CLINICAL TRIAL PROTOCOL

Protocol Title: 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)

Protocol Number: ZP1848-20060

Substance: Glepaglutide

Trial Phase: 3b

Short Title: The long-term effect on intestinal absorption and safety of treatment with Glepaglutide in patients with short bowel syndrome

Acronym: EASE SBS 4

Sponsor Name: Zealand Pharma A/S

Legal Registered Address: Sydmarken 11, DK-2860 Søborg, Denmark

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SIGNATORY PAGE

Sponsor Signatory:

[redacted]
I am the Approver
06 Jul 2021 10:27:57 +02:00
cosign

[redacted] MD, PhD, Medical Director — Date

[redacted]
I am the Approver
06 Jul 2021 10:53:21 +02:00
cosign

[redacted] PhD, Senior Director, Biometrics — Date

[redacted]
Signing on behalf of
06 Jul 2021 11:21:46 +02:00
cosign

[redacted] Senior Clinical Trial Manager — Date

Investigator Signatory:

[redacted] Prof., MD, Ph.D — 09 JUL 2021 — Date

Medical Monitor Name and Contact Information will be provided separately.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Rationale

The purpose of the present phase 3b trial is to investigate the long-term effect on the intestinal absorption, nutritional status and the long-term safety of treatment with glepaglutide in patients with SBS.

The efficacy assessments in the ongoing phase 3 program are focused on the effects of glepaglutide on reduction of parenteral support (PS) volume and content in patients with SBS with intestinal failure (SBS-IF) with at least 3 days of PS at baseline. The present phase 3b trial serves to investigate the effect of glepaglutide on absorption of fluids, micro- and macro nutrients in patients with SBS with intestinal insufficiency (SBS-II) and SBS-IF employing the gold standard of metabolic balance studies.

Trial period

Estimated date first patient first visit (FPFV): Q3, 2021

Estimated date last patient last visit (LPLV): Q4, 2023

Objectives and Endpoints

Primary Objective

- To demonstrate the 24-week effect of glepaglutide on the absorption of fluids.

Secondary Objectives

- 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.

Exploratory Objectives

- 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.
- To investigate the microbiome composition of patients with SBS.
- To investigate the pharmacokinetics of glepaglutide.

Primary Endpoint

- Absorption of wet weight/fluids: Change from baseline to Week 24 assessed by 48-hour metabolic balance studies.

Secondary Endpoints

Key Secondary Endpoint

- Absorption of energy (oral intake minus fecal excretion): Change from baseline to Week 24 measured by 48-hour metabolic balance studies. Energy absorption is measured by bomb calorimetry.

Secondary Efficacy Endpoints

- Absorption of individual macronutrients (carbohydrates, lipids and proteins): Change from baseline to Week 24 measured by 48-hour metabolic balance studies.
- Absorption of electrolytes (sodium, potassium, calcium and magnesium): Change from baseline to Week 24 measured by 48-hour metabolic balance studies.
- For patients with SBS-IF only:
    - Weekly PS volume: Change from baseline to Week 12 and 24.
    - Weekly PS macronutrients (carbohydrates, lipids and proteins) and electrolytes (sodium, potassium, calcium, and magnesium): Change from baseline to Week 12 and 24.

Safety Endpoints

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

Exploratory Endpoints

- Body weight: Change from baseline to Week 12, 24 and 52.
- 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.
- Citrulline: Change from baseline to Week 12, 24 and 52.
- Aldosterone: Change from baseline to Week 12, 24 and 52.
- Estimated glomerular filtration rate (eGFR), creatinine clearance and liver function tests: Change from baseline to Week 12, 24 and 52.
- Hemoglobin A1c (HbA1c): Change from baseline to Week 4, 12, 24 and 52.
- Patient reported outcome (PRO) (patient's global impression of change [PGIC]). At Week 12**,** 24 and 52.
- PRO: SBS -impact scale (SBS-I) and EQ-5D-5L. Change from baseline to Week 12, 24 and to Week 52.
- Pharmacokinetic (PK) parameters ($t_{½}$ and C_{trough}).
- To investigate the luminal- and mucosae-associated microbiota of patients with SBS from baseline to Week 24.
- Urinary excretion of electrolytes (sodium, potassium, calcium, magnesium) and urea: Change from baseline to Week 24.
- Fluid Composite Effect: Change from baseline to Week 12, 24 and 52.
- Drinking volume during 48-hour periods: Change from Week 24 to 52.
- For patients with SBS-IF only:
    - Weekly PS volume: Change from baseline to Week 52.
    - Weekly PS macronutrients (carbohydrates, lipids and proteins) and electrolytes (sodium, potassium and magnesium): Change from baseline to Week 52.
    - Weekly days on PS: Change from baseline to Week 12, 24 and 52.

