# STATISTICAL ANALYSIS PLAN

## A Single-Center Phase 3b Trial Investigating the Long-term Effect on Intestinal Absorption, Nutritional Status and Long-Term Safety of treatment with Glepaglutide in Patients with Short Bowel Syndrome (SBS)

**Sponsor Code: ZP1848-20060 (EASE SBS 4)**

**EudraCT No: 2020-005194-27**

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**Evaluation: KLIFO GmbH, Munich (Germany)**

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**Previous Version(s): None**

## DOCUMENT HISTORY

| Version Number | Version Date | Main reason for new version | Summary of changes |
|---|---|---|---|
| 1.0 | 05Aug2022 | Initial Version | Not applicable |
| 2.0 | 15Nov2022 | Details on interim analysis added | Section 5 and 8 updated and Section 7.4 (including Appendix D) added |
| | | | |
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## ABBREVIATIONS

| | |
|---|---|
| *ADR* | *Adverse drug reaction* |
| *AE* | *Adverse event* |
| *AESI* | *Adverse Event of Special Interest* |
| *ALP* | *Alkaline Phosphatase* |
| *AUC* | *Area Under The Curve* |
| *ATC* | *Anatomical Therapeutical Chemical* |
| *CT* | *Computed Tomography* |
| *CV* | *Coefficient of Variation* |
| *DEXA* | *Dual-Energy X-ray Absorptiometry* |
| *ECG* | *Electrocardiogram* |
| *eCRF* | *Electronic Case Report Form* |
| *eGFR* | *Estimated Glomerular Filtration Rate* |
| *EOT* | *End Of Treatment* |
| *FAS* | *Full Analysis Set* |
| *GLP* | *Glucagon-Like Peptide* |
| *HbA1c* | *Hemoglobin A1c* |
| *IF* | *Intestinal Failure* |
| *II* | *Intestinal Insufficiency* |
| *M2* | *Metabolite ZP1848$_{1-34}$* |
| *MBS* | *Metabolic Balance Study* |
| *MDRD* | *Modification of Diet in Renal Disease* |
| *MedDRA* | *Medical Dictionary for Regulatory Activities* |
| *PGIC* | *Patient's Global Impression of Change* |
| *PK* | *Pharmacokinetic* |
| *PPS* | *Per-Protocol Set* |
| *PRO* | *Patient Reported Outcome* |
| *PS* | *Parenteral Support* |
| *PT* | *Preferred Term* |
| *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-II* | *Short Bowel Syndrome with Intestinal Insufficiency* |
| *SOC* | *System Organ Class* |
| *SOP* | *Standard Operating Procedure* |
| *TE* | *Treatment Emergent* |

# 1 GENERAL

This Statistical Analysis Plan (SAP) specifies the statistical methods to be applied in the final analysis of this study. It was written by the responsible biostatistician prior to database lock.

This SAP Plan is based upon the Study Protocol (version 2.0 of 18Feb2021) and Protocol Amendment (version 3.0 of 02Jul2021) and contains a specification of the statistical methods described therein. The analysis will be performed according to Standard Operating Procedures (SOPs) of KLIFO.

The primary objective of this phase 3b study is to demonstrate the 24-week effect of glepaglutide on the absorption of fluids.

For this purpose, this trial has been designed as a single-center, single-arm, fixed dose, phase 3b trial to investigate the long-term effect on intestinal absorption and nutritional status and to assess long-term safety of treatment with glepaglutide in patients with Short Bowel Syndrome (SBS).

All patients will receive the same treatment.

The primary endpoint is the change from baseline to Week 24 in the absorption of wet weight/fluids as assessed by 48-hour metabolic balance studies.

The study phase for an individual patient consists of a screening period of up to 3 weeks, a treatment period of 52 weeks, during which all trial patients will receive treatment of glepaglutide, and a follow-up period of 4 weeks.

A total of 14 visits are scheduled:

| | |
|---|---|
| Screening visit (SCR): | Up to 21 days before V1, |
| Baseline visit (V1): | Day -3 to Day 1 (Week 0), |
| Ten visits (V2-V11): | Week 1 to Week 40, |
| End of treatment (EOT) / Withdrawal visit (V12): | Week 52, |
| Follow-up visit (FU): | Week 56. |

# 2 EFFICACY AND SAFETY VARIABLES

## 2.1 General procedures

### 2.1.1 Time definitions and handling of visits

#### *2.1.1.1 Scheduled visits*

A total of 14 visits with investigations are planned.

For all patients who withdraw from the trial, a withdrawal visit should be carried out. The withdrawal visit has to be conducted as a Week 52 end of treatment (EOT) examination and documented in the electronic case report form (eCRF).

Details on the scheduled visits and how they will be presented in the analysis are shown in the table below.

| Visit | Scheduled for / as | Documented in eCRF as Visit | Presented in this Analysis as Visit |
|---|---|---|---|
| Screening (SCR) | Up to 21 days before V1 | SCR | Screening |
| Baseline (V1) | Day -3 to day 1 (W0) | Visit 1 – Week 0 – [Day 1 – Day 4] $ | Baseline & |
| Visit (V2) | Week 1 | Visit 2 – Week 1 | Week 1 |
| Visit (V3) | Week 2 | Visit 3 – Week 2 | Week 2 |
| Visit (V4) | Week 4 | Visit 4 – Week 4 | Week 4 |
| Visit (V5) | Week 8 | Visit 5 – Week 8 | Week 8 |
| Visit (V6) | Week 12 | Visit 6 – Week 12 | Week 12 |
| Visit (V7) | Week 16 | Visit 7 – Week 16 | Week 16 |
| Visit (V8) | Week 20 | Visit 8 – Week 20 | Week 20 |
| Visit (V9) | Week 24 | Visit 9 – Week 24 – [Day 1 – Day 4] $ | Week 24 & |
| Visit (V10) | Week 32 | Visit 10 – Week 32 | Week 32 |
| Visit (V11) | Week 40 | Visit 11 – Week 40 | Week 40 |
| EOT visit (V12) | Week 52 (completers) | EOT – Visit 12 – Week 52 | Week 52<br>EOT |
| EOT visit (V12) | EOT (non-completers) | EOT – Visit 12 – Week 52 | EOT |
| Follow-up (FU) | Week 56 | Follow-up Visit | Follow-up |

$ Data at this visit will be collected over a period of 4 days (documented in the eCRF as Day 1, Day 2, Day 3, and Day 4) which includes a 48-hour Metabolic Balance Study (MBS).

& For parameters of the 48-hour MBS Study for which separate measurements are available for the first and second 24-hour period, these values will be averaged to obtain a single per day value for this analysis visit. In case one of these measurements is missing, please refer to Section 2.2.1 for calculation of the per day value.

This means, variables will in general be analyzed according to the visit as documented in the eCRF. Variables documented in the eCRF at visit 'EOT – Visit 12 – Week 52' will be presented in summary tables at visit 'EOT'. Values documented at this visit for completers will in addition be presented in summary tables at visit 'Week 52'. Whenever the subsequent text states that a variable or change will be summarized at 'Week 52 (EOT)', then this means it will be summarized at 'Week 52' (completers only) and separately at 'EOT' (all patients).

#### *2.1.1.2 Data documented at unscheduled visits*

Data collected at unscheduled visits will only be listed in by patient listings. In the summary tables, each parameter will only be tabulated for the visits at which it is scheduled.

### 2.1.2 Calculation of Changes

#### *2.1.2.1 Change from baseline*

The absolute change from baseline (V1) to any visit during the treatment phase or to the follow-up (FU) visit will be calculated as the value at the visit minus the baseline value. If any of the two values is missing, the absolute change from baseline will be missing.

The relative change (fold increase) [%] is calculated by dividing the absolute change by the baseline value and by multiplying this ratio by 100 to obtain a percentage. If the absolute change is missing or if the baseline value is zero, the fold increase from baseline will be missing.

Concerning efficacy parameters of the 48-hour metabolic balance studies (MBS, see Section 2.2.1) for which separate measurements are available for the first and second 24-hour period, absolute changes from baseline to Week 24 (V9) are calculated as average of the measures obtained during the first 24-hour period (documented in the eCRF at Day 2) and during the second 24-hour period (documented in the eCRF at Day 3) of the MBS at V9 minus the average of the measures obtained during the first and second 24-hour period of the MBS at V1 (see calculation formula in Section 2.2.1). Dealing with missing measurements for one of the 24-hour periods at V1 (or V9, respectively) is described in Section 2.2.1. If any of the two averaged values is missing, the absolute change from baseline to Week 24 (V9) will be missing.

The baseline value will be the value tabulated for the 'Baseline' visit as described in Section 2.1.1.

#### *2.1.2.2 Change from Visit x to Visit y*

The absolute change from Visit x to a certain Visit y after Visit x will be calculated as the value at the Visit y minus the value at Visit x. If any of the two values is missing, the absolute change from Visit x to Visit y will be missing.

### 2.1.3 Safety Laboratory parameters: Values reported as '< x' or '> x'

Values reported as '< x' or '> x' will be set to 'x' for quantitative analyses (e.g. for the calculation of mean values in summary tables and for the calculation of changes between visits). This means that values below the lower limit of quantification will be set to the lower limit of quantification for quantitative analyses.

## 2.2 Primary Endpoint

The primary objective of this study, which investigates the effect on intestinal absorption, is to demonstrate the 24-week effect of glepaglutide on the absorption of fluids. Therefore, the primary endpoint is change from baseline to Week 24 in absorption of wet weight/fluids assessed by 48-hour MBS.

### 2.2.1 Metabolic Balance Study

An 48-hour MBS will be conducted at baseline (V1) and at V9. The start of the 48-hour sample collection should be on Day 2 of the MBS in the morning, collection continues throughout Day 3 of the MBS and ends on Day 4 of the MBS in the morning.

Several efficacy parameters of the MBS are collected separately for the first and second 24-hour period:

- oral wet weight intake [solid and fluid]
- wet weight output [fecal and urinary]
- energy intake and output
- intake and fecal output of macronutrients
- intake and fecal output of electrolytes and
- urinary excretion of electrolytes.

Data for the first 24-hour period are documented in the eCRF at Day 2 (MBS) and data for the second 24-hour period are documented in the eCRF at Day 3 (MBS). To obtain per day measures for these parameters, values of the first and second 24-hour period will be averaged.

Thus, the following formula is used to obtain an average per day measure at baseline:

Efficacy data item (unit/d) =

{Efficacy data item (unit/d) [Visit 1 – Week 0 – Day 2 (MBS)] + Efficacy data item (unit/d) [Visit 1 – Week 0 – Day 3 (MBS)]} / 2

In case one of the measures assessed for the first or second 24-hour period (Day 2 or Day 3 in the eCRF) is missing, the per day measure is obtained as follows:

**For patients without parenteral support (PS)**:

If at least one of the two 24-hour measurements from the assessments of the 48-hour MBS period is recorded, the assessment will be used in the analysis.

**For patients with PS:**

As data recorded during one of the 24-hour period (on PS) is not representative for the other 24-hour period (off PS), both assessments need to be available to use the average of these values for analysis.

In case both 24-hour measuresments are missing, the respective average per day measure is also missing.

Analogously, the efficacy data items for Week 24 are calculated based on the information in the eCRF at Visit 9 – Week 24 – Day 2 (MBS) and Visit 9 – Week 24 – Day 3 (MBS).

### 2.2.2 Fixed fluid intake and 48-hour urine volume

The oral liquid intake should be kept constant, i.e. the fixed drinking menu should be followed during the following time periods:

- During the 48-hour of MBS (at V1 and V9)
- During the 48-hour pre-visit urine collection periods (prior to V2 -V8).

After V9 (i.e. V10 to V12 and Follow-Up Visit), patients should record their fluid intake during the 48-hours pre-visit urine collection periods, which is not restricted to the fixed drinking menu any more.

In the eCRF, the total drinking volume (mL) (equal to total oral liquid intake in fixed drinking menu or deviating total oral intake) during the 48-hour MBS at V1 and V9 and during the

48-hour pre-visit urine collection periods prior to V2 to V8, V10 to V12 and the Follow-Up Visit is documented.

Urine volume will be recorded in the diary during the defined 48-hour measurement periods prior to a trial visit. Additionally, total urine volume (mL) is recorded during the 48-hour MBS at V1 and V9. Urine volumes (mL) during the first and second 24-hour periods of the 48-hour periods are transcribed to the eCRF and summed to obtain a total 48-hour urine volume.

### 2.2.3 Absorption of Wet Weight/Fluids

Absorption of wet weight/fluids is calculated as oral intake (liquid and solid) minus fecal output, thus:

Absorption of wet weight/fluids (g/d) = Wet weight intake: oral fluid (g/d) + Wet weight intake: oral solid food (g/d) – Wet weight output: Feces (g/d)

The values of the following efficacy data items will be calculated as described in Section 2.2.1:

- Oral wet weight intake (liquid) (g/d) [collected in eCRF as 'wet weight intake: oral fluid (g/d)']
- Oral wet weight intake (solid) (g/d) [collected in eCRF as 'wet weight intake: oral solid food (g/d)']
- Fecal wet weight output (g/d) [collected in eCRF as 'wet weight output: Feces (g/d)']

Absorption of wet weight/fluids (g/d) will be analyzed at baseline and Week 24. Change from baseline to Week 24 for absorption of wet weight/fluids (g/d) is calculated as described in Section 2.1.2. and will be analyzed at Week 24.

The primary analysis will be based on observed data, missing data will not be replaced.

## 2.3 Secondary Endpoints

Secondary objectives of this study are:

- To assess the effects of glepaglutide on absorption of energy, absorption of the individual macronutrients and absorption of electrolytes
- To evaluate the long-term efficacy of glepaglutide in patients with SBS
- To describe the long-term safety of glepaglutide.

These objectives are operationalized by the following secondary endpoints:

### 2.3.1 Key secondary endpoint

The key secondary endpoint is change from baseline to Week 24 in absorption of energy (oral intake minus fecal excretion) measured by 48-hour metabolic balance studies. Energy absorption is measured by bomb calorimetry.

