biliary and pancreatic disease	PT: Hypercholia	
Gallbladder, biliary and pancreatic disease	PT: Liver disorder	
Gallbladder, biliary and pancreatic disease	PT: Oedema due to hepatic disease	
Gallbladder, biliary and pancreatic disease	PT: Bilirubin excretion disorder	
Gallbladder, biliary and pancreatic disease	PT: Hepatic function abnormal	

AESI Category	SMQ or CQ	SMQ Scope
Gallbladder, biliary and pancreatic disease	PT: Hypertransaminasaemia	
Gallbladder, biliary and pancreatic disease	PT: Cholestatic liver injury	
Gallbladder, biliary and pancreatic disease	PT: Drug-induced liver injury	
Gallbladder, biliary and pancreatic disease	PT: Hepatitis	
Gallbladder, biliary and pancreatic disease	PT: Hepatitis acute	
Gallbladder, biliary and pancreatic disease	PT: Hepatitis toxic	
Gallbladder, biliary and pancreatic disease	PT: Hepatocellular injury	
Gallbladder, biliary and pancreatic disease	PT: Hepatotoxicity	
Gallbladder, biliary and pancreatic disease	PT: Liver injury	
Gallbladder, biliary and pancreatic disease	PT: Mixed liver injury	
Gallbladder, biliary and pancreatic disease	PT: Non-alcoholic steatohepatitis	
Gallbladder, biliary and pancreatic disease	PT: Nonalcoholic fatty liver disease	
Gallbladder, biliary and pancreatic disease	PT: Steatohepatitis	
Gastrointestinal obstructions	SMQ Gastrointestinal obstruction	Narrow
Gastrointestinal obstructions	SMQ Gastrointestinal perforation, ulcer, haemorrhage, obstruction non-specific findings/procedures	Broad+Narrow
Gastrointestinal obstructions	PT: Intestinal obstruction	
Malignancies	SMQ Malignancy related conditions	Narrow
Malignancies	SMQ Malignancy related therapeutic and diagnostic procedures	Narrow
Malignancies	SMQ Malignant or unspecified tumours	Narrow
Colorectal polyps	PT: Anal polyp	
Colorectal polyps	PT: Anorectal haemangioma	
Colorectal polyps	PT: Appendix adenoma	
Colorectal polyps	PT: Benign anorectal neoplasm	
Colorectal polyps	PT: Benign duodenal neoplasm	
Colorectal polyps	PT: Benign gastric neoplasm	
Colorectal polyps	PT: Benign gastrointestinal neoplasm	
Colorectal polyps	PT: Benign mesenteric neoplasm	
Colorectal polyps	PT: Benign neoplasm of islets of Langerhans	
Colorectal polyps	PT: Benign oesophageal neoplasm	
Colorectal polyps	PT: Benign pancreatic neoplasm	
Colorectal polyps	PT: Benign peritoneal neoplasm	
Colorectal polyps	PT: Benign small intestinal neoplasm	
Colorectal polyps	PT: Colon adenoma	
Colorectal polyps	PT: Duodenal polyp	
Colorectal polyps	PT: Gastric adenoma	
Colorectal polyps	PT: Gastric cyst	
Colorectal polyps	PT: Gastric haemangioma	
Colorectal polyps	PT: Gastric leiomyoma	
Colorectal polyps	PT: Gastric polyps	