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

Overall Design

This is a single-center, single-arm, fixed dose, phase 3b trial to investigate the long-term effect on intestinal absorption and nutritional status and assess long-term safety of treatment with glepaglutide in patients with SBS.

The main inclusion criteria are:

- Age ≥ 18 years and ≤ 90 years at screening.
- Stable condition of SBS either with intestinal failure (IF) or intestinal insufficiency. For patients with SBS-IF, a stable condition is defined as < 25% change in PS volume or energy content for 4 weeks prior to screening.
- Stable body weight (<5% change in weight in the 3 months prior to screening).
- Wet weight of fecal excretion ≥1,500 g/day demonstrated during a hospital stay prior to screening.

The main exclusion criteria are:

- More than 2 SBS-related or PS-related hospitalizations (e.g., catheter-related bacteremia/sepsis, bowel obstruction, severe water-electrolytes disturbances, etc.) within 6 months prior to screening.
- Poorly controlled inflammatory bowel disease (IBD) that is moderately or severely active or fistula interfering with measurements or examinations required in the trial.
- Current bowel obstruction.
- Known radiation enteritis or significant villous atrophy, e.g., due to active celiac disease.
- Cardiac disease defined as: decompensated heart failure (New York Heart Association [NYHA] Class III-IV), unstable angina pectoris, and/or myocardial infarction within the last 6 months prior to screening.
- Any history of colon cancer. History of any other cancers (except margin-free resected cutaneous basal or squamous cell carcinoma or adequately treated in situ cervical cancer) unless disease-free state for at least 5 years.
- Use of GLP-1, GLP-2, human growth hormone (HGH), somatostatin, or analogs thereof, within 3 months prior to screening.

Number of Patients

A minimum of 6 and a maximum of 16 patients are planned to be enrolled in the trial (see Section 9.2). Patients with SBS-II and SBS-IF will be included in the trial, with an aim of an equal distribution between the 2 groups (see Section 5). A screen failure rate of 10% is expected, hence, a maximum of approximately up to 18 patients are expected to be screened.

Treatment Groups and Duration

This is a single-arm, fixed dose trial and all patients will receive the same treatment.

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

The trial treatment is provided in single-use autoinjector containing 0.5 mL of a clear, essentially colorless solution for injection, containing 20 mg/mL glepaglutide. Patients will receive 10 mg glepaglutide once-weekly as a subcutaneous injection.

Data Monitoring Committee

No Data Monitoring Committee will be established in this trial.

1.2 Flow Chart

Table 1 Flowchart

Procedure	Screening	Treatment Period											EoT	Follow-up
Visit	**SCR**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**FU**
Visit day or week		Day -3 to day 1 (W0)	W1	W2	W4	W8	W12	W16	W20	W24	W32	W40	W52	W56
Time window (days)	Up to 21 days before V1.		±2	±3	±5	±5	±5	±7	±7	±7	±14	±14	±14	±14
Visit type: Site (S), In-house (I)	S	I	S	S	S	S	S	S	S	I	S	S	S	S
General Assessments														
Informed consent	X[1]													
Inclusion and exclusion criteria	X	X[2]												
Dosing criteria		X												
Demography	X													
SBS characteristics and history	X													
Body weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height and BMI	X													
Medical history/concomitant illness[3]	X													
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety assessments														
ECG (12 lead)	X	X					X			X			X	X
Vital signs[4]	X	X					X			X			X	X
Physical examination[5]	X	X					X			X			X	X
Colonoscopy	X[6]													X
AE review	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory parameters														
Fasting requirement		X			X		X			X			X	X
HIV, Hepatitis B and C screening	X													

[1] Informed consent must be signed before any other trial-related activities.
[2] Eligibility criteria to be checked prior to initiating 48-hour Metabolic Balance Study.
[3] Also includes patient history of drug and/or alcohol abuse, information on smoking and current alcohol consumption. Concomitant illness to be divided into SBS-related or not.
[4] Pulse rate, blood pressure and body temperature.
[5] Full physical examination at Screening. At the other visits, an abbreviated examination will be performed driven by SBS.
[6] Patients with a remnant colon are required to have a colonoscopy as part of the screening procedures and the follow-up visit (Week 56). Colonoscopy results must be available for Visit 1. Colonoscopies performed up to 6 months prior to screening are acceptable. If a remnant colon is present, but a colonoscopy may not be appropriate, a computerized tomography (CT) scan, colon capsule endoscopy (CCE) or magnetic resonance imaging (MRI) will suffice at the discretion of the Investigator.