Absorption of energy during the MBS at V1 and V9 is measured as oral intake (liquid and solid) minus fecal output and thus calculated as

Absorption of energy (kj/d) = Energy metabolism: energy intake (kj/d) – Energy metabolism: energy output (kj/d)

The calculation of the following items

- Energy metabolism: energy intake (kj/d)
- Energy metabolism: energy output (kj/d)

is done as described in Section 2.2.3.

Absorption of Energy (kj/d) will be analyzed at Baseline and Week 24. Change from baseline to Week 24 for Absorption of energy (kj/d) is calculated as described in Section 2.1.2 and will be analyzed at Week 24.

### 2.3.2 Secondary efficacy endpoints

Seondary efficacy endpoints are:

- *Absorption of individual macronutrients (carbohydrates, lipids and proteins): Change from baseline to Week 24 measured by 48-hour metabolic balance studies*

  Absorption of individual macronutrients during the MBS at V1 and V9 is measured as oral intake (liquid and solid) minus fecal output.

  Then Absorption of individual macronutrients: Carbohydrates (g/d) is calculated as

  Absorption of individual macronutrients: Carbohydrates (g/d) =

  Macronutrients:Carbohydrate intake (g/d) - Macronutrients: Carbohydrate fecal output (g/d)

  The calculation of the following items

  - Macronutrients: Carbohydrate intake (g/d)
  - Macronutrients: Carbohydrate fecal output (g/d)

  is done as described in Section 2.2.3.

  Absorption of individual macronutrients: Carbohydrates (g/d) will be analyzed at Baseline and Week 24. Change from baseline to Week 24 for Absorption of individual macronutrients: Carbohydrates (g/d) is calculated as described in Section 2.1.2 and will be analyzed at Week 24.

  Furthermore,

  - Absorption of individual macronutrients: Lipids (g/d) [collected in the ecRF as “Fat (g/d)”] and
  - Absorption of individual macronutrients: Proteins (g/d) [collected in the eCRF as “Nitrogen (g/d)”]

  as well as their changes from baseline to Week 24 are calculated and analyzed analogously to Absorption of individual macronutrients: Carbohydrates (g/d) and its change from baseline to Week 24.

- *Absorption of electrolytes (sodium, potassium, calcium and magnesium): Change from baseline to Week 24 measured by 48-hour metabolic balance studies.*

  Absorption of electrolytes during the MBS at V1 and V9 is measured as oral intake (liquid and solid) minus fecal output.

  Then Absorption of Electrolytes: Sodium (mmol/d) is calculated as

Absorption of Electrolytes: Sodium (mmol/d) =

Electrolytes: Sodium intake (mmol/d) - Electrolytes: Sodium fecal output (mmol/d)

The calculation of the following items

- Electrolytes: Sodium intake (mmol/d)
- Electrolytes: Sodium fecal output (mmol/d)

is done as described in Section 2.2.3.

Absorption of Electrolytes: Sodium (mmol/d) will be analyzed at Baseline and Week 24. Change from baseline to Week 24 for Absorption of Electrolytes: Sodium (mmol/d) is calculated as described in Section 2.1.2 and will be analyzed at Week 24.

Furthermore,

- Absorption of electrolytes: Potassium (mmol/d),
- Absorption of electrolytes: Calcium (mmol/d) and
- Absorption of electrolytes: Magnesium (mmol/d)

as well as their changes from baseline to Week 24 are calculated and analyzed analogously to Absorption of Electrolytes: Sodium (mmol/d) and its change from baseline to Week 24.

- *For patients with Short Bowel Syndrome with Intestinal Failure (SBS-IF) only:*
  - *Weekly parenteral support (PS) volume: Change from baseline to Week 12 and 24.*

PS volumes (mL) are documented by the patient in the diary and then transcribed to the eCRF page "Diary PS use". Weekly PS volume (mL) at a certain visit is calculated as sum of PS volumes (mL) for all PS bag ids over the seven days of the preceding week (date of visit – 1 to date of visit – 7) based on the information in the eCRF.

Here the date of visit used at baseline is the date of Visit 1 – Week 0 – Day 4 as documented in the eCRF. At Week 24, the date of Visit 9 – Week 24 – Day 4 is used. Weekly PS volume (mL) will be missing, in case any unknown volume is documented.

In case information on Diary PS use in the week before the baseline visit is available for less than seven days, weekly PS volume (mL) at baseline is determined based on prescribed PS over the seven days before the date of Visit 1 – Week 0 – Day 4. Thus, all PS prescriptions which are valid on date of "Visit 1 – Week 0 – Day 3" are determined. Then, the Weekly PS volume (mL) at baseline is calculated as sum of all weekly volumes (L) for these prescriptions as documented in the eCRF and multiplied by 1000.

Weekly PS volume (mL) will be analyzed at baseline and at Week 12 and 24. The change of weekly PS volume (mL) from baseline to Week 12 and Week 24 is calculated as described in Section 2.1.2 and will be analyzed at Week 12 and Week 24.

- *Weekly PS macronutrients (total and individual energy content of carbohydrates, lipids and proteins) and individual electrolytes (sodium, potassium, and magnesium): Change from baseline to Week 12 and 24.*

The total weekly PS bag volume (mL) of a certain PS bag administered to a patient in the week preceding a certain visit (date of visit – 1 to date of visit – 7) is obtained by summing the volume (mL) documented for the corresponding bag identifier on each of the seven days of the week on corresponding "Diary PS use" page in the eCRF. Here the date of visit used at baseline is the date of Visit 1 – Week 0 – Day 4 as documented in the eCRF. At Week 24,

the date of Visit 9 – Week 24 – Day 4 is used. The total weekly PS bag volume (mL) will be missing in case the administered amount was unknown for at least one of the seven days in the time interval used for calculation.

In case information on Diary PS use in the week before the baseline visit is available for less than seven days, the total weekly PS bag volume (mL) of a certain PS bag at baseline is based on the prescription of this PS bag to a patient on date of "Visit 1 – Week 0 – Day 3". It is calculated as the weekly volume (L) for this prescription as documented in the eCRF multiplied by 1000. For each administered (or, in the special case for the baseline visit, prescribed) PS bag in the week preceding a visit, e.g. the weekly carbohydrate (kjoule) intake [based on eCRF information "Macronutrients: Glucose/Dextrose (kjoule/L)" on the "content of PS" page] is calculated as:

(Total weekly PS bag volume (mL) of this PS bag) x [Carbohydrate (kjoule/L) content of this PS bag/1000]

Then this amount is summed over all administered (or, in the special case for the baseline visit, prescribed) PS bags to obtain Weekly PS macronutrients: Carbohydrates (kjoule).

Analogously,

- Weekly PS macronutrients: Lipids (kjoule) [based on eCRF information "Macronutrients: Lipids (kjoule/L)"]
- Weekly PS macronutrients: Proteins (kjoule) [based on eCRF information "Macronutrients: Amino acids (kjoule/L)"

are calculated.

For the weekly content of the following electrolytes the above formula can also be applied with replacement of the unit "kjoule" by "mmol":

- Weekly PS electrolytes: Sodium (mmol) [based on eCRF information "Micronutrients: Sodium (mmol/L)"]
- Weekly PS electrolytes: Potassium (mmol) [based on eCRF information "Micronutrients: Potassium (mmol/L)"]
- Weekly PS electrolytes: Calcium (mmol) [based on eCRF information "Micronutrients: Calcium (mmol/L)"]
- Weekly PS electrolytes: Magnesium (mmol) [based on eCRF information "Micronutrients: Magnesium (mmol/L)"]

Weekly PS macronutrients: Total (kjoule) is calculated as:

Weekly PS macronutrients: Carbohydrates (kjoule) + Weekly PS macronutrients: Lipids (kjoule) + Weekly PS macronutrients: Proteins (kjoule).

Weekly PS macronutrients (total and individual energy content of carbohydrates, lipids and proteins) and electrolytes (sodium, potassium, calcium, and magnesium) will be analyzed at Baseline, Week 12 and Week 24. Changes from baseline to Week 12 and Week 24 are calculated as described in Section 2.1.2 and will be analyzed at Week 12 and Week 24.

## 2.4 Exploratory Endpoints

Exploratory objectives are:

- To investigate the effect of treatment with glepaglutide on nutritional status, organ function and fluid balance
- To investigate the effect of treatment with glepaglutide on patient reported outcomes (PROs)
- To investigate the microbiome composition of subjects with SBS
- To investigate the pharmacokinetics of glepaglutide.

Exploratory endpoints are:

- *Body weight: Change from baseline to Week 12, 24 and 52.*

  Body weight (kg) will be analyzed at Baseline, Week 12, Week 24 and Week 52 (EOT). The change of body weight (kg) from baseline to Week 12, Week 24 and Week 52 (EOT) is calculated as described in Section 2.1.2 and will be analyzed at Week 12, Week 24 and Week 52 (EOT).

- *Body composition (lean body mass, fat mass and bone mineral content) by dual-energy X-ray absorptiometry (DEXA): Change from baseline to Week 12, 24 and 52.*

  The total lean body mass, total fat mass, fat percent, total bone mineral content, bone mineral density as well as the T-score and Z-score will be measured using DEXA scan.

  During the whole trial, four DEXA scans will be performed: during the MBS at the baseline Visit (V1), at Week 12 (V6), during the MBS at Week 24 (V9) and at Week 52 (V12). During the MBS at V1 and V9, the DEXA scan may be done either on Day 2 or on Day 3.

  The parameters

  - Lean body mass (kg)
  - Fat mass (kg)
  - Bone mineral content (kg)

  will be analyzed at Baseline, Week 12, Week 24 and Week 52 (EOT). Changes from baseline to Week 12, Week 24 and Week 52 (EOT) are calculated as described in Section 2.1.2 and will be analyzed at Week 12, Week 24 and Week 52 (EOT).

  DEXA parameters fat percent, bone mineral density, T-score and Z-score will only be listed.

- *Citrulline: Change from baseline to Week 12, 24 and 52.*

  Citrulline will be analyzed at Baseline, Week 12, Week 24 and Week 52 (EOT). Changes from baseline to Week 12, Week 24 and Week 52 (EOT) are calculated as described in Section 2.1.2 and will be analyzed at Week 12, Week 24 and Week 52 (EOT).

- *Aldosterone: Change from baseline to Week 12, 24 and 52.*

  Aldosterone will be analyzed at Baseline, Week 12, Week 24, Week 52 (EOT). Changes from baseline to Week 12, Week 24 and Week 52 (EOT) are calculated as described in Section 2.1.2 and will be analyzed at Week 12, Week 24 and Week 52 (EOT).

- *Estimated glomerular filtration rate (eGFR), creatinine clearance and liver function tests: Change from baseline to Week 12, 24 and 52.*

Estimated glomerular filtration rate (eGFR) is calculated based on the modification of diet in renal disease (MDRD) formula.

The parameters eGFR, estimated creatinine clearance (assessed by biochemistry laboratory) and liver function parameters (ALT, AST, ALP, albumin and total bilirubin) will be analyzed at Baseline, Week 12, Week 24 and Week 52 (EOT). Changes from baseline to Week 12, Week 24 and Week 52 (EOT) are calculated as described in Section 2.1.2 and will be analyzed at Week 12, Week 24 and Week 52 (EOT).

- *Hemoglobin A1c (HbA1c): Change from baseline to Week 4, 12, 24 and 52.*

  This endpoint will only be analyzed for the subgroup of patients who reach Week 4 after protocol amendment #2 has become effective. In case of a missing Baseline value, it will be replaced by the HbA1c value at Week 4 and the changes from baseline will instead be calculated from Week 4. For the presentation of this parameter by visit, all assessments will be analyzed at the timepoint they were taken.

  HbA1c will be analyzed at Baseline, Week 4, Week 12, Week 24, Week 52 (EOT). Changes from baseline to Week 4, Week 12, Week 24 and Week 52 (EOT) are calculated as described in Section 2.1.2 and will be analyzed at Week 4, Week 12, Week 24 and Week 52 (EOT).

- *PRO: patient's global impression of change (PGIC). At Week 12, 24 and 52.*

  PRO: patient's global impression of change (PGIC) will be analyzed at Week 12, Week 24, and Week 52 (EOT).

- *PRO: SBS -impact scale (SBS-I) and EQ-5D-5L. Change from baseline to Week 12, 24 and to Week 52.*

  The SBS-I has the following eight items

  1. How affected have you been by gastrointestinal symptoms related to SBS such as diarrhea, nausea or bloating in the last week?
  2. How affected have you been by pain in your muscles or bones due to your illness (SBS) in the last week?
  3. How affected have you been by pain in your abdomen due to your illness (SBS) in the last week?
  4. How exhausted or tired have you been due to your illness (SBS) in the last week?
  5. How much has your illness (SBS) affected your sleep in the last week?
  6. To what degree has your illness (SBS) interfered with the things you wanted to do in the last week?
  7. How much has your illness (SBS) affected your mood in the last week?
  8. How affected have you been by stress or anxiety related to SBS in the last week?

Each item is rated on a discrete scale from 0 to 10. Each SBS-I item score will be analyzed overall and separately for patients with SBS-II and patients with SBS-IF at Baseline, Week 12, Week 24 and Week 52 (EOT). Changes from baseline to Week 12, Week 24 and Week 52 (EOT) are calculated as described in Section 2.1.2 and will be analyzed at Week 12, Week 24 and Week 52 (EOT).

The EQ-5D-5L has five domains (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) with the following five response levels: no problems (1), slight problems (2), moderate problems (3), severe problems (4), and unable to/extreme problems to do something (5). Additionally, the current health should be assessed on a visual analogue scale between 0 and 100.