AESI Category	SMQ or CQ	SMQ Scope
Colorectal polyps	PT: Gastrointestinal polyp	
Colorectal polyps	PT: Gastrointestinal polyp haemorrhage	
Colorectal polyps	PT: Gastrointestinal tract adenoma	
Colorectal polyps	PT: Intestinal angioma	
Colorectal polyps	PT: Intestinal cyst	
Colorectal polyps	PT: Intestinal polyp	
Colorectal polyps	PT: Intra-abdominal haemangioma	
Colorectal polyps	PT: Intraductal papillary mucinous neoplasm	
Colorectal polyps	PT: Large intestine fibroma	
Colorectal polyps	PT: Large intestine polyp	
Colorectal polyps	PT: Oesophageal cyst	
Colorectal polyps	PT: Oesophageal papilloma	
Colorectal polyps	PT: Oesophageal polyp	
Colorectal polyps	PT: Rectal adenoma	
Colorectal polyps	PT: Rectal polyp	
Colorectal polyps	PT: Small intestine polyp	
Injection site reactions	PT: Administration site abscess	
Injection site reactions	PT: Administration site abscess sterile	
Injection site reactions	PT: Administration site anaesthesia	
Injection site reactions	PT: Administration site atrophy	
Injection site reactions	PT: Administration site bruise	
Injection site reactions	PT: Administration site calcification	
Injection site reactions	PT: Administration site cellulitis	
Injection site reactions	PT: Administration site coldness	
Injection site reactions	PT: Administration site cyst	
Injection site reactions	PT: Administration site dermatitis	
Injection site reactions	PT: Administration site discharge	
Injection site reactions	PT: Administration site discolouration	
Injection site reactions	PT: Administration site discomfort	
Injection site reactions	PT: Administration site dryness	
Injection site reactions	PT: Administration site dysaesthesia	
Injection site reactions	PT: Administration site eczema	
Injection site reactions	PT: Administration site erosion	
Injection site reactions	PT: Administration site erythema	
Injection site reactions	PT: Administration site exfoliation	
Injection site reactions	PT: Administration site extravasation	
Injection site reactions	PT: Administration site fibrosis	
Injection site reactions	PT: Administration site granuloma	
Injection site reactions	PT: Administration site haematoma	
Injection site reactions	PT: Administration site haemorrhage	

AESI Category	SMQ or CQ	SMQ Scope
Injection site reactions	PT: Administration site hyperaesthesia	
Injection site reactions	PT: Administration site hypersensitivity	
Injection site reactions	PT: Administration site hypertrophy	
Injection site reactions	PT: Administration site hypoaesthesia	
Injection site reactions	PT: Administration site indentation	
Injection site reactions	PT: Administration site induration	
Injection site reactions	PT: Administration site infection	
Injection site reactions	PT: Administration site inflammation	
Injection site reactions	PT: Administration site injury	
Injection site reactions	PT: Administration site irritation	
Injection site reactions	PT: Administration site ischaemia	
Injection site reactions	PT: Administration site laceration	
Injection site reactions	PT: Administration site lymphadenopathy	
Injection site reactions	PT: Administration site macule	
Injection site reactions	PT: Administration site mass	
Injection site reactions	PT: Administration site necrosis	
Injection site reactions	PT: Administration site nerve damage	
Injection site reactions	PT: Administration site nodule	
Injection site reactions	PT: Administration site oedema	
Injection site reactions	PT: Administration site pain	
Injection site reactions	PT: Administration site pallor	
Injection site reactions	PT: Administration site papule	
Injection site reactions	PT: Administration site paraesthesia	
Injection site reactions	PT: Administration site phlebitis	
Injection site reactions	PT: Administration site photosensitivity reaction	
Injection site reactions	PT: Administration site plaque	
Injection site reactions	PT: Administration site pruritus	
Injection site reactions	PT: Administration site pustule	
Injection site reactions	PT: Administration site rash	
Injection site reactions	PT: Administration site reaction	
Injection site reactions	PT: Administration site recall reaction	
Injection site reactions	PT: Administration site scar	
Injection site reactions	PT: Administration site swelling	
Injection site reactions	PT: Administration site thrombosis	
Injection site reactions	PT: Administration site ulcer	
Injection site reactions	PT: Administration site urticaria	
Injection site reactions	PT: Administration site vasculitis	
Injection site reactions	PT: Administration site vesicles	
Injection site reactions	PT: Administration site warmth	
Injection site reactions	PT: Injection site abscess	