Procedure	Screening	Treatment Period											EoT	Follow-up
Visit	**SCR**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**FU**
Visit day or week		Day -3 to day 1 (W0)	W1	W2	W4	W8	W12	W16	W20	W24	W32	W40	W52	W56
Time window (days)	Up to 21 days before V1.		±2	±3	±5	±5	±5	±7	±7	±7	±14	±14	±14	±14
Visit type: Site (S), In-house (I)	S	I	S	S	S	S	S	S	S	I	S	S	S	S
Serum pregnancy test (hCG) (WOCBP only)	X	X			X	X	X	X	X	X	X	X	X	X
FSH[7]	X													
Urine dipstick test	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis		X								X				
Hematology, biochemistry[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Citrulline[9]		X			X		X			X			X	X
Aldosterone		X			X		X			X			X	X
Cholesterol and triglyceride		X								X			X	
ADA[10]		X			X		X			X			X	X
HbA1c		X			X		X			X			X	X
PK, See Table 3		X			X		X			X			X	X
Metabolic balance study														
Collection and measurement of urine, fecal output and food and liquids for analysis, see Table 2		X								X				
Efficacy														
PS regimen (patients with SBS-IF only)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Set drinking menu for 48-hour periods	X													
Registration of drinking and urine volumes during 48-hour periods[11]		X	X	X	X	X	X	X	X	X	X	X	X	X
DEXA scan		X					X			X			X	
Microbiome composition[12]		X								X				
Trial materials and reminders														
Dispensing of trial product		X					X			X		X		

[7] As needed in women of non-childbearing potential only. See additional information in Section 10.4.
[8] Magnesium and zinc should be measured at visit 1, 9 and 12 only.
[9] Blood samples for citrulline will be collected after a 10-hour (±1 hour) overnight fast (since app. 22:00h); water ad libitum is allowed. Smoking is not permitted the last 2 hours prior to blood sampling.
[10] ADA samples to be taken before dosing (if the dosing is on the day of site visit). A baseline sample must be taken pre-dose at day 1.
[11] 48-hour period assessments should be performed within 7 days before each visit, except for V1 and V9.
[12] Samples to be taken as soon as possible, but after 12:00 on day of admission, prior to the 48h balance study.

Procedure	Screening	Treatment Period											EoT	Follow-up
Visit	**SCR**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**FU**
Visit day or week		Day -3 to day 1 (W0)	W1	W2	W4	W8	W12	W16	W20	W24	W32	W40	W52	W56
Time window (days)	Up to 21 days before V1.		±2	±3	±5	±5	±5	±7	±7	±7	±14	±14	±14	±14
Visit type: Site (S), In-house (I)	S	I	S	S	S	S	S	S	S	I	S	S	S	S
Dispensing of instructions for use[13]		X					X			X		X		
Administration of trial product		X								X[14]				
Return of trial product							X			X			X	
Handout of diaries and urine measuring cups	X	X	X	X	X	X	X	X	X	X	X	X		
Collection of diaries		X	X	X	X	X	X	X	X	X	X	X	X	
Handout of patient card	X													
PGIC[15]							X			X			X	
SBS-I[15]		X					X			X			X	X
EQ-5D-5L[15]		X					X			X			X	X
End of treatment													X	
End of trial														X

ADA = anti-drug antibodies; AE = adverse event; BMI = body mass index; DEXA = dual-energy x-ray absorptiometry; ECG = electrocardiogram; EoT = End of Treatment; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HIV = human immunodeficiency virus; in-house = hospital admission at site; PGIC = patient's global impression of change; PK = pharmacokinetics; PS = parenteral support; SBS = short bowel syndrome; SBS-I = SBS impact scale; SBS-IF = SBS with intestinal failure; WOCBP = women of childbearing potential

[13] Patients to receive instructions orally and in writing.

[14] Trial product administration at visit 9 according to treatment schedule.

[15] Questionnaires must be completed at site visits prior to any other trial related assessment. It is recommended that the PGIC is completed first, followed by the SBS-I, then the EQ-5D 5L. All PROs are to be completed during treatment as indicated in the flowchart.