Furthermore, an EQ-5D-5L index value summarizing the values from all domains will be analyzed. It is calculated based on the Danish standardisation study for the EQ-5D-5L (Jensen, C.E. et al. The Danish EQ-5D-5L Value Set: A Hybrid Model Using cTTO and DCE Data. Appl Health Econ Health Policy 19, 579–591 (2021). https://doi.org/10.1007/s40258-021-00639-3). If all domain values are non-missing, it is calculated using the following algorithm:

```
IF (mobility=1) THEN_mo=0
IF (mobility=2) THEN_mo=0.041
IF (mobility=3) THEN_mo=0.054
IF (mobility=4) THEN_mo=0.157
IF (mobility=5) THEN_mo=0.220

IF (selfcare=1) THEN_sc=0
IF (selfcare=2) THEN_sc=0.035
IF (selfcare=3) THEN_sc=0.050
IF (selfcare=4) THEN_sc=0.144
IF (selfcare=5) THEN_sc=0.209

IF (usual_activities=1) THEN_ua=0
IF (usual_activities=2) THEN_ua=0.033
IF (usual_activities=3) THEN_ua=0.040
IF (usual_activities=4) THEN_ua=0.139
IF (usual_activities=5) THEN_ua=0.174

IF (pain_discomfort=1) THEN_pd=0
IF (pain_discomfort=2) THEN_pd=0.048
IF (pain_discomfort=3) THEN_pd=0.094
IF (pain_discomfort=4) THEN_pd=0.381
IF (pain_discomfort=5) THEN_pd=0.537

IF (anxiety_depression=1) THEN_ad=0
IF (anxiety_depression=2) THEN_ad=0.072
IF (anxiety_depression=3) THEN_ad=0.191
IF (anxiety_depression=4) THEN_ad=0.430
IF (anxiety_depression=5) THEN_ad=0.618

total= mo + sc + ua + pd + ad

EQ5D5L_Index_Value = 1-total
```

In case any of the domain values is missing, the index value will be missing.

The EQ-5D-5L domains, the current health and the index value will be analyzed at Baseline, Week 12, Week 24 and Week 52 (EOT). Changes from baseline to Week 12, Week 24 and Week 52 (EOT) of the five domains will be analyzed at Week 12, Week 24 and Week 52 (EOT). Changes from baseline to Week 12, Week 24 and Week 52 (EOT) of the current health are calculated as described in Section 2.1.2 and will be analyzed at Week 12, Week 24 and Week 52 (EOT).

- *Pharmacokinetic (PK) parameter ($C_{trough}$).*

Pharmacokinetic analysis will be done for the parent drug, the metabolites M1 and M2 and the constructed analyte glepaglutide (defined as parent drug + M1 + M2). PK sampling will be done at V1, V4, V6, V9 (six samples: one sample each at MBS Day 1 and Day 4, and two samples each on Day 2 and Day 3 [at least 6h in between sampling on Day 2 and Day 3]), V12 and FU.

Descriptive statistics will be provided for $C_{trough}$ for Week 4, Week 12, Week 24 and Week 52 (EOT).

Results from V4, V6, V9 and V12 samples will be considered and analyzed as trough levels, as long as trial product was not administered within the last at least 6*24=144 hours prior to drawing the sample. At V9, determine all samples which fulfill the criterion above (trial product was not administered within the last at least 6x24h=144h) and select for analysis the sample for which time since last trial product administration is closest to 7*24=168.

All PK concentrations will be listed.

- *The luminal- and mucosae-associated microbiota of patients with SBS from baseline to Week 24.*

  Luminal- and mucosae-associated microbiota may be assessed at the MBS at baseline (V1) and Week 24 (V9).

  Luminal- and mucosae-associated microbiota may be analyzed at Baseline and Week 24. The change from baseline to Week 24 is calculated as described in Section 2.1.2 and may be analyzed at Baseline and Week 24.

- *Urinary excretion of electrolytes (sodium, potassium, calcium, magnesium) and urea: Change from baseline to Week 24.*

  Urinary excretion of electrolytes: Sodium (mmol/d) is derived as described in Section 2.2.3 based on the eCRF item Urinary electrolytes: Sodium (mmol/d).

  Change from baseline to Week 24 for Urinary excretion of electrolytes: Sodium (mmol/d) is calculated as described in Section 2.1.2 and analyzed at Week 24.

  Furthermore,

  - Urinary excretion of electrolytes: Potassium (mmol/d) [based on eCRF information "Urinary electrolytes: Potassium (mmol/d)"],
  - Urinary excretion of electrolytes: Calcium (mmol/d) [based on eCRF information "Urinary electrolytes: Calcium (mmol/d)"],
  - Urinary excretion of electrolytes: Magnesium (mmol/d) [based on eCRF information "Urinary electrolytes: Magnesium (mmol/d)"], and
  - Urinary excretion of electrolytes: Urea (mmol/d) [based on eCRF information "Urinary electrolytes: Urea (mmol/d)"]

  as well as their changes from baseline to Week 24 are calculated and analyzed analogously to Urinary excretion of electrolytes: Sodium (mmol/d) and its change from baseline to Week 24.

- *Fluid Composite Effect: Change from baseline to Week 12, 24 and 52.*

  The fluid composite effect has been defined as parenteral volume + oral fluid volume – urine volume. Thus, fluid composite effect (L/d) at a certain visit will be calculated as:

Fluid composite effect (L/d) = [current PS volume (L/week)/7] + [oral fluid volume (L/d)] – [urine volume (L/d)].

Oral fluid volume (L/d) is based on 48-hour total drinking volume during the 48-hour urine collection period in the week prior to a visit (V2 to V8 and V10 to V12) or on the 48-hour total drinking volume during the MBS at V1 and V9:

Oral fluid volume (L/d) = [48-hour total drinking volume (mL)/1000]/2

Urine volume (L/d) is based on the total urine volume during the 48-hour urine collection period in the week prior to a visit (V2 to V8 and V10 to V12) or on the 48-hour urine volume collected during the MBS at V1 and V9.:

Urine volume (L/d) = [48-hour total urine volume (mL)/1000]/2

Current PS volume (L/week) will be derived as described in Section 2.3.2.

Fluid composite effect (L/d) will be analyzed at Baseline, Week 12, Week 24 and Week 52 (EOT). Changes from baseline to Week 12, Week 24 and Week 52 (EOT) are calculated as described in Section 2.1.2 and will be analyzed at Week 12, Week 24 and Week 52 (EOT).

- *Drinking volume during 48-hour periods: Change from Week 24 to 52.*

  Drinking volume during 48-hour periods is based on the eCRF item Drinking volume: 48-hour total drinking volume (mL) and will be analyzed at Baseline, Week 24 and Week 52 (EOT). Change from Week 24 to Week 52 (EOT) for Drinking volume during 48-hour periods is calculated as described in Section 2.1.2 and will be analyzed at Week 52 (EOT).

- *For patients with SBS-IF only:*

  - *Weekly PS volume: Change from baseline to Week 52.*

    Calculation of current weekly PS volume has been described in Section 2.3.2.

    Additionally to the analysis time points stated in Section 2.3.2, weekly PS volume will be analyzed at Week 52 (EOT), and the change of weekly PS volume from baseline to Week 52 (EOT) will be analyzed at Week 52 (EOT).

  - *Weekly PS macronutrients (total and individual energy content of carbohydrates, lipids and proteins) and electrolytes (sodium, potassium and magnesium): Change from baseline to Week 52.*

    Calculation of weekly PS macronutrients and electrolytes has been described in Section 2.3.2.

    Additionally to the analysis time points stated in Section 2.3.2, weekly PS macronutrients will be analyzed at Week 52 (EOT), and the change of weekly PS macronutrients from baseline to Week 52 (EOT) will be analyzed at Week 52 (EOT).

  - *Weekly days on PS: Change from baseline to Week 12, 24 and 52.*

    The number of weekly days on PS is derived based on the eCRF page “Diary PS use” as the sum of days in the week prior to the visit (date of visit -1 to date of visit -7) for which a volume has been documented (i.e. > 0 mL and not unknown) for at least one PS bag identifier. Here the date of visit used at baseline is the date of Visit 1 – Week 0 – Day 4 as documented in the eCRF. At Week 24, the date of Visit 9 – Week 24 – Day 4 is used. The number of weekly days on PS for a certain visit after baseline will be missing in case only unknown volumes have been documented for at least one day or if

the Diary PS use page is missing for at least one day in the time interval used for calculation.

In case information on Diary PS use in the week before the baseline visit is available for less than seven days, the number of weekly days on PS is derived based on prescribed PS over the week before the date of Visit 1 – Week 0 – Day 4. Thus, all PS prescriptions which are valid on date of "Visit 1 – Week 0 – Day 3" are determined. The number of weekly days on PS at baseline is then calculated as the average over the number of days per week as documented in the eCRF for all these prescriptions.

Weekly days on PS will be analyzed at Baseline, Week 12, Week 24 and Week 52 (EOT). Changes from baseline to Week 12, Week 24 and Week 52 (EOT) are calculated as described in Section 2.1.2 and will be analyzed at Week 12, Week 24 and Week 52 (EOT).

- *For patients with SBS with intestinal insufficiency (SBS-II) only:*
  - *Urine output: Change from baseline to Week 12, 24 and 52.*

    Total 48-hour urine volumes will be analyzed at Baseline, Week 12, Week 24 and Week 52 (EOT). Changes from baseline to Week 12, Week 24 and Week 52 (EOT) will be calculated as described in Section 2.1.2 and analyzed at Week 12, Week 24 and Week 52 (EOT). The change from Week 24 to Week 52 (EOT) will be calculated as described in Section 2.1.2 and analyzed at Week 52 (EOT).

## 2.5 Safety Endpoints and Variables

Safety endpoints are:

- Treatment-emergent adverse events (TEAEs) until follow-up at Week 56
- Immunogenicity (anti-glepaglutide antibodies, reactivity to M2 (referred to as $ZP1848_{1-34}$ in the clinical trial protocol), cross-reactivity to glucagon-like peptide [GLP]-2, glepaglutide neutralizing antibodies) at baseline (W0), Week 4, 12, 24, 52, and 56.

The following safety variables will be analyzed in this context:

- TEAEs

TEAEs are defined as AEs with onset date on or after the day of first administration of trial product.

- Immunogenicity

Immunogenicity will be assessed by the following:

- Anti-glepaglutide antibodies
- Reactivity to M2
- Cross-reactivity to GLP-2
- Glepaglutide neutralizing antibodies

and will be evaluated at Baseline, Week 4, Week 12, Week 24, Week 52 (EOT), and FU.

In addition, the following other safety variables will be analyzed:

- Vital signs (body temperature, systolic/diastolic blood pressure, pulse rate) and body weight

Values and absolute changes from baseline to post-baseline visits with assessment of vital signs (as defined in Section 2.1.2.1) will be summarized by visit using descriptive statistics.

- Clinical laboratory tests (hematology, biochemistry, and urinalysis)

Values and absolute changes from baseline to post-baseline visits with an assessment of the respective clinical laboratory parameter (as defined in Section 2.1.2.1) will be summarized by visit using descriptive statistics.

- Physical Examination

This will be summarized by presenting number and percentage of patients with normal/abnormal findings per body system at each visit.

- Electrocardiogram

Values and absolute changes from baseline to post-baseline visits with assessment of ECG (as defined in Section 2.1.2.1) will be summarized by visit using descriptive statistics.

# 3 STATISTICAL ANALYSIS SETS

The analysis of efficacy will be performed based on the Full Analysis Set (FAS, primary statistical analysis) and based on the Per-protocol set (PPS, supportive analysis). The analysis of safety will also be done based on the FAS if this is equal to the Safety Analysis Set (SAS), and based on the Safety Analysis Set otherwise. Allocation of patients to analysis sets will be done prior to data base lock.

Patients who cannot be included in any of the analysis sets mentioned below will be excluded from the statistical analysis, relevant data of these patients will be listed.

## 3.1 Full Analysis Set

The FAS comprises all patients assigned to trial treatment who received at least one dose of trial product.

## 3.2 Per-protocol Set

The PPS comprises all FAS patients without major protocol deviations.

Major protocol deviations may include:

- Violation of one or more relevant inclusion/exclusion criteria
- Absence of on-treatment data
- Insufficient compliance with administration of trial product
- Use of prohibited concomitant therapy
- Insufficient compliance with other procedures/instructions like
  - Deviation from fixed drinking menu / PS volume / Urine volume collection
  - Deviation concerning collection of urine/feces:

    An answer of “No” to one or more of the following questions in the eCRF

- Fasting requirement (PS allowed) (Day 2)
- Urinate / defecate / empty stoma bag – prior to MBS collection start (Day 2)
- Collection of duplicate food and liquids (Day 2/3/4)
- Urinate / defecate / empty stoma bag – end of study (Day 4)

- Other relevant protocol deviations.

The final allocation to and exclusion from the PPS will be made prior to database lock and will be approved by the sponsor. The PPS will be used for supplementary analyses of the primary and key secondary efficacy endpoints.

### 3.3 Safety Analysis Set

The SAS comprises all patients who received at least one dose of trial product. If FAS and SAS include the same patients, safety analyses will be performed on the FAS.

## 4 STATISTICAL EVALUATION

### 4.1 General

The statistical analysis will be performed using the software package SAS® version 9.4 or higher.

Patient listings will be generated for all data items collected in the eCRF.

In general, data will be summarized using the following standard descriptive statistics: Continuous data will be summarized by presenting the number of non-missing observations, arithmetic mean and standard deviation (geometric mean and coefficient of variation (CV), where applicable), median, minimum, lower quartile, upper quartile and maximum. Categorical data will be summarized by presenting the number and percentage of patients for each category as well as the number of events (where applicable, e.g. for AEs).

As results of several analyses are not only of interest for the overall population, but also for patients with SBS-IF and patients with SBS-II separately, summary tables will present these two subgroups in separate columns [rows] in addition to a total column [row], unless this is not reasonable or feasible (e.g., in case of endpoints which cannot be calculated for one of the two subgroups, like PS-related endpoints). Where such subgroup analyses are of particular importance, this is explicitly stated again in the relevant sections of this SAP.

Changes from the methods planned in this SAP will be justified in the clinical trial report.

### 4.2 Study Patients

#### 4.2.1 Disposition of Patients

The following information will be tabulated:

- Number of patients screened, number of patients included in each analysis set, and reasons for exclusion from analysis sets
- Completion of treatment phase, reason for premature discontinuation
- Treatment duration: Duration of trial product administration during treatment phase [days]

Duration of trial product administration will be calculated as date of last administration – date of first administration +1.

- Study duration: Last visit during treatment phase

  Last visit during treatment phase will be the last visit of V1 to V12 where a visit date is documented in the eCRF.