AESI Category	SMQ or CQ	SMQ Scope
Injection site reactions	PT: Injection site abscess sterile	
Injection site reactions	PT: Injection site anaesthesia	
Injection site reactions	PT: Injection site atrophy	
Injection site reactions	PT: Injection site bruising	
Injection site reactions	PT: Injection site calcification	
Injection site reactions	PT: Injection site cellulitis	
Injection site reactions	PT: Injection site coldness	
Injection site reactions	PT: Injection site cyst	
Injection site reactions	PT: Injection site deformation	
Injection site reactions	PT: Injection site dermatitis	
Injection site reactions	PT: Injection site discharge	
Injection site reactions	PT: Injection site discolouration	
Injection site reactions	PT: Injection site discomfort	
Injection site reactions	PT: Injection site dryness	
Injection site reactions	PT: Injection site dysaesthesia	
Injection site reactions	PT: Injection site eczema	
Injection site reactions	PT: Injection site erosion	
Injection site reactions	PT: Injection site erythema	
Injection site reactions	PT: Injection site exfoliation	
Injection site reactions	PT: Injection site extravasation	
Injection site reactions	PT: Injection site fibrosis	
Injection site reactions	PT: Injection site granuloma	
Injection site reactions	PT: Injection site haematoma	
Injection site reactions	PT: Injection site haemorrhage	
Injection site reactions	PT: Injection site hyperaesthesia	
Injection site reactions	PT: Injection site hypersensitivity	
Injection site reactions	PT: Injection site hypertrophy	
Injection site reactions	PT: Injection site hypoaesthesia	
Injection site reactions	PT: Injection site induration	
Injection site reactions	PT: Injection site infection	
Injection site reactions	PT: Injection site inflammation	
Injection site reactions	PT: Injection site injury	
Injection site reactions	PT: Injection site irritation	
Injection site reactions	PT: Injection site ischaemia	
Injection site reactions	PT: Injection site laceration	
Injection site reactions	PT: Injection site lymphadenopathy	
Injection site reactions	PT: Injection site macule	
Injection site reactions	PT: Injection site mass	
Injection site reactions	PT: Injection site necrosis	
Injection site reactions	PT: Injection site nerve damage	

AESI Category	SMQ or CQ	SMQ Scope
Injection site reactions	PT: Injection site nodule	
Injection site reactions	PT: Injection site oedema	
Injection site reactions	PT: Injection site pain	
Injection site reactions	PT: Injection site pallor	
Injection site reactions	PT: Injection site papule	
Injection site reactions	PT: Injection site paraesthesia	
Injection site reactions	PT: Injection site phlebitis	
Injection site reactions	PT: Injection site photosensitivity reaction	
Injection site reactions	PT: Injection site plaque	
Injection site reactions	PT: Injection site pruritus	
Injection site reactions	PT: Injection site pustule	
Injection site reactions	PT: Injection site rash	
Injection site reactions	PT: Injection site reaction	
Injection site reactions	PT: Injection site recall reaction	
Injection site reactions	PT: Injection site scar	
Injection site reactions	PT: Injection site swelling	
Injection site reactions	PT: Injection site telangiectasia	
Injection site reactions	PT: Injection site thrombosis	
Injection site reactions	PT: Injection site ulcer	
Injection site reactions	PT: Injection site urticaria	
Injection site reactions	PT: Injection site vasculitis	
Injection site reactions	PT: Injection site vesicles	
Injection site reactions	PT: Injection site warmth	
Injection site reactions	PT: Injection site hypoaesthesia	
Injection site reactions	PT: Application site hypersensitivity	
Injection site reactions	PT: Immediate post-injection reaction	
Injection site reactions	PT: Skin reaction	
Injection site reactions	PT: Anaphylactic reaction	
Injection site reactions	PT: Anaphylactic shock	
Injection site reactions	PT: Anaphylactoid reaction	
Injection site reactions	PT: Anaphylactoid shock	
Fluid overload	PT: Fluid overload	
Fluid overload	PT: Hypervolaemia	
Fluid overload	PT: Oedema	

APPENDIX 4: ADDENDUM TO STATISTICAL ANALYSIS PLAN

Refer to NTF issued by Sponsor on 06DEC2022 (Topic: TA799-013 Statistical Analysis Plan) and linked to this version of SAP via eTMF.