Table 2 Flowchart for 48-hour Metabolic Balance Study

	48-hour metabolic balance study (Visit 1 and Visit 9)			
Procedures	**Day 1**	**Day 2**	**Day 3**	**Day 4**
Admission to hospital	X (≥ 16 hours prior to metabolic balance samples collection start)			
Confirmation of eligibility	X (Visit 1 only)			
Adverse events	X	X	X	X
Concomitant medication	X	X	X	X
Physical examination	X			
ECG (12-lead)	X			
Vital signs (blood pressure, pulse rate, temperature)[1]	X	X	X	X
Body weight[1]	X	X	X	X
Biochemistry	X			
Hematology	X			
Urinalysis	X			
Serum pregnancy test (WOCBP only)	X			
Citrulline	X			
PK, see Table 3	X	X (Visit 9 only)	X (Visit 9 only)	X (Visit 9 only)
Aldosterone	X			
Cholesterol and triglyceride	X			
ADA[2]	X			
Fasting requirement (PS regimen allowed)	X (start 22:00h ±30min)	X (until start of MBS[3] collections)		
Urinate/ defecate/ empty stoma bag – prior to MBS collection start		X (-15 min)		
Urinate/ defecate/ empty stoma bag – end of study				X (-15 min)
Start of balance study collection		X		
Collection of urine		X	X	X
Collection of feces		X	X	X
Collection of duplicate food and liquids		X	X	X
End of collection				X (48h from start ±1 hour)
Confirm drinking menu	X (Visit 1 only)			
Fixed oral fluid intake		X	X	X
Define baseline PS type, volume, content[4]	X (Visit 1 only)			
DEXA scan[5]		X		
PGIC		X (Visit 9 only)		
SBS-I		X		
EQ-5D-5L		X		
Luminal- and mucosa-associated microbiota[6]	X			
Adjustment of PS (at visit 9 only, if applicable)				X
Trial product administration				X (Visit 1) [7]
Trial product dispensing				X
Hospital discharge				X

[1] Body weight and vital signs will be performed at the same time point each day, in the morning prior to breakfast and by 08:00 (±2 hour).
[2] ADA sample should be taken pre-dose at visit 1. At visit 9 the ADA sample should be taken as long time after last dose as possible and before next dosing during the admission.
[3] Metabolic Balance Study (MBS).
[4] Based on current weekly average PS volume.
[5] DEXA scan may be done on Day 2 or Day 3 to allow for study site flexibility.
[6] To be collected after 12:00 – preferably as close to 12:00 as possible. To be frozen at -80◦C as fast as possible.
[7] Trial product administration at visit 9 according to treatment schedule.

Table 3 Flowchart of PK sampling

Sample	Sampling time	V1	V4	V6	V9				V12 EoT	FU
					Day 1	Day 2	Day 3	Day 4		
PK	Prior to administration [1]	X	X	X	X	X	X	X	X	X
	Minimum 6 hours between samples on Visit 9, day 2 and day 3					X	X			

[1] To be collected prior to trial product administration if dosing occurs on the visit day.

2 INTRODUCTION

2.1 Trial Rationale

The purpose of the present phase 3b trial is to investigate the long-term effect on intestinal absorption, nutritional status and the long-term safety of treatment with glepaglutide in patients with SBS.

The efficacy assessments in the ongoing phase 3 program are focused on the effects of glepaglutide on reduction of PS volume and content in patients with SBS with intestinal failure (SBS-IF) with at least 3 days of PS at baseline. The present phase 3b trial serves to investigate the long-term effect of glepaglutide on absorption of fluids, nutrients, electrolytes, and trace elements in patients with SBS with intestinal insufficiency (SBS-II) and SBS-IF employing the gold standard of metabolic balance studies.

2.2 Background

Patients with SBS are characterized by reduced intestinal absorptive surface area due to extensive surgical bowel resection or congenital diseases, such as recurrent Crohn's disease or mesenteric vascular disease (1,2,3,4), resulting in decreased absorptive capacity of the gut (5). This causes a reduced uptake of nutrients, fluids, electrolytes, vitamins, and trace elements, leading to difficulties with maintaining metabolic balances when receiving a conventional diet (6). The malabsorption can lead to dehydration, malnutrition, and weight loss if left untreated (7).

Less severely affected SBS patients are able to compensate for their malabsorption by increasing oral intake (hyperphagia) and adapt metabolically or pharmacologically. These patients suffer from intestinal insufficiency (SBS-II). More severely affected patients with intestinal failure (SBS-IF) depend upon the safe and well-adjusted provision of PS of nutrients, fluids, electrolytes, vitamins, and trace elements to maintain body function, growth, homeostasis, and health (8). For those dependent on PS, it is life-sustaining but at the same time associated with life-threatening complications. Among those are catheter-related blood stream infections or sepsis (9), central vein thrombosis, liver damage (10), and renal impairment (11). In addition, the treatment burden of PS is substantial. Often 10-28 liters of PS per week are required. In addition to 10- to 12-hour overnight PS infusions in such patients, additional hours during daytime may be required to compensate for losses. While liberating patients during daytime, night-time infusions disturb sleep and exacerbate the need for nocturnal urination. Adding to the treatment burden, patients on PS often need frequent follow-up checks at the hospital, and for many there is a need for help from a homecare nurse.