- Study duration: Follow-up visit performed

  This will be 'yes', if a visit date is documented at the follow-up visit and 'no' otherwise.

#### 4.2.2 Protocol Deviations

The following protocol deviations will be tabulated:

- Violation of inclusion/exclusion criteria
- Compliance with time window for Week 52 (EOT): Difference between date of baseline visit date and date of Week 52 (EOT) within or outside the allowed window, for patients who completed the treatment phase.

#### 4.2.3 Demographic and Other Baseline Characteristics

The following demographic data, SBS characteristics and history, medical history/concomitant illness and other baseline data will be summarized using descriptive statistics. Other baseline characteristics data will be listed.

- Demographic data:
  - Sex,
  - Age [years] (calculated as date of baseline visit minus date of birth divided by 365),
  - Race,
  - Ethnicity
- SBS characteristics and history:
  - Type of SBS
  - Severity of SBS based on the ESPEN Functional and Clinical Classification of Chronic Intestinal Failure
  - Cause of SBS
  - Time since diagnosis of underlying disease
  - Time since SBS diagnosis
  - Surgery:
    - Time since most recent resection
    - Reason for resection
  - Remaining bowel sections:
    - Colon-in-continuity (including type)
    - End-jejunostomy/SBS anatomical group 1
    - Ileostomy/SBS anatomical group 1
    - Colostomy
    - Presence of ileocecal valve
  - Bowel lengths
    - Length of the remnant small bowel
    - The remnant colon in percent (according to Cummings classification)
  - Time since start of PS, if applicable.

Time since diagnosis of underlying disease [months] will be calculated as follows: (date of baseline visit – date of diagnosis of underlying disease) [number of days]/30.5.

Time since SBS diagnosis [months], time since most recent resection [months] and time since start of PS [months] will be calculated analogously.

In case of an incomplete date of diagnosis of underlying disease, date of SBS diagnosis, date of most recent resection or date of start of PS (if applicable), a missing day will be replaced with "15" and a missing month will be replaced with "July" for the calculation. Negative time, which may occur rarely because of the replacement of missing days or months, will be set to missing.

- Medical History/Concomitant Illness
  - Encephalopathy
  - Ascites
  - Cholestasis
  - Steatosis
  - Cirrhosis
- Substance Abuse:
  - Alcohol abuse
  - Drug abuse
  - Tobacco smoking
- Body weight (kg) at baseline and body height (cm) at screening (may be included in the tabulation of demographic data).

#### 4.2.4 Drug Exposure and Treatment Compliance

The selected dose for this trial is 10 mg glepaglutide once-weekly for 52 weeks.
Summary tables presenting descriptive statistics will be provided for:

- Drug exposure
- Treatment compliance.

Drug exposure will be measured by the number of trial product administrations per patient.

Treatment compliance will be calculated by dividing the actual number of trial product administrations per patient by the number of trial product administrations theoretically to be applied during the patient's individual treatment period. That means, the actual number of trial product administrations per patient will be divided by [1 + the number of weeks until visit Week 52 (EOT)], whereby number of weeks is the integer part of {[date of Week 52 (EOT) visit – date of first administration of trial product] / 7}. The result will be multiplied by 100 to obtain a percentage.

#### 4.2.5 Pre-treatment and Concomitant Therapy

Pre-treatment therapies are defined as treatments with stop date prior to date of first dose (including those with incomplete start date). Concomitant therapies are subdivided into 1) treatments ongoing or commenced at the date of first dose and 2) treatments commenced after the date of first dose. Depending on the start date, therapies with incomplete stop date are allocated to concomitant therapy group 1) or 2). All other therapies (therapies with unknown start and/or stop date which can not be allocated to one of the categories above) will be allocated to all three therapy groups.

Pre-treatment and concomitant therapies will be coded and frequencies will be calculated by the first and the fourth level of the Anatomical Therapeutical Chemical (ATC) classification. Separate summary tables will be provided for pre-treatment, concomitant therapies ongoing or commenced at the date of first dose and concomitant therapies commenced after the date of first dose.

## 4.3 Efficacy Evaluation

The evaluation of efficacy will be performed for the FAS (primary analysis) and for the PPS (supportive analysis of primary and key secondary endpoints).

### 4.3.1 Estimands

The primary estimand for the primary endpoint is defined in the clinical trial protocol according to the intention-to-treat principle as follows: The population will be the FAS, the variable will be 24 week change in absorption of wet weight/fluids, the population level summary will be the arithmetic mean, and intercurrent events will be handled as follows: With regards to intercurrent events like lack of compliance with intake of trial product, lack of compliance with instructions concerning intake of food, fluids or PS, or use of prohibited concomitant medication, the treatment policy strategy will be applied, i.e. data will be included in the analysis even if collected after occurrence of such an intercurrent event.

Clinical question of interest:

The primary clinical question of interest targets to estimate the change in the absorption of wet weight/fluids in the patient population defined by the inclusion and exclusion criteria after 24 weeks of glepaglutide treatment, whereby:

- The population studied are adult patients with SBS (for details on inclusion and exclusion criteria see the clinical trial protocol)
- The treatment is 24 weeks treatment with 10 mg glepaglutide once-weekly as subcutaneous injection
- Treatment with trial product and collection of treatment phase data is discontinued after withdrawal from treatment phase
- Change from baseline to Week 24 in absorption of wet weight/fluids assessed by 48-hour metabolic balance studies is defined as described in Section 2.2.

The clinical question of interest will be evaluated based on the FAS and the PPS. The analysis based on the FAS will include all results regardless of actual eligibility according to inclusion and exclusion criteria, regardless of duration of and compliance with administration of trial product, regardless of the use of prohibited concomitant therapies and regardless of other protocol violations. This will be handled differently in the analysis based on the PPS as can be seen from the details provided below.

Estimand in the FAS:

The attributes of the estimand which will be analyzed based on the FAS are as follows:

- Treatment: 24 weeks treatment with 10 mg glepaglutide once-weekly,
- Population: Patients who received at least one administration of trial product, i.e. FAS patients

- Variable: Change from baseline to Week 24 in absorption of wet weight/fluids,
- Population-level summary: Arithmetic mean, whereby patients in the analysis set with available data are included in the calculation,
- Strategies to handle intercurrent events: With regards to intercurrent events like insufficient compliance with administration of trial product, insufficient compliance with other procedures/instructions, use of prohibited concomitant therapy, and other protocol violations, the treatment policy strategy will be applied, i.e., data will be included in the analysis even if collected after occurrence of such an intercurrent event.

Estimand in the PPS:

The attributes of the estimand which will be analyzed based on the PPS are as follows:

- Treatment: 24 weeks treatment with 10 mg glepaglutide once-weekly,
- Population: Patients who received at least one administration of trial product and who do not have a major violation of relevant eligibility criteria (criteria as defined in the PPS definition),
- Variable: Change from baseline to Week 24 in absorption of wet weight/fluids,
- Population-level summary: Arithmetic mean, whereby patients in the analysis set with available data are included in the calculation of the mean value, i.e. only patients without major protocol violations are included,
- Strategies to handle intercurrent events: With regards to intercurrent events like insufficient compliance with administration of trial product, insufficient compliance with other procedures/instructions, use of prohibited concomitant therapy, and other protocol violations, the treatment policy strategy will be applied, i.e., data will be included in the analysis even if collected after occurrence of such an intercurrent event. However, if such intercurrent event is a major protocol violation leading to exclusion from the PPS, the strategy for handling such intercurrent events is to exclude the patient from the analysis, as described under population-level summary.

### 4.3.2 Evaluation of the Primary and Key Secondary Efficacy Endpoints

The evaluation of the primary efficacy endpoint (change from baseline to Week 24 for absorption of wet weight/fluids assessed by 48-hour MBS, as defined in Section 2.2) will be performed based on the FAS and the PPS. The primary analysis will be based on the FAS.

The evaluation of the key secondary efficacy endpoint (change from baseline to Week 24 for absorption of energy (kj/d) assessed by 48-hour MBS, as defined in Section 2.3.1) will also be performed based on the FAS and the PPS. The primary analysis will be based on the FAS.

Descriptive summary statistics will be provided for both endpoints overall and separately for patients with SBS-II and patients with SBS-IF.

The primary confirmatory analysis will use a one-sample t-test (two-sided level of significance alpha= 0.05) to analyze the mean change from baseline in absorption of wet weight/fluids to Week 24.

The primary statistical null hypothesis $H_0$ is defined as

$H_0$: *mean* (24-week change in absorption of wet weight/fluids) = 0

With the alternative hypothesis being defined as

$H_a$: *mean* (24-week change in absorption of wet weight/fluids) ≠ 0.

For the key secondary endpoint the corresponding null hypothesis $H_0$ is defined as

$H_0$: *mean* (24-week change in absorption of energy ) = 0

With the alternative hypothesis being defined as

$H_a$: (*mean* 24-week change in absorption of energy) ≠ 0.

The statistical hypotheses will be tested sequentially in a hierarchical testing procedure, such that the rejection of the primary hypothesis leads to the test of the secondary hypothesis, whereas the acceptance of the primary hypothesis prevents confirmatory testing of the secondary null hypothesis.

In addition to the overall analysis, supplementary analyses will be performed separately for SBS-II and SBS-IF patients. Theses supplementary analyses will however not be part of the confirmatory testing strategy.

#### 4.3.3 Evaluation of Secondary Efficacy Endpoints

The evaluation of the key secondary endpoint is described in Section 4.3.2.

Further secondary efficacy endpoints (as defined in Section 2.3.2)

- Absorption of Individual Macronutrients
- Absorption of Electrolytes
- Weekly PS Volume (SBS-IF patients only)
- Weekly PS Macronutrients and Electrolytes (SBS-IF patients only)

will be analyzed using descriptive summary statistics based on the FAS.

Descriptive summary statistics will be provided for all secondary efficacy endpoints (except for those to be analyzed in patients with SBS-IF only) overall and separately for patients with SBS-II and patients with SBS-IF.

#### 4.3.4 Evaluation of Exploratory Endpoints

Exploratory endpoints (as defined in Section 2.4) will be analyzed using descriptive summary statistics based on the FAS.

#### 4.3.5 Influence of Covariates, Stratified Analyses

Primary and key secondary endpoints will be analyzed stratified by patients with SBS-II versus SBS-IF.

### 4.4 Safety Evaluation

The evaluation of safety variables (as defined in Section 2.5) will be performed based on the SAS (or FAS, if both analysis sets include the same patients).

- ***Adverse Events***

Adverse events (AE) will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

TEAEs will be tabulated and non-TEAEs will be listed.

AEs will be categorized as non-TE or TE using the start date of the AE and the date of first administration of trial product as follows:

**Non-TEAEs** are defined as AEs with onset date prior to the day of first administration of trial product.

**Treatment-emergent AEs (TEAEs)** are defined as AEs with onset date on or after the day of first administration of trial product.

In case of an incomplete or missing AE start date, the AE will be categorized as TE (worst case).

An AE overview summary table will be prepared for the following AE categories and will present the number and percentage of patients reporting at least one AE in this category and the number of events reported for this category:

- TEAEs
- TE adverse drug reactions (ADRs) [ADRs are defined as events with relationship to study treatment, i.e. judged by the Investigator as possible or probable]
- TE serious adverse events (SAEs)
- TEAEs leading to permanent discontinuation of study treatment.

In addition, separate summary tables will be generated for each of the above AE categories. These will present the number of events as well as number and percentage of patients with an AE in the respective category classified in MedDRA system organ classes (SOCs) and preferred terms (PTs).
An overview summary table will present the number and percentage of patients with at least one TEAE by severity, seriousness, relationship, action taken with study treatment, and outcome.

In addition, summary tables will present the number and percentage of patients with each PT grouped by severity, seriousness, relationship, action taken with study treatment, and outcome.

Individual patient data listings will be provided for AEs, SAEs (including deaths), ADRs, Adverse events of special interest (AESIs) [defined as neoplasms (malignant and benign), suspicion of liver injury, pancreatitis and cholecystitis], and for AEs leading to permanent discontinuation of study treatment. In these patient data listings, AEs will be flagged as non-TE and TE.

Non-TEAEs will in addition be listed separately based on all patients included into the trial.

- **Vital signs** (body temperature, systolic/diastolic blood pressure, pulse rate) and body weight

For vital signs and body weight, standard descriptive summary statistics will be calculated for values at visits and for absolute changes from baseline.

- **Physical Examination**

This will be summarized by the number and percentage of patients with normal/abnormal findings per body system at each visit.

- **Electrocardiograms (ECG)**

For the ECG parameters (heart rate, PR, QRS, QT, QTcF, RR), standard descriptive summary statistics will be calculated for values at visits and for absolute changes from baseline. Additional ECGs performed for cause as needed to evaluate AEs will only be listed.

- **Laboratory parameters** (hematology, biochemistry and urinalysis)

Values and absolute changes from baseline to post-baseline visits with an assessment of the respective clinical laboratory parameter (as defined in Section 2.1.2.1) will be summarized by visit using descriptive statistics. Further details on the handling of laboratory parameters are described in Section 2.1.3.

- **Immunogenicity Assessments**

A serum sample is defined as anti-drug antibody (ADA)-positive if results of the anti-glepaglutide antibody screening and confirmatory assays are positive. If positive, a titer (highest dilution factor that still yields a positive reading) will be reported. Patients without any ADA data (evaluable samples) will be excluded from the analysis.

1. Pre-existing ADA (Yes/No) is defined, at the patient level, by the ADA status at trial baseline (i.e. Day 4 of MBS at V1), according to the presence or absence of ADA. This will be missing for patients without a valid ADA assessment at baseline.
2. A treatment-boosted ADA positive patient (Yes/No) is defined, at the patient level, by an at least 4 fold increase from trial baseline in ADA-titer at any visit for patients with pre-existing ADA (and a titer at baseline). Thus, it will be missing, if pre-existing ADA is missing or no post-baseline sample is available. It will be “Yes”, if the sample at any visit shows a 4 fold increase from baseline and “No” otherwise.
3. A treatment-induced ADA positive patient (Yes/No) is defined, at the patient level, by a positive ADA sample at any visit without pre-existing ADA (based on a negative baseline ADA measurement). Thus, it will be missing, if pre-existing ADA is missing or if no post-baseline sample is available. It will be “Yes”, if pre-existing ADA is “No” and the sample at any visit is ADA-positive. Otherwise, it will be “No”.
4. An ADA positive patient (Yes/No) is defined by being either treatment-boosted or treatment-induced ADA positive during the trial (for patients with a baseline ADA measurement). Thus, it will be missing, if pre-existing ADA is missing or if no post-baseline sample is available.

Confirmed positive ADA samples will be further evaluated in three different ADA characterization assays: for in vitro glepaglutide neutralizing potential (NAb), for reactivity to the predominant metabolite (M2) and for cross-reactivity towards GLP-2. In case of a positive result in the ADA characterization assays, a titer will be estimated.

For ADA negative samples, the missing assessments for in vitro glepaglutide neutralizing potential (NAb), for reactivity to the predominant metabolite (M2) and for cross-reactivity towards GLP-2 will be considered negative in all below presentations.

In case of positive results at study baseline (Day 1) in the ADA characterization assays (‘Pre-existing NAb’, ‘pre-existing M2 reactivity’, ‘pre-existing GLP-2 cross-reactivity’), the

definitions and calculations for pre-existing ADA and treatment boosted ADA will correspondingly apply.

In case of a negative assessment in either of the four assays (ADA, NAb, M2 reactivity and GLP-2 cross-reactivity) the titer value will be set to ¼ MRD (Minimal Required Dilution) for illustration purposes.

**Immunogenicity Statistical Methodology**

All analyses will be done for all four ADA assessments (ADA, NAb, M2 reactivity and GLP-2 cross-reactivity), unless otherwise specified.

Analysis of ADA positive patients by visit will be done separately and combined, for patients with and without pre-existing ADA. For patients with pre-existing ADA, 'treatment-boosted ADA by sample' is defined as a post-baseline ADA positive sample at a given visit with a titer that has increased at least 4-fold from baseline. For patients without pre-existing ADA, 'treatment-induced ADA by sample' is defined as a post-baseline ADA positive sample at a given visit. For all patients, "ADA positive by sample" is defined as either treatment-boosted by sample or treatment-induced by sample.

The overall anti-glepaglutide antibody incidences (all ADA positive patients) will be presented.

The percentage of "ADA positive by sample" patients will be summarized by visit.

Similar tables will be made separately for "treatment boosted ADA by sample" and "treatment induced ADA by sample", if both types are observed.

For all treatment induced ADA positive patients, the titer levels will be summarized by visit using descriptive statistics including median, geometric mean, geometric CV%, inter-quartile range, minimum, maximum, and number of observations (positive samples only).

For all treatment boosted ADA positive patients (if applicable), the titer levels and fold increases from baseline of titers will be summarized by visit using descriptive statistics including median, geometric mean, geometric CV%, inter-quartile range, minimum, maximum, and number of observations (positive samples only).

All immunogenicity data will be listed, including corresponding PK concentrations.

### 4.5 Handling of Missing, Unused and Spurious Data

As a general rule, missing values will not be replaced unless specified otherwise.

## 5 INTERIM ANALYSIS

An interim analysis will be performed when the last patient has collected last primary endpoint data. An interim clinical trial report will prepared based on data collected up to Visit 9 (Week 24) solely. For each patient, the database cut-off date will be the date of their Visit 9 - Week 24 - Day 4. Further details on the derivation of the interim analysis database can be found in the Data Management Plan.

The following variables are derived only for the interim analysis:

- Completion of treatment phase until Visit 9, reason for premature discontinuation before Visit 9
- Treatment duration until Visit 9: Duration of trial product administration until Visit 9 [days]

Duration of trial product administration until Visit 9 will be calculated as date of last administration until the individual cut-off date – date of first administration +1.

- Study duration until Visit 9: Last visit during treatment phase until Visit 9

  Last visit during treatment phase until Visit 9 will be the last visit of V1 to V9 where a visit date is documented in the eCRF.

- Drug exposure until Visit 9 will be measured by the number of trial product administrations per patient until the individual cut-off date.

- Treatment compliance until Visit 9 will be calculated by dividing the actual number of trial product administrations per patient until the individual cut-off date by the number of trial product administrations theoretically to be applied administered until the individual cut-off date. That means, the actual number of trial product administrations per patient until individual cut-off date will be divided by [1 + the number of weeks until individual cut-off date], whereby number of weeks is the integer part of {[individual cut-off date – date of first administration of trial product] / 7}. The result will be multiplied by 100 to obtain a percentage. For patients withdrawn before Visit 9, date of withdrawal will be used instead of individual cut-off date.

- A treatment-boosted ADA positive (until Visit 9) patient (Yes/No) is defined, at the patient level, by an at least 4 fold increase from trial baseline in ADA-titer at any visit until Visit 9 for patients with pre-existing ADA (and a titer at baseline). Thus, it will be missing, if pre-existing ADA is missing or no post-baseline sample is available. It will be "Yes", if the sample at any visit shows a 4 fold increase from baseline and "No" otherwise.

- A treatment-induced ADA positive (until Visit 9) patient (Yes/No) is defined, at the patient level, by a positive ADA sample at any visit until Visit 9 without pre-existing ADA (based on a negative baseline ADA measurement). Thus, it will be missing, if pre-existing ADA is missing or if no post-baseline sample is available. It will be "Yes", if pre-existing ADA is "No" and the sample at any visit is ADA-positive. Otherwise, it will be "No".

- An ADA positive (until Visit 9) patient (Yes/No) is defined by being either treatment-boosted or treatment-induced ADA positive (until Visit 9) (for patients with a baseline ADA measurement). Thus, it will be missing, if pre-existing ADA is missing or if no post-baseline sample is available.

- Overall anti-glepaglutide antibody incidence until Visit 9, i.e. all ADA positive (until Visit 9) patients.

# 6 CHANGES FROM PROTOCOL

The analyses planned in this analysis plan deviate in the following point from the provisions in the clinical trial protocol:

- Concerning 8.2.20 Weekly days on PS (SBS-IF only):

  Weekly average administration time will not be analyzed as it was decided not to collect information on duration of PS use in the patient diary (change from clinical trial protocol version 1.0 to version 2.0).

- Concerning exploratory endpoint "Pharmacokinetic (PK) parameters ($t_{½}$ and $C_{trough}$)":

  The parameter $t_{½}$ will not be analyzed as it cannot be calculated based on the samples taken (the dosing time prior to Visit 9 may vary between patients).

No relevant deviations from the statistical methods foreseen in the clinical trial protocol are planned.

# 7 SUMMARY TABLES AND DATA LISTINGS

## 7.1 Summary Tables

The summary tables planned for this analysis are listed in Appendix A.

The treatment group will be labelled as Glepaglutide – Once Weekly.

General format for categorical variables (SAS output):

| **Glepaglutide – Once Weekly** | | **Type of SBS** | | | | | |
|---|---|---|---|---|---|---|---|
| | | *SBS-IF* | | *SBS-II* | | ***Total*** | |
| | | *N* | *%* | *N* | *%* | *N* | *%* |
| ***Analysis Visit*** | ***X-Variable*** | | | | | | |
| *Week x* | *Category 1* | | | | | | |
| | *Category 2* | | | | | | |
| | ***Number of patients*** | | | | | | |
| *Week y* | ***X-Variable*** | | | | | | |
| | *Category 1* | | | | | | |
| | *Category 2* | | | | | | |
| | ***Number of patients*** | | | | | | |

More than one X-variable may be analyzed within a table. Variables can have more than two categories. Percentages are displayed with 1 decimal.

General format for continuous variables (SAS output):

| **Glepaglutide – Once Weekly** | | **X-variable** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Valid n** | **Mean** | **Std. Dev.** | **Min.** | **Q25%** | **Median** | **Q75%** | **Max.** | **Missing n** |
| **Type of SBS** | **Analysis Visit** | | | | | | | | | |
| *SBS-IF* | *Week x* | | | | | | | | | |
| | *Week y* | | | | | | | | | |
| *SBS-II* | *Week x* | | | | | | | | | |
| | *Week y* | | | | | | | | | |
| **Total** | *Week x* | | | | | | | | | |
| | *Week y* | | | | | | | | | |

More than one x-variable may be analyzed within a table.

The number of decimals used for minima and maxima depends on the scaling of the respective data. Mean, median and percentiles will be displayed with one additional decimal. Standard deviations will be displayed with two additional decimals. Frequencies (valid n and missing n) will be displayed with no decimals.

## 7.2 Data Listings

The data listings planned are listed in Appendix B.

Data of all patients screened will be listed. Flags will be provided in the listings indicating which patients are included in the different analysis sets. Patients will be sorted by the screening number and by whether they have SBS-II or SBS-IF.

## 7.3 Figures

The figures planned are listed in Appendix C.

## 7.4 Modifications of Summary Tables and Data Listings for Interim Analysis

Modifications of summary tables and data listings are listed in Appendix D.

# 8 SIGNATURES

**Sponsor:**

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# 9 APPENDICES

A List of Summary Tables

B List of Data Listings

C List of Figures

D Modifications of Summary Tables and Data Listings for Interim Analysis

## List of Summary Tables

Analysis Sets:
ALL = All Patients Included into the Trial
FAS = Full Analysis Set
PPS = Per-Protocol Set
SAS = Safety Analysis Set (Note: if FAS=SAS, then FAS will be used)

| No. | Title/Content | Analysis Sets |
|---|---|---|
| **1. Study Patients** | | |
| 1-1.1 | Number of patients screened and included in each analysis set | ALL |
| 1-1.2 | Reasons for exclusion from per-protocol analysis set | FAS |
| 1-1.3 | Study completion: Completion of treatment phase and reasons for premature discontinuation | FAS |
| 1-1.4 | Treatment duration: Duration of trial product administration during treatment phase | FAS |
| 1-1.5.1 | Study duration: Last visit during treatment phase | FAS |
| 1-1.5.2 | Study duration: Follow-up visit performed | FAS |
| 1-2.1 | Inclusion criteria | FAS |
| 1-2.2 | Exclusion criteria | FAS |
| 1-2.3.1 | Protocol violations - Overview | FAS |
| 1-2.3.2 | Protocol violations - Details | FAS |
| 1-2.4 | Compliance with time window for Week 52 (EOT) for completers | FAS |
| 1-3.1 | Demographic data: Sex, age, race, ethnicity, body height and weight | FAS / PPS |
| 1-3.2.1 | SBS characteristics and history: Type, cause and severity of SBS, time since diagnosis of underlying disease, time since SBS diagnosis | FAS / PPS |
| 1-3.2.2 | SBS characteristics and history: Time since most recent resection, reason for resection | FAS / PPS |
| 1-3.2.3 | SBS characteristics and history - Remaining bowel sections<br>- Colon-in-continuity (including type)<br>- End-jejunostomy/SBS anatomical group 1<br>- Ileostomy/SBS anatomical group 1<br>- Colostomy<br>- Presence of ileocecal valve | FAS |

| No. | Title/Content | Analysis Sets |
|---|---|---|
| 1-3.2.4 | SBS characteristics and history - Bowel lengths<br>- Length of the remnant small bowel<br>- Remnant colon in percent | FAS |
| 1-3.2.5 | SBS characteristics and history: Time since start of PS (if applicable) | FAS |
| 1-3.3 | Medical history/concomitant illness<br>- Encephalopathy<br>- Ascites<br>- Cholestasis<br>- Steatosis<br>- Cirrhosis | FAS |
| 1-3.4 | Baseline characteristics: Substance abuse<br>- Alcohol abuse<br>- Drug abuse<br>- Tobacco smoking | FAS |
| 1-4 | Drug exposure and treatment compliance | FAS / PPS |
| 1-5.1 | Pre-treatment therapies | FAS |
| 1-5.2 | Concomitant therapies commenced or ongoing at date of first administration of trial product | FAS |
| 1-5.3 | Concomitant therapies commenced after date of first administration of trial product | FAS |

| No. | Title/Content | Analysis Sets |
|---|---|---|
| **2. Efficacy Evaluation and Other Variables** | | |
| 2-1.1 | Primary Endpoint: Change from baseline to Week 24 in absorption of wet weight/fluids | FAS / PPS |
| 2-1.2 | Absorption of wet weight/fluids by visit | FAS / PPS |
| 2-2.1.1 | Key secondary endpoint: Change from baseline to week 24 in absorption of energy | FAS / PPS |
| 2-2.1.2 | Absorption of energy by visit | FAS / PPS |
| 2-2.2.1.1-2-2.2.1.3 | Absorption of individual macronutrients: Change from baseline to Week 24<br>- Carbohydrates [g/d]<br>- Lipids [g/d]<br>- Proteins [g/d] | FAS / PPS |
| 2-2.2.2.1-2-2.2.2.3 | Absorption of individual macronutrients by visit<br>- Carbohydrates [g/d]<br>- Lipids [g/d]<br>- Proteins [g/d] | FAS / PPS |
| 2-2.3.1.1-2-2.3.1.4 | Absorption of electrolytes: Change from baseline to Week 24<br>- Sodium [mmol/d]<br>- Potassium [mmol/d]<br>- Calcium [mmol/d]<br>- Magnesium [mmol/d] | FAS / PPS |
| 2-2.3.2.1-2-2.3.2.4 | Absorption of electrolytes by visit<br>- Sodium [mmol/d]<br>- Potassium [mmol/d]<br>- Calcium [mmol/d]<br>- Magnesium [mmol/d] | FAS / PPS |
| 2-2.4.1 | Weekly parenteral support volume: Change from baseline to Week 12 and 24 (SBS-IF only) | FAS / PPS |
| 2-2.4.2 | Weekly parenteral support volume by visit (SBS-IF only) | FAS / PPS |