Glucagon-like peptide (GLP)-2 is a specific pro-adaptive factor that plays a role in enhancing small intestinal mucosal morphology, function, and integrity both under normal as well as pathophysiological conditions. Exogenous GLP-2 induces significant growth of the small intestinal mucosal epithelium via the stimulation of stem cell proliferation in the crypts and inhibition of apoptosis on the villi (12). This trophic effect of GLP-2 has been observed in numerous species, including humans (13). Additional effects of GLP-2 include inhibition of gastric emptying and gastric acid secretion, stimulation of nutrient absorption, enhancement of intestinal barrier function, and increase in intestinal blood flow (13,14,15,16,17,18,19). The short half-life of native GLP-2 of 5-7 minutes in circulation is a major drawback for its use in a therapeutic setting, and with the approval of teduglutide (US: Gattex®, EU: Revestive®) for the

treatment of adult patients with SBS to improve intestinal absorption of fluids and nutrients, the therapeutic relevance of a GLP-2 analog in SBS has been established.

Glepaglutide is a potent, long-acting GLP-2 analog comprised of 39 L-amino acids, all of which are naturally occurring. Glepaglutide has 9 amino acid substitutions compared with native GLP-2 and a C-terminal structure inducing probe tail consisting of 6 lysines. The sequence similarity of the backbone is about 64% compared with native GLP-2.

When glepaglutide is injected into the subcutaneous (SC) compartment, 2 well-described and functionally active metabolites are formed ($ZP1848_{1-34}$ and $ZP1848_{1-35}$). Under steady-state conditions, the majority of the functional effect on the GLP-2 receptor derives from the main metabolite $ZP1848_{1-34}$, which accumulates during continued use. Thus, the pharmacokinetic (PK) profile and the pharmacological effects of glepaglutide are described and should be understood as a composite effect of the drug substance and its 2 metabolites.

Glepaglutide shows significantly protracted PK. The half-life after SC injection has been shown to differ for glepaglutide and its 2 main metabolites, with the longest half-life observed for the main metabolite $ZP1848_{1-34}$. This suggests that a SC depot is formed and that release of glepaglutide and metabolites from the depot into the systemic circulation is the rate-limiting step that governs the plasma half-life.

The efficacy of 3 weeks of treatment with glepaglutide was demonstrated in a phase 2 trial (trial ZP1848-15073) in a small number of stable SBS patients, where glepaglutide was shown to significantly improve fluid absorption and showed tendencies to improve absorption of macronutrients.

This phase 3b trial is being conducted to confirm the findings from the phase 2 trial, but after long-term treatment and investigate the safety and efficacy of glepaglutide on the amount of PS needed for patients to maintain a satisfactory hydration level.

Based on data from the phase 2 trial (ZP1848-15173) and the PK data from the phase 1 PK trial (ZP1848-16182), one dosing regimen of glepaglutide, 10 mg once-weekly, will be investigated (see Section 4.3 for the rationale for these doses).

For more information on glepaglutide, please refer to the Investigator's Brochure.

2.3 Benefit/Risk Assessment

Main benefits and risks are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of glepaglutide may be found in the Investigator's Brochure.

2.3.1 Risk Assessment

Overall Risk Profile
The results from clinical and non-clinical studies and the safety profile described to date do not give rise to specific safety concerns.

Specifically, the completed non-clinical chronic toxicity program raises no concerns in relation to the extended treatment period of the present trial. The evaluation of chronic toxicity included a study in rats receiving up to 1, 3, and 10 mg/kg/day glepaglutide for 26 weeks and a study in Beagle dogs receiving 0.25, 1, and 5 mg/kg/day glepaglutide for 39 weeks. In both studies, glepaglutide caused a range of findings in the intestinal tract that were attributable to its pharmacological action. In the study in rats, changes occurred in the liver and kidney, which

were likely physiological adaptations to high dose levels of the test material. The systemic no-observed-adverse-effect-level (NOAEL) in this study was therefore determined to 10 mg/kg/day. In the study in Beagle dogs, reduced weight gain was noted in females receiving the highest dose level of 5 mg/kg/day glepaglutide, and the systemic NOAEL in this study was therefore determined to 5 mg/kg/day in males and 1 mg/kg/day in females. Local irritation at the injection sites occurred at all dose levels in both studies. The identified NOAEL exposure level in rats and dogs is ≥86 and ≥48 times higher, respectively, than the expected maximum exposure level in this trial. The carcinogenic potential of glepaglutide has been tested in a mouse and a rat carcinogenicity study. Subcutaneous administration of glepaglutide to CD-1 mice for up to 104 weeks at doses up to 1.0 mg/kg/day, caused a range of findings in the intestinal tract that were attributable to its pharmacological action. There were no neoplastic findings due to treatment demonstrating that ZP1848 was not carcinogenic to the CD-1 mouse. Subcutaneous administration of glepaglutide to Wistar rats at doses up to 2.0 mg/kg/day for 104 weeks caused a range of findings in the intestinal tract that were attributable to its pharmacological action. Mucosal hypertrophy/hyperplasia is considered part of the continuum leading to adenoma and adenocarcinoma formation, and this was considered the cause for the presence of such tumors in the duodenum in a few males given 2.0 mg/kg/day (at exposure approx. 25 times higher than the expected maximum exposure level in this trial. Chronic inflammatory changes at the injection sites seen in both the mouse and the rat carcinogenicity study, resulting from repeated daily subcutaneous injection, occurred at all dose levels and led to an increased incidence of cutaneous pleomorphic fibrosarcomas in males. Pleomorphic fibrosarcomas are considered a group of largely undifferentiated or primitive sarcomas and are the most common type induced in rodents by repeated subcutaneous injection of agents not considered carcinogens (solutions of glucose and other sugars, sodium chloride, certain water-soluble food colourings and surfactants, carboxymethycellulose and macromolecular dextrans (20,21).

Glepaglutide was well tolerated at daily doses of up to 10 mg in the phase 2 trial ZP1848-15073 conducted in SBS patients. Consistent with the clinical setting, the most frequently reported AEs (reported in >20% of patients) in the phase 2 trial were nausea, abdominal pain, abdominal distension, vomiting, stoma complication, fatigue, dizziness, polyuria, decreased appetite, peripheral edema and cough. Treatment-emergent serious adverse events (SAEs) comprised 8 events, with no dose dependency or clustering of events being observed. Injection site reactions were dose dependent, mild to moderate in severity and transient by nature. The most frequently reported symptoms were itching and redness. No deaths were reported in this or any other trials with glepaglutide.

No specific safety issues were raised from the phase 1 clinical trial program; for further details please see the Investigator's Brochure.

In addition to the gastrointestinal tract, there are also GLP-2 receptors in the lung, brain, and hypothalamus (22). So far, clinically significant off-intestinal targeted effects resulting from these additional receptor sites have not been seen.

Experiences with native GLP-2 and teduglutide suggest that expected common AEs for this class of compounds include abdominal pain and distension, injection site reactions, nausea, headache, upper respiratory tract infection, and (in some studies) vomiting, and fluid overload (23).

Immunogenicity

Based on the current non-clinical and clinical knowledge of glepaglutide, the risk of immunogenicity (development of anti-drug antibodies [ADAs]) following administration of glepaglutide is considered high. However, longer-term clinical treatment is required to

investigate whether such a response will be transient or persistent. As no acute or non-acute AEs or effects on PK or pharmacodynamics have been linked to the immune response towards glepaglutide in the completed clinical trials, the effects and potential consequences of the anti-glepaglutide response are so far considered of minor criticality. Glepaglutide ADAs will be monitored in this trial, including their glepaglutide neutralizing potential and reactivity to the main glepaglutide metabolite ($ZP1848_{1-34}$), as well as cross-reaction with native GLP-2.

Cardiovascular Safety
No cardiovascular safety issues have been identified for glepaglutide. A concentration-response analysis of the potential of glepaglutide to cause QT prolongation ruled out any clinically concerning effect at the intended dose level, on which grounds a waiver for a dedicated TQT study was granted by the US Food and Drug Administration (FDA) in April 2018.

Patients with severe and acute cardiac disease are excluded from trial participation (see Section 5.2).

Neoplasms
GLP-2 stimulates development of colonic adenomas in rodent models (24,25,26). Increases in plasma citrulline concentrations as seen with GLP-2 analog treatment might promote growth of existing tumors in patients during long-term treatment. Although the risk of malignancy is hypothetical in humans and colonoscopy can be difficult in these patients, a baseline and a follow-up colonoscopy has been suggested for patients taking GLP-2 analogs who have residual colons (24,25,26). Therefore a screening colonoscopy (within 6 months prior to screening) and a Week 56 colonoscopy is a requirement for patients in the present trial, and patients with a pre-existing recent history of cancer (except for select, treated, and highly curable in situ cancers) are excluded from the trial. If a remnant colon is present, but a colonoscopy may not be appropriate, a computerized tomography (CT) scan, colon capsule endoscopy (CCE) or magnetic resonance imaging (MRI) will suffice at the discretion of the Investigator.