| No. | Title/Content | Analysis Sets |
|---|---|---|
| 2-2.5.1.1-2-2.5.1.7 | Weekly parenteral support macronutrients and electrolytes (SBS-IF only): Change from baseline to Week 12 and 24<br>- Macronutrient: Carbohydrates [kjoule]<br>- Macronutrient: Lipids [kjoule]<br>- Macronutrient: Proteins [kjoule]<br>- Macronutrient: Total content [kjoule]<br>- Electrolyte: Sodium [mmol]<br>- Electrolyte: Potassium [mmol]<br>- Electrolyte: Magnesium [mmol] | FAS / PPS |
| 2-2.5.2.1-2-2.5.2.7 | Weekly parenteral support macronutrients and electrolytes (SBS-IF only) by visit<br>- Macronutrient: Carbohydrates [kjoule]<br>- Macronutrient: Lipids [kjoule]<br>- Macronutrient: Proteins [kjoule]<br>- Macronutrient: Total content [kjoule]<br>- Electrolyte: Sodium [mmol]<br>- Electrolyte: Potassium [mmol]<br>- Electrolyte: Magnesium [mmol] | FAS / PPS |
| 2-3.1.1 | Body weight [kg]: Change from baseline to Week 12, 24 and 52 | FAS |
| 2-3.1.2 | Body weight [kg] by visit | FAS |
| 2-3.2.1.1-2-3.2.1.3 | Body composition by dual-energy X-ray absorptiometry (DEXA): Change from baseline to Week 12, 24 and 52<br>- Lean body mass [kg]<br>- Fat mass [kg]<br>- Bone mineral content [kg] | FAS |
| 2-3.2.2.1-2-3.2.2.3 | Body composition by dual-energy X-ray absorptiometry (DEXA) by visit<br>- Lean body mass [kg]<br>- Fat mass [kg]<br>- Bone mineral content [kg] | FAS |
| 2-3.3.1 | Citrulline: Change from baseline to Week 12, 24 and 52 | FAS |
| 2-3.3.2 | Citrulline by visit | FAS |
| 2-3.4.1 | Aldosterone: Change from baseline to Week 12, 24 and 52 | FAS |
| 2-3.4.2 | Aldosterone by visit | FAS |
| 2-3.5.1.1 | Estimated glomerular filtration rate (eGFR): Change from baseline to Week 12, 24, and 52 | FAS |

| No. | Title/Content | Analysis Sets |
|---|---|---|
| 2-3.5.1.2 | Estimated glomerular filtration rate (eGFR) by visit | FAS |
| 2-3.5.2.1 | Creatinine clearance: Change from baseline to Week 12, 24, and 52 | FAS |
| 2-3.5.2.2 | Creatinine clearance by visit | FAS |
| 2-3.5.3.1.1-<br>2-3.5.3.1.5 | Liver function: Change from baseline to Week 12, 24, and 52<br>- ALT<br>- AST<br>- ALP<br>- Albumin<br>- Total bilirubin | FAS |
| 2-3.5.3.2.1-<br>2-3.5.3.2.5 | Liver function by visit<br>- ALT<br>- AST<br>- ALP<br>- Albumin<br>- Bilirubin | FAS |
| 2-3.6.1 | Hemoglobin A1c: Change from baseline to Week 4, 12, 24 and 52 | FAS |
| 2-3.6.2 | Hemoglobin A1c by visit | FAS |
| 2-3.7 | Patient reported outcome: Patient's global impression of change (PGIC) at Week 12, 24 and 52 | FAS |
| 2-3.8.1.1.1-<br>2-3.8.1.1.8 | Patient reported outcome: SBS -impact scale (SBS-I): Change from baseline to Week 12, 24 and 52:<br>- Item 1<br>- Item 2<br>- Item 3<br>- Item 4<br>- Item 5<br>- Item 6<br>- Item 7<br>- Item 8 | FAS |

| No. | Title/Content | Analysis Sets |
|---|---|---|
| 2-3.8.1.2.1-<br>2-3.8.1.2.8 | Patient reported outcome: SBS -impact scale (SBS-I) by visit:<br>- Item 1<br>- Item 2<br>- Item 3<br>- Item 4<br>- Item 5<br>- Item 6<br>- Item 7<br>- Item 8 | FAS |
| 2-3.8.2.1.1-<br>2-3.8.2.1.5 | Patient reported outcome: EQ-5D-5L Domains: Change from baseline to Week 12, 24 and 52:<br>- Mobility<br>- Self-care<br>- Usual activities<br>- Pain/discomfort<br>- Anxiety/depression | FAS |
| 2-3.8.2.2.1-<br>2-3.8.2.2.5 | Patient reported outcome: EQ-5D-5L Domains by visit:<br>- Mobility<br>- Self-care<br>- Usual activities<br>- Pain/discomfort<br>- Anxiety/depression | FAS |
| 2-3.8.3.1 | Patient reported outcome: EQ-5D-5L Current Health Visual Analogue Scale: Change from baseline to Week 12, 24 and 52 | FAS |
| 2-3.8.3.2 | Patient reported outcome: EQ-5D-5L Current Health Visual Analogue Scale by visit | FAS |
| 2-3.8.4.1 | Patient reported outcome: EQ-5D-5L Index: Change from baseline to Week 12, 24 and 52 | FAS |
| 2-3.8.4.2 | Patient reported outcome: EQ-5D-5L Index by visit | FAS |
| 2-3.9.1-<br>2-3.9.4 | Pharmacokinetic Analysis: Trough concentrations by visit<br>- Parent drug<br>- Metabolite M1<br>- Metabolite M2<br>- Glepaglutide | FAS |
| 2-3.10.1 | Luminal- and mucosae-associated microbiota of patients with SBS: Change from baseline to Week 24 | FAS |

| No. | Title/Content | Analysis Sets |
|---|---|---|
| 2-3.10.2 | Luminal- and mucosae-associated microbiota of patients with SBS by visit | FAS |
| 2-3.11.1.1.1-<br>2-3.11.1.1.4 | Urinary excretion of electrolytes: Change from baseline to Week 24<br>- Sodium [mmol/d]<br>- Potassium [mmol/d]<br>- Calcium [mmol/d]<br>- Magnesium [mmol/d] | FAS / PPS |
| 2-3.11.1.2.1-<br>2-3.11.1.2.4 | Urinary excretion of electrolytes by visit<br>- Sodium [mmol/d]<br>- Potassium [mmol/d]<br>- Calcium [mmol/d]<br>- Magnesium [mmol/d] | FAS / PPS |
| 2-3.11.2.1 | Urinary excretion of urea [mmol/d]: Change from baseline to Week 24 | FAS / PPS |
| 2-3.11.2.2 | Urinary excretion of urea [mmol/d] by visit | FAS / PPS |
| 2-3.12.1 | Fluid composite effect [L/d]: Change from baseline to Week 12, 24 and 52 | FAS / PPS |
| 2-3.12.2 | Fluid composite effect [L/d] by visit | FAS / PPS |
| 2-3.13.1 | Drinking volume during 48-hour periods: Change from Week 24 to 52 | FAS / PPS |
| 2-3.13.2 | Drinking volume during 48-hour periods by visit | FAS / PPS |
| 2-3.14 | Weekly parenteral support volume: Change from baseline to Week 52 (SBS-IF only) | FAS / PPS |
| 2-3.15.1-<br>2-3.15.7 | Weekly parenteral support macronutrients and electrolytes (SBS-IF only): Change from baseline to Week 52<br>- Macronutrient: Carbohydrates [kjoule]<br>- Macronutrient: Lipids [kjoule]<br>- Macronutrient: Proteins [kjoule]<br>- Macronutrient: Total content [kjoule]<br>- Electrolyte: Sodium [mmol]<br>- Electrolyte: Potassium [mmol]<br>- Electrolyte: Magnesium [mmol] | FAS / PPS |
| 2-3.16.1 | Weekly days on PS: Change from baseline to Week 12, 24, and 52 (SBS-IF only) | FAS / PPS |
| 2-3.16.2 | Weekly days on PS by visit (SBS-IF only) | FAS / PPS |

| No. | Title/Content | Analysis Sets |
|---|---|---|
| 2-3.17.1 | Urine output: Change from baseline to Week 12, 24 and 52 (SBS-II only) | FAS / PPS |
| 2-3.17.2 | Urine output by visit (SBS-II only) | FAS / PPS |

| No. | Title/Content | Analysis Sets |
|---|---|---|
| **3. Safety Evaluation** | | |
| 3-1.1 | Number of patients with different adverse event categories, overview | SAS |
| 3-1.2 | Treatment-emergent adverse events by MedDRA System Organ Class (SOC) and Preferred Term (PT) | SAS |
| 3-1.3 | Treatment-emergent adverse drug reactions by MedDRA System Organ Class (SOC) and Preferred Term (PT) | SAS |
| 3-1.4 | Treatment-emergent serious adverse events by MedDRA System Organ Class (SOC) and Preferred Term (PT) | SAS |
| 3-1.5 | Adverse events leading to permanent discontinuation of study treatment by System Organ Class (SOC) and Preferred Term (PT) | SAS |
| 3-1.6 | Treatment-emergent adverse events by severity, seriousness, relationship, action taken with study treatment, and outcome, overview | SAS |
| 3-1.7 | Treatment-emergent adverse events by severity and Preferred Term (PT) | SAS |
| 3-1.8 | Treatment-emergent adverse events by seriousness and Preferred Term (PT) | SAS |
| 3-1.9 | Treatment-emergent adverse events by relationship and Preferred Term (PT) | SAS |
| 3-1.10 | Treatment-emergent adverse events by action taken with study treatment and Preferred Term (PT) | SAS |
| 3-1.11 | Treatment-emergent adverse events by outcome and Preferred Term (PT) | SAS |
| 3-2.1.1-<br>3-2.1.4 | Vital signs: Change from baseline by visit<br>- Systolic blood pressure<br>- Diastolic blood pressure<br>- Pulse rate<br>- Body temperature | SAS |
| 3-2.2.1-<br>3-2.2.4 | Vital signs by visit<br>- Systolic blood pressure<br>- Diastolic blood pressure<br>- Pulse rate<br>- Body temperature | SAS |
| 3-2.3.1 | Body weight: Change from baseline by visit | SAS |
| 3-2.3.2 | Body weight by visit | SAS |
| 3-3 | Physical examination by visit | SAS |

| No. | Title/Content | Analysis Sets |
|---|---|---|
| 3-4.1.1-<br>3-4.1.6 | Electrocardiogram parameters: Absolute changes from baseline by visit<br>- Heart rate [beats/min]<br>- PR [msec]<br>- QRS [msec]<br>- QT [msec]<br>- QTcF [msec]<br>- RR [msec] | SAS |
| 3-4.2.1-<br>3-4.2.6 | Electrocardiogram parameters by visit<br>- Heart rate [beats/min]<br>- PR [msec]<br>- QRS [msec]<br>- QT [msec]<br>- QTcF [msec]<br>- RR[msec] | SAS |
| 3-5.1.1-<br>3-5.1.10 | Laboratory parameters (hematology): Absolute change from baseline by visit<br>- Hemoglobin [mmol/L]<br>- Hematocrit [vol.fr]<br>- Red blood cell count [x10^12/L]<br>- White blood cell count with differential: [x10^9/L]<br>- Neutrophils [x10^9/L]<br>- Lymphocytes [x10^9/L]<br>- Monocytes [x10^9/L]<br>- Eosinophils [x10^9/L]<br>- Basophils [x10^9/L]<br>- Platelet Count [x10^9/L] | SAS |
| 3-5.2.1-<br>3-5.2.10 | Laboratory parameters (hematology) by visit<br>- Hemoglobin [mmol/L]<br>- Hematocrit [vol.fr]<br>- Red blood cell count [x10^12/L]<br>- White blood cell count with differential: [x10^9/L]<br>- Neutrophils [x10^9/L]<br>- Lymphocytes [x10^9/L]<br>- Monocytes [x10^9/L]<br>- Eosinophils [x10^9/L]<br>- Basophils [x10^9/L]<br>- Platelet Count [x10^9/L] | SAS |

| No. | Title/Content | Analysis Sets |
|---|---|---|
| 3-5.3.1-<br>3-5.3.28 | Laboratory parameters (biochemistry): Absolute change from baseline by visit<br>• Sodium [mmol/L]<br>• Potassium [mmol/L]<br>• Chloride [mmol/L]<br>• Bicarbonate [mmol/L]<br>• Blood Urea Nitrogen [mmol/L]<br>• Creatinine [umol/L]<br>• Creatinine Clearance (estimated) [mL/min]<br>• Glucose [mmol/L]<br>• Calcium [mmol/L]<br>• Phosphorous [mmol/L]<br>• ALP (alkaline phosphatase) [U/L]<br>• ALT (alanine aminotransferase) [U/L]<br>• AST (aspartate aminotransferase) [U/L]<br>• INR<br>• Gamma-glutamyl transferase (GGT) [U/L]<br>• Lactic dehydrogenase [U/L]<br>• Conjugated bilirubin [umol/L]<br>• Unconjugated bilirubin [umol/L]<br>• Total bilirubin [umol/L]<br>• Total protein [g/L]<br>• Albumin [g/L]<br>• Amylase [U/L]<br>• Uric acid [mmol/L]<br>• C-reactive protein [mg/L]<br>• Cholesterol, measured orally fasting [mmol/L]<br>• Triglycerides, measured orally fasting [mmol/L]<br>• Magnesium [mmol/L]<br>• Zinc [umol/L] | SAS |

| No. | Title/Content | Analysis Sets |
|---|---|---|
| 3-5.4.1-<br>3-5.4.28 | Laboratory parameters (biochemistry) by visit<br>• Sodium [mmol/L]<br>• Potassium [mmol/L]<br>• Chloride [mmol/L]<br>• Bicarbonate [mmol/L]<br>• Blood Urea Nitrogen [mmol/L]<br>• Creatinine [umol/L]<br>• Creatinine Clearance (estimated) [mL/min]<br>• Glucose [mmol/L]<br>• Calcium [mmol/L]<br>• Phosphorous [mmol/L]<br>• ALP (alkaline phosphatase) [U/L]<br>• ALT (alanine aminotransferase) [U/L]<br>• AST (aspartate aminotransferase) [U/L]<br>• INR<br>• Gamma-glutamyl transferase (GGT) [U/L]<br>• Lactic dehydrogenase [U/L]<br>• Conjugated bilirubin [umol/L]<br>• Unconjugated bilirubin [umol/L]<br>• Total bilirubin [umol/L]<br>• Total protein [g/L]<br>• Albumin [g/L]<br>• Amylase [U/L]<br>• Uric acid [mmol/L]<br>• C-reactive protein [mg/L]<br>• Cholesterol, measured orally fasting [mmol/L]<br>• Triglycerides, measured orally fasting [mmol/L]<br>• Magnesium [mmol/L]<br>• Zinc [umol/L] | SAS |
| 3-5.5.1-<br>3-5.5.5 | Laboratory parameters (urinalysis - by dipstick): Absolute changes from baseline by visit<br>• Blood [x10^6/L]<br>• Glucose [mmol/L]<br>• Leukocytes [x10^6/L]<br>• pH<br>• Protein [g/L] | SAS |
| 3-5.6.1-<br>3-5.6.5 | Laboratory parameters (urinalysis - by dipstick) by visit<br>• Blood [x10^6/L]<br>• Glucose [mmol/L]<br>• Leukocytes [x10^6/L]<br>• pH<br>• Protein [g/L] | SAS |

| No. | Title/Content | Analysis Sets |
|---|---|---|
| 3-5.7.1-<br>3-5.7.6 | Laboratory parameters (urinalysis): Absolute changes from baseline by visit<br>- Sodium<br>- Potassium<br>- Calcium<br>- Magnesium<br>- Urea<br>- Creatinine | SAS |
| 3-5.8.1-<br>3-5.8.6 | Laboratory parameters (urinalysis) by visit<br>- Sodium<br>- Potassium<br>- Calcium<br>- Magnesium<br>- Urea<br>- Creatinine | SAS |
| 3-5.9.1-<br>3-5.9.2 | Laboratory parameters aldosterone and citrulline: Absolute changes from baseline by visit | SAS |
| 3-5.10.1-<br>3-5.10.2 | Laboratory parameters aldosterone and citrulline by visit | SAS |
| 3-6.1 | Overall anti-glepaglutide antibody incidence<br>*Note: Only patients with any evaluable ADA sample* | SAS |
| 3-6.2 | ADA positive by sample by visit, for patients with/without pre-existing ADA and overall<br>*Note: Only patients with any evaluable ADA sample* | SAS |
| 3-6.3 | Treatment boosted ADA by sample by visit<br>*Note: Only patients with pre-existing ADA* | SAS |
| 3-6.4 | Treatment induced ADA by sample by visit<br>*Note: Only patients without pre-existing ADA* | SAS |
| 3-6.5.1-<br>3-6.5.4 | Titer levels of treatment induced ADA positive patients by visit<br>- Anti-glepaglutide antibodies (ADA)<br>- Reactivity to M2<br>- Cross-reactivity to glucagon-like peptide [GLP]-2<br>- Glepaglutide neutralizing antibodies (NAb)<br><br>*Note: Only treatment induced ADA positive patients* | SAS |

| No. | Title/Content | Analysis Sets |
|---|---|---|
| 3-6.6.1-<br>3-6.6.4 | Titer levels of treatment boosted ADA positive patients by visit<br>- Anti-glepaglutide antibodies (ADA)<br>- Reactivity to M2<br>- Cross-reactivity to glucagon-like peptide [GLP]-2<br>- Glepaglutide neutralizing antibodies (NAb)<br><br>*Note: Only treatment boosted ADA positive patients* | SAS |
| 3-6.7.1-<br>3-6.7.4 | Fold increase [%] in titer levels of treatment boosted ADA positive patients from baseline by visit<br>- Anti-glepaglutide antibodies (ADA)<br>- Reactivity to M2<br>- Cross-reactivity to glucagon-like peptide [GLP]-2<br>- Glepaglutide neutralizing antibodies (NAb)<br><br>*Note: Only treatment boosted ADA positive patients* | SAS |

## List of Data Listings

Analysis Sets:
ALL = All Patients Included into the Trial
ENR = Enrolled Patients

| No. | Title | Set | Variables to be included/Variables of the following form in the eCRF and corresponding derived variables |
|---|---|---|---|
| **Patient Disposition and Baseline Characteristics** | | | |
| 1-1 | Patient disposition - Allocation to analysis sets, reasons for exclusion from analysis sets | ALL | Date of birth, Screening date; Informed consent date; Rescreenings; FAS, PPS, SAF; exclusion from FAS, PPS, SAF; |
| 1-2 | Inclusion and exclusion criteria | ALL | Eligibility check variables (Dosing Criteria – Eligibility and Inclusion/Exclusion Criteria forms) |
| 1-3.1 | Study completion | ENR | Completion of treatment phase; Reasons for premature discontinuation (Treatment Completion Status form); Compliance with time window for Week 52 (EOT) |
| 1-3.2 | Completion of full study | ENR | Completion of full study; Reason for non-completion (Trial Completion Status form) |
| 1-4.1 | Study duration | ENR | Last Visit during treatment phase; Withdrawal Date; Follow-up visit performed |
| 1-4.2 | Treatment duration | ENR | First and last trial product administration; Duration of trial product administration; Drug exposure; |
| 1-5 | Visit dates | ENR | Visit; Visit Date incl. unscheduled visits and corresponding reason (Date of Visit form) |
| 1-6.1 | Protocol deviations - overall | ENR | Data from protocol deviations log |

| No. | Title | Set | Variables to be included/Variables of the following form in the eCRF and corresponding derived variables |
|---|---|---|---|
| 1-6.2 | Protocol deviations | ENR | Type of deviation with specification and details; minor or major; reason if minor |
| 1-7 | Trial product administration | ENR | Diary Trial Drug Administration form |
| 1-8 | Treatment compliance | ENR | All related variables |
| 1-9.1 | Demographic data (Part 1) | ENR | Sex, age, race, ethnicity; height, weight; BMI (Demographics and Body Measurements forms) |
| 1-9.2 | Demographic data (Part 2)I: Women related information | ENR | Child-bearing potential; Pregnancy Test (Demographics and Pregnancy Test forms) |
| 1-10.1 | SBS characteristics and history (Part 1) | ENR | Type, severity and cause of SBS; Time since diagnosis of SBS and of underlying disease; Use of PS at Screening (SBS characteristics and history form) |
| 1-10.2 | SBS characteristics and history (Part 2) | ENR | Surgery (including time since most recent resection), remaining bowel sections and bowel lengths (SBS characteristics and history form) |
| 1-11 | Medical History/Concomitant Illness | ENR | Any medical condition or event; Medical condition or event; start date; Ongoing at screening; End date; Relatedness to SBS; MedDRA coding (Medical History/Concomitant Illness Header and cont. forms) |
| 1-12 | Medical history - SBS | ENR | Encephalopathy, ascites, cholestasis, steatosis and cirrhosis related variables<br>(Medical History – SBS form) |
| 1-13 | Substance Abuse | ENR | Substance Abuse form |
| 1-14 | Colonoscopy | ENR | Colonoscopy form |
| 1-15 | HIV, Hepatitis B and C | ENR | HIV, Hepatitis B and C form |
| 1-16 | Drinking Menu | ENR | Drinking Menu and Set Drinking Menu forms |

| No. | Title | Set | Variables to be included/Variables of the following form in the eCRF and corresponding derived variables |
|---|---|---|---|
| 1-17 | Physical examination at screening | ENR | Performed; Date; Systems assessed; Evaluation; Clinical Significance (Physical Examination form) |
| 1-18 | Parenteral Support Prescription | ENR | Parenteral Support Prescription form |
| 1-19.1 | Concomitant medication (Part 1) | ENR | ATC Levels including preferred name and code |
| 1-19.2 | Concomitant medication (Part 2) | ENR | CM Number; Indication; Dose (Concomitant Medication form) |
| 1-19.3 | Concomitant medication (Part 3) | ENR | Route of Administration; Specification other route of administration; Start and End of drug therapy; Therapy ongoing; Used pre-treatment;(Concomitant Medication Form); Concomitant medicationcategory (pre-treatment, at first dose, after first dose) |
| 1-20 | Formal fields (several parts) | ENR | |

| No. | Title | Set | Variables |
|---|---|---|---|
| **Efficacy Evaluation and Other Variables** | | | |
| 2-1 | Primary endpoint and key secondary endpoint | ENR | Visit; Analysis Visit; Absorption of wet weight/fluids; Change from baseline to Week 24 in absorption of wet weight/fluids;<br>Absorption of energy; Change from baseline to week 24 in absorption of energy |
| 2-2.1 | Absorption of wet weight/fluids by visit (eCRF) | ENR | Visit; Wet weight intake (oral solid food and oral fluid); Wet weight output (urine and feces); (Metabolic Balance Study Efficacy Data (24Hr) form) |
| 2-2.2 | Absorption of energy by visit (eCRF) | ENR | Visit; Energy Metabolism: energy intake; Energy Metabolism: energy output; (Metabolic Balance Study Efficacy Data (24Hr) form) |
| 2-3.1 | Absorption of individual macronutrients by visit | ENR | Visit; Analysis Visit; Absorption of individual macronutrients: *Macronutrient* [g/d]; Change from baseline in Absorption of individual macronutrients: M*acronutrient* [g/d];<br><br>Note: *Macronutrient* is one of Carbohydrate, Lipids, Proteins |
| 2-3.2 | Absorption of individual macronutrients by visit (eCRF) | ENR | Visit; Macronutrients: *Macronutrient* [g/d] intake; Macronutrients: *Macronutrient* [g/d] fecal output;<br><br>Note: *Macronutrient* is one of Carbohydrate, Lipids, Proteins (Metabolic Balance Study Efficacy Data (24Hr) form) |
| 2-4.1 | Absorption of electrolytes by visit | ENR | Visit; Analysis Visit; Absorption of individual Electrolytes: *Electrolyte* [g/d]; Change from baseline in Absorption of individual Electrolytes: *Electrolyte* [g/d];<br><br>Note: *Electrolyte* is one of Sodium, Potassium, Calcium, Magnesium |

| | | | |
|---|---|---|---|
| 2-4.2 | Absorption of electrolytes by visit (eCRF) | ENR | Visit; Electrolytes: *Electrolyte* [mmol/d] intake; Electrolytes: *Electrolyte* [mmol/d] output;<br><br>Note: *Electrolyte* is one of Sodium, Potassium, Calcium, Magnesium (Metabolic Balance Study Efficacy Data (24Hr) form) |
| 2-5.1 | Metabolic Balance Study Day 1 (Formal Fields) | ENR | Metabolic Balance Study Day 1 form |
| 2-5.2 | Metabolic Balance Study Day 2 (Formal Fields) | ENR | Metabolic Balance Study Day 2 form |
| 2-5.3 | Metabolic Balance Study Day 3 (Formal Fields) | ENR | Metabolic Balance Study Day 3 form |
| 2-5.4 | Metabolic Balance Study Day 4 (Formal Fields) | ENR | Metabolic Balance Study Day 4 form |
| 2-6 | Registration of drinking and urine volumes | ENR | Registration of drinking and urine volumes form |
| 2-7.1 | Diary Parenteral Support Use | ENR | Diary Parenteral Support Use/Volume form and Diary PS use form |
| 2-7.2 | Weekly parenteral support volume by visit (SBS-IF only) | ENR | Visit; Analysis Visit; Weekly parenteral support volume and corresponding change from baseline<br><br>Note: Only patients with SBS-IF |
| 2-8 | Content of Parenteral Support | ENR | Content of Parenteral Support form |
| 2-9 | Parenteral Support Prescription | ENR | Parenteral Support Prescription form |
| 2-10 | Parenteral Support Adjustment | ENR | Parenteral Support Adjustment form |
| 2-11 | Weekly parenteral support macronutrients by visit (SBS-IF only) | ENR | Visit; Analysis Visit; Macronutrient: Carbohydrates [kjoule], Macronutrient: Lipids [kjoule], Macronutrient: Proteins [kjoule], Macronutrient: Total content [kjoule] and corresponding changes from baseline<br><br>Note: Only patients with SBS-IF |

| | | | |
|---|---|---|---|
| 2-12 | Weekly parenteral support electrolytes by visit (SBS-IF only) | ENR | Visit; Analysis Visit; Electrolyte: Sodium [mmol], Electrolyte: Potassium [mmol], Electrolyte: Magnesium [mmol] and corresponding changes from baseline<br><br>Note: Only patients with SBS-IF |
| 2-13 | Body weight [kg] by visit | ENR | Visit; Analysis Visit; Body weight [kg] and corresponding change from baseline |
| 2-14 | Body composition by dual-energy X-ray absorptiometry (DEXA) by visit | ENR | Visit; Analysis Visit; Lean body mass [kg], Fat mass [kg], Bone mineral content [kg] and corresponding changes from baseline |
| 2-15 | Body composition by dual-energy X-ray absorptiometry (DEXA) by visit (eCRF) | ENR | Visit; further variables from DEXA scan form |
| 2-16 | Citrulline and Aldosterone by visit | ENR | Visit; Analysis Visit; Citrulline, Aldosterone and corresponding changes from baseline<br><br>Note: Only analysis visits baseline, week 12, 24 and 52 |
| 2-17 | Estimated glomerular filtration rate (eGFR) and creatinine clearance by visit | ENR | Visit; Analysis Visit; eGFR, Creatinine Clearance and corresponding changes from baseline<br><br>Note: Only analysis visits baseline, week 12, 24 and 52 |
| 2-18 | Liver function by visit | ENR | Visit; Analysis Visit; ALT, AST, ALP, Albumin, Bilirubin and corresponding changes from baseline<br><br>Note: Only analysis visits baseline, week 12, 24 and 52 |
| 2-19 | Patient's global impression of change (PGIC) by visit | ENR | Visit; Analysis Visit; Patient's global impression of change |
| 2-20.1 | SBS-impact scale (SBS-I) by visit | ENR | Visit; Analysis Visit; Items 1 to 8 and corresponding changes from baseline |
| 2-20.2 | PRO: EQ-5D-5L Domains by visit | ENR | Visit; Analysis Visit; Domain values and corresponding changes from baseline |