If a remnant colon is present, but not connected to the passage of foods and thereby dormant, a colonoscopy may not be appropriate and in this case a CT scan or MRI (if standard of care at site) will suffice at the discretion of the Investigator to document the absence of concerns regarding malignancy. These are considered adequate precautionary measures. Neoplasms (malignant and benign) are defined as adverse events of special interest (AESIs) for the trial.

Risk of Underdosing
The PK results and exposure-response analyzes for glepaglutide substantiates that once-weekly dosing of 10 mg glepaglutide results in glepaglutide concentrations within the therapeutically effective dose range. Regardless, a risk of inadequate dosing in individual patients receiving 10 mg glepaglutide once-weekly cannot be excluded.

2.3.2 Benefit Assessment

For the conducted dose-finding trial ZP1848-15073 testing glepaglutide in SBS patients with or without the need of PS, the primary endpoint of change in wet weight of ostomy/diarrhea output (‘wet weight output’) was chosen as the most direct measure of the impact of glepaglutide on intestinal absorption. The trial met its primary efficacy endpoint by showing statistically significant and clinically relevant reductions in wet weight of ostomy/diarrhea output (‘wet weight output’) with glepaglutide dosed 1 mg/day (estimated reduction of 592 g/day; p=0.002) and 10 mg/day (estimated reduction of 833 g/day; p=0.0002). Results for wet weight absorption

and urine weight supported the results for the primary endpoint, with statistically significant improvements demonstrated for 1 mg/day and 10 mg/day glepaglutide. In addition, absorption of macronutrients increased in the combined 1+10 mg and 1 mg dose groups, and improvements were observed for absolute absorption of sodium and potassium at the higher glepaglutide dose levels. In conclusion, the phase 2, dose-finding trial of glepaglutide in SBS patients showed consistent and clinically relevant benefit for 1 mg/day and 10 mg/day glepaglutide in improving intestinal function. For further efficacy results please see the Investigator's Brochure for glepaglutide.

Patients receiving glepaglutide treatment in the present phase 3b trial are likely to experience similar or better improvements in intestinal function.

2.3.3 Overall Benefit: Risk Conclusion

In conclusion, the benefit-risk ratio for the proposed glepaglutide treatment regimen is considered favorable for the intended trial population, and potential risks are considered appropriately handled and mitigated.

3 OBJECTIVES AND ENDPOINTS

Table 4 Objectives and Endpoints.

Objectives	Endpoints
Primary	
1. To demonstrate the 24-week effect of glepaglutide on the absorption of fluids.	1. Absorption of wet weight/fluids: Change from baseline to Week 24 assessed by 48-hour metabolic balance studies.
Secondary	
Secondary Objectives 1. To assess the effects of glepaglutide on absorption of energy, absorption of the individual macronutrients and absorption of electrolytes. 2. To evaluate the long-term efficacy of glepaglutide in patients with SBS. 3. To describe the long-term safety of glepaglutide.	**Key Secondary endpoint:** 1. Absorption of energy (oral intake minus fecal excretion): Change from baseline to Week 24 measured by 48-hour metabolic balance studies. Energy absorption is measured by bomb calorimetry. **Secondary efficacy endpoints:** 2. Absorption of individual macronutrients (carbohydrates, lipids and proteins): Change from baseline to Week 24 measured by 48-hour metabolic balance studies. 3. Absorption of electrolytes (sodium, potassium, calcium and magnesium): Change from baseline to Week 24 measured by 48-hour metabolic balance studies. <u>For patients with SBS-IF only:</u> 4. Weekly PS volume: Change from baseline to Week 12 and 24. 5. Weekly PS macronutrients (carbohydrates, lipids and proteins) and electrolytes (sodium, potassium and magnesium): Change from baseline to Week 12 and 24. **Safety endpoints:** 6. Treatment-emergent AEs until follow-up at Week 56. 7. Immunogenicity (anti-glepaglutide antibodies, reactivity to $ZP1848_{1-34}$, cross-reactivity to glucagon-like peptide [GLP]-2, glepaglutide neutralizing antibodies) at baseline (W0), Week 4, 12, 24, 52, and 56.
Explorative	
Exploratory objectives 1. To investigate the effect of treatment with glepaglutide on nutritional status, organ function and fluid balance. 2. To investigate the effect of treatment with glepaglutide on patient reported outcomes.	**Exploratory endpoints** 1. Body weight: Change from baseline to Week 12, 24 and 52. 2. Body composition (lean body mass, fat mass and bone mineral content) by DEXA: Change from baseline to Week 12, 24 and 52. 3. Citrulline: Change from baseline to Week 12, 24 and 52. 4. Aldosterone: Change from baseline to Week 12, 24 and 52.