| | | | |
|---|---|---|---|
| 2-20.3 | PRO: EQ-5D-5L Current Health Visual Analogue Scale and EQ-5D-5L Index by visit | ENR | Visit; Analysis Visit; Current Health Visual Analogue Scale and Index value and corresponding changes from baseline |
| 2-21.1 | Pharmacokinetic Analysis: Concentrations by visit | ENR | Visit; Concentrations of parent drug, metabolite M1, metabolite M2 and glepaglutide |
| 2-21.2 | Pharmacokinetic parameter $C_{trough}$ concentrations by visit | ENR | Visit; Analysis visit; $C_{trough}$ concentrations of parent drug, metabolite M1, metabolite M2 and glepaglutide |
| 2-22 | Luminal- and mucosae-associated microbiota of patients with SBS by visit | ENR | Visit; Analysis Visit; Luminal- and mucosae-associated microbiota and corresponding changes from baseline |
| 2-23.1 | Urinary excretion of electrolytes and urea by visit | ENR | Visit; Analysis Visit;<br>Urinary excretion of Sodium [mmol/d], Potassium [mmol/d], Calcium [mmol/d], Magnesium [mmol/d]; Urea [mmol/d] and corresponding changes from baseline |
| 2-23.2 | Urinary excretion of electrolytes by visit (eCRF) | ENR | Visit;<br>Urinary excretion of Sodium [mmol/d], Potassium [mmol/d], Calcium [mmol/d], Magnesium [mmol/d]; Urea [mmol/d]; Creatinine [mmol/d]<br>(Metabolic Balance Study Efficacy Data (24Hr) form) |
| 2-24 | Fluid composite effect [L/d] by visit | ENR | Visit; Analysis Visit; Fluid composite effect [L/d] and corresponding change from baseline |
| 2-25 | Drinking volume during 48-hour periods by visit | ENR | Visit; Analysis Visit; Drinking volume during 48-hour periods and corresponding change from baseline |
| 2-26 | Weekly days on parenteral support by visit (SBS-IF only) | ENR | Visit; Analysis Visit; Weekly days on parenteral support and corresponding change from baseline<br><br>Note: Only patients with SBS-II |

| | | | |
|---|---|---|---|
| 2-27 | Urine output by visit (SBS-II only) | ENR | Visit; Analysis Visit; Urine output, corresponding change from baseline and corresponding change from Week 24<br><br>Note: Only patients with SBS-II |

| No. | Title | Set | Variables |
|---|---|---|---|
| **Safety** | | | |
| 3-1 | Adverse events | ENR | Variables from Adverse event form |
| 3-2 | Adverse events of special interest (AESI) | ENR | Variables from Adverse Event of Special Interest form |
| 3-3 | Adverse drug reactions (ADR) | ENR | see Listing 3 - 1 |
| 3-4 | Serious adverse events and deaths | ENR | see Listing 3 - 1 |
| 3-5 | Adverse events leading to permanent discontinuation of study treatment | ENR | see Listing 3 - 1 |
| 3-6 | Pre-treatment adverse events of all patients included into the study | ALL | see Listing 3 - 1 |
| 3-7 | Other important events | ENR | Other Important Event form |
| 3-8.1 | Vital signs by visit: blood pressure and pulse rate | ENR | Visit; Values and corresponding changes from baseline |
| 3-8.2 | Vital signs by visit: body temperature | ENR | Visit; Values and corresponding change from baseline; Temperature Location (Vital signs form) |
| 3-9 | Body weight by visit | ENR | Visit; Values and corresponding change from baseline (Weight form) |
| 3-10 | Safety laboratory: Formal fields | ENR | Formal fields and sampling dates and time for Hematology, Biochemistry; Urine dipstick test; Citrulline; Aldosterone; Anti-drug antibodies; Urinalysis (Laboratory Assessment form) |
| 3-11.1-3-11.10 | Laboratory parameters (hematology) by visit<br>- Hemoglobin [mmol/L]<br>- Hematocrit [vol.fr]<br>- Red blood cell count [x10^12/L]<br>- White blood cell count with differential: [x10^9/L]<br>- Neutrophils [x10^9/L]<br>- Lymphocytes [x10^9/L]<br>- Monocytes [x10^9/L]<br>- Eosinophils [x10^9/L]<br>- Basophils [x10^9/L]<br>- Platelet Count [x10^9/L] | ENR | Visit; Value; Unit; Lower and upper reference limit Valid; Change from baseline |

| | | | |
|---|---|---|---|
| 3-12.1-<br>3-12.28 | Laboratory parameters (biochemistry) by visit<br>• Sodium [mmol/L]<br>• Potassium [mmol/L]<br>• Chloride [mmol/L]<br>• Bicarbonate [mmol/L]<br>• Blood Urea Nitrogen [mmol/L]<br>• Creatinine [umol/L]<br>• Creatinine Clearance (estimated) [mL/min]<br>• Glucose [mmol/L]<br>• Calcium [mmol/L]<br>• Phosphorous [mmol/L]<br>• ALP (alkaline phosphatase) [U/L]<br>• ALT (alanine aminotransferase) [U/L]<br>• AST (aspartate aminotransferase) [U/L]<br>• INR<br>• Gamma-glutamyl transferase (GGT) [U/L]<br>• Lactic dehydrogenase [U/L]<br>• Conjugated bilirubin [umol/L]<br>• Unconjugated bilirubin [umol/L]<br>• Total bilirubin [umol/L]<br>• Total protein [g/L]<br>• Albumin [g/L]<br>• Amylase [U/L]<br>• Uric acid [mmol/L]<br>• C-reactive protein [mg/L]<br>• Cholesterol, measured orally fasting [mmol/L]<br>• Triglycerides, measured orally fasting [mmol/L]<br>• Magnesium [mmol/L]<br>• Zinc [umol/L] | ENR | Visit; Value; Unit; Lower and upper reference limit; Valid; Change from baseline |
| 3-13.1-<br>3-13.5 | Laboratory parameters (urinalysis - by dipstick) by visit<br>• Blood [x10^6/L]<br>• Glucose [mmol/L]<br>• Leukocytes [x10^6/L]<br>• pH<br>• Protein [g/L] | ENR | Visit; Value; Unit; Lower and upper referencelimit NR;Valid; Change from baseline |

| | | | |
|---|---|---|---|
| 3-14.1-<br>3-14.6 | Laboratory parameters (urinalysis) by visit<br>- Sodium<br>- Potassium<br>- Calcium<br>- Magnesium<br>- Urea<br>- Creatinine | ENR | Visit; Value and corresponding change from baseline; further related variables |
| 3-15 | Laboratory parameters aldosterone and citrulline by visit | ENR | Visit; Value and corresponding change from baseline; further related variables |
| 3-16.1-<br>3-16.6 | Electrocardiogram parameters by visit<br>- Heart rate [beats/min]<br>- PR [msec]<br>- QRS [msec]<br>- QT [msec]<br>- QTcF [msec]<br>- RR [msec] | ENR | Visit; Date; Value and corresponding change from baseline (ECG [12-Lead] form) |
| 3-16.7 | Electrocardiogram by visit - Overall assessment | ENR | Visit; Date; Interpretation; Clincal Significance (ECG [12-Lead] form) |
| 3-16.8 | Electrocardiogram by visit – Additional ECD | ENR | Visit; Date; ECG performed due to AE or other; AE ID (Additional ECG form) |
| 3-17.1 | Immunogenicity Assessments by visit<br>- Anti-glepaglutide antibodies<br>- Reactivity to M2 (ZP1848_1-34)<br>- Cross-reactivity to GLP-2<br>- Glepaglutide neutralizing antibodies | ENR | All related variables |
| 3-17.2 | Immunogenicity Assessments – By patient<br><br>*Note: Only patients with any evaluable ADA sample.* | ENR | Patient with pre-existing ADA; ADA positive patient; treatment boosted ADA positive patient; treatment induced ADA positive patient; |
| 3-17.3 | Immunogenicity Assessments – By Visit<br><br>*Note: Only patients with any evaluable ADA sample.* | ENR | Visit; ADA positive by sample; treatment-boosted ADA by sample; treatment induced ADA by sample; |

| | | | |
|---|---|---|---|
| 3-17.4 | Immunogenicity Assessments – Titer levels by visit<br><br>*Note: Only patients with any evaluable ADA sample.* | ENR | Visit; Date; Anti-glepaglutide antibodies (ADA); Reactivity to M2; Cross-reactivity to glucagon-like peptide [GLP]-2; Glepaglutide neutralizing antibodies (NAb) |
| 3-17.5 | Immunogenicity Assessments – Fold increase [%] in titer levels from baseline by visit<br><br>*Note: Only patients with any evaluable ADA sample.* | ENR | Visit; Date; Anti-glepaglutide antibodies (ADA); Reactivity to M2; Cross-reactivity to glucagon-like peptide [GLP]-2; Glepaglutide neutralizing antibodies (NAb) |
| 3-18 | Physical examination by visit | ENR | Performed; Date; Systems assessed; Evaluation; Clinical Significance (Physical Examination form) |

NOTE: The wording may be adapted in the final output, also some listings may be split into two or more parts if they do not fit on the page, and several listings may be combined where reasonable depending on size.

## List of Figures

Analysis Sets:
FAS = Full Analysis Set
PPS = Per-Protocol Set

| No. | Title/Content | Type | Analysis Set |
|---|---|---|---|
| **Primary and Key Secondary Endpoints** | | | |
| 2-1 | Primary Endpoint: Change from baseline to Week 24 in absorption of wet weight/fluids – Subject profile | Line chart | FAS/PPS |
| 2-2 | Key secondary endpoint: Change from baseline to week 24 in absorption of energy – Subject profile | Line chart | FAS/PPS |

## Modifications of Summary Tables and Data Listings for Interim Analysis

The following adaptations to the summary tables and data listings for the interim analysis will be done:

- Only data up to the individual cut-off date of Visit 9 – Week 24 – Day 4 will be shown.
- No summary tables will be produced for the per-protocol set.
- The title of summary tables which specify to show data after Week 24 will be adapted as for example for summary table 2-3.1.1:
    - Title as specified in Appendix A:

      Body weight [kg]: Change from baseline to Week 12, 24 and 52
    - Adapted title for interim analysis:

      Body weight [kg]: Change from baseline to Week 12 and 24
- The following summary tables will not be shown for the interim analysis:

| No. | Title/Content |
|---|---|
| 1-1.2 | Reasons for exclusion from per-protocol analysis set |
| 1-1.5.2 | Study duration: Follow-up visit performed |
| 1-2.3.1 | Protocol violations - Overview |
| 1-2.3.2 | Protocol violations - Details |
| 1-2.4 | Compliance with time window for Week 52 (EOT) for completers |
| 2-3.13.1 | Drinking volume during 48-hour periods: Change from Week 24 to 52 |
| 2-3.14 | Weekly parenteral support volume: Change from baseline to Week 52 (SBS-IF only) |
| 2-3.15.1 - 2-3.15.7 | Weekly parenteral support macronutrients and electrolytes (SBS-IF only): Change from baseline to Week 52<br>- Macronutrient: Carbohydrates [kjoule]<br>- Macronutrient: Lipids [kjoule]<br>- Macronutrient: Proteins [kjoule]<br>- Macronutrient: Total content [kjoule]<br>- Electrolyte: Sodium [mmol]<br>- Electrolyte: Potassium [mmol]<br>- Electrolyte: Magnesium [mmol] |

- The following summary tables will have an adapted content and title for the interim analysis:

| No. | Title/Content |
|---|---|
| 1-1.4 | (IA) Treatment duration until Visit 9: Duration of trial product administration until Visit 9 |
| 1-1.5.1 | (IA) Study duration until Visit 9: Last visit during treatment phase until Visit 9 |
| 1-4 | (IA) Drug exposure and treatment compliance until Visit 9 |
| 3-6.1 | (IA) Overall anti-glepaglutide antibody incidence until Visit 9 |
| 3-6.5.1 - 3-6.5.4 | (IA) Titer levels of treatment induced ADA positive (until Visit 9) patients by visit<br>- Anti-glepaglutide antibodies (ADA)<br>- Reactivity to M2<br>- Cross-reactivity to glucagon-like peptide [GLP]-2<br>- Glepaglutide neutralizing antibodies (NAb)<br><br>*Note: Only treatment induced ADA positive (until Visit 9) patients* |
| 3-6.6.1 - 3-6.6.4 | (IA) Titer levels of treatment boosted ADA positive (until Visit 9) patients by visit<br>- Anti-glepaglutide antibodies (ADA)<br>- Reactivity to M2<br>- Cross-reactivity to glucagon-like peptide [GLP]-2<br>- Glepaglutide neutralizing antibodies (NAb)<br><br>*Note: Only treatment boosted ADA positive (until Visit 9) patients* |
| 3-6.7.1 - 3-6.7.4 | (IA) Fold increase [%] in titer levels of treatment boosted ADA positive (until Visit 9) patients from baseline by visit<br>- Anti-glepaglutide antibodies (ADA)<br>- Reactivity to M2<br>- Cross-reactivity to glucagon-like peptide [GLP]-2<br>- Glepaglutide neutralizing antibodies (NAb)<br><br>*Note: Only treatment boosted ADA positive (until Visit 9) patients* |

- The following data listings will not be shown for the interim analysis:

| No. | Title |
|---|---|
| 1-3.2 | Completion of full study |
| 1-6.1 | Protocol deviations - overall |
| 1-6.2 | Protocol deviations |

- The following data listings will have an adapted content and title for the interim analysis:

| No. | Title | Set | Variables to be included/Variables of the following form in the eCRF and corresponding derived variables |
|---|---|---|---|
| 1-3.1 | (IA) Study completion until Visit 9 | ENR | Completion of treatment phase until Visit 9; Reasons for premature discontinuation before Visit 9 |
| 1-4.1 | (IA) Study duration until V9 | ENR | Last visit during treatment phase up to Visit 9; Withdrawal Date before Visit 9 |
| 1-4.2 | (IA) Treatment duration until Visit 9 | ENR | First and last trial product administration until Visit 9; Duration of trial product administration until Visit 9; Drug exposure until Visit 9 |
| 1-8 | (IA) Treatment compliance until Visit 9 | ENR | All related variables |