3. To investigate the microbiome composition of subjects with SBS. 4. To investigate the pharmacokinetics of glepaglutide.	5. Estimated glomerular filtration rate (eGFR), creatinine clearance and liver function tests: Change from baseline to Week 12, 24 and 52. 6. HbA1c: Change from baseline to Week 4, 12, 24 and 52. 7. PRO: patient's global impression of change (PGIC). At Week 12**,** 24 and 52. 8. PRO: SBS -impact scale (SBS-I) and EQ-5D-5L. Change from baseline to Week 12, 24 and to Week 52. 9. Pharmacokinetic (PK) parameters ($t_{½}$ and C_{trough}). 10. To investigate the luminal- and mucosae-associated microbiota of patients with SBS from baseline to Week 24. 11. Urinary excretion of electrolytes (sodium, potassium, calcium, magnesium) and urea: Change from baseline to Week 24. 12. Fluid Composite Effect: Change from baseline to Week 11, 24 and 52. 13. Drinking volume during 48-hour periods: Change from Week 24 to 52. <u>For patients with SBS-IF only:</u> 14. Weekly PS volume: Change from baseline to Week 52. 15. Weekly PS macronutrients (carbohydrates, lipids and proteins) and electrolytes (sodium, potassium and magnesium): Change from baseline to Week 52. 16. Weekly days on PS: Change from baseline to Week 12, 24 and 52. <u>For patients with SBS-II only:</u> 17. Urine output: Change from baseline to Week 12, 24 and 52.

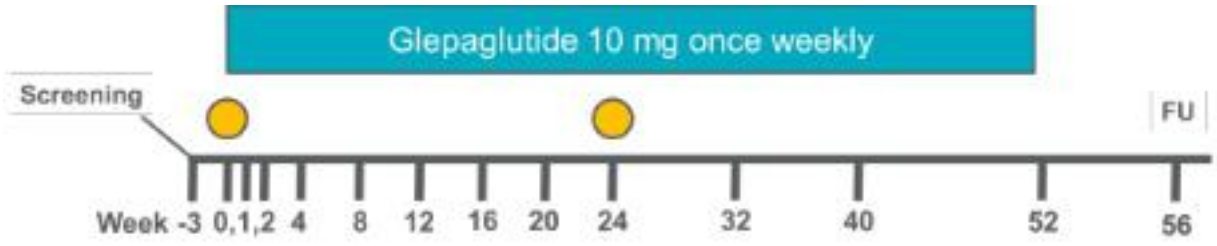
4 TRIAL DESIGN

4.1 Overall Design

This is a single-center phase 3b trial investigating the long-term effect on intestinal absorption and nutritional status and long-term safety of treatment with glepaglutide in patients with SBS.

It is planned to enroll a minimum of 6 and a maximum of 16 patients for the trial, where enrollment is defined as receiving trial product.

The overall trial design is presented in Figure 1.



The orange circles represent 48-hour in-house metabolic balance studies. Visits are indicated with lines and the week number from Visit 1 is indicated.

Figure 1 Overall Trial Design

The trial consists of a screening period, a treatment period and a follow-up period.

After signing informed consent, patients will be screened for initial confirmation of eligibility. The screening procedures should be performed within 3 weeks prior to Visit 1 (baseline).

At Visit 1, eligible patients will complete a 48-hour in-house (admission to the hospital, at site) baseline metabolic balance study as well as other baseline assessments, where after they will start treatment with glepaglutide 10 mg once-weekly for 52 weeks. The treatment period covers 12 visits at the week numbers indicated in Figure 1.

All patients will have in-house stays for 48-hour metabolic balance studies at baseline and at Visit 9; see Figure 1. During the in-house periods, they must follow an individual drinking menu, but may vary the food intake according to their own choice.

All patients will have a 48-hour period scheduled before each Visit (except Visit 1 and 9 where balance studies are done), during which they must record their fluid intake and urine output. During the screening phase, all patients need to construct an individual fixed drinking menu to be kept during all 48-hour "pre-visit" periods until Visit 9. The same individual drinking menu will be followed during both scheduled in-house 48-hour metabolic balance studies (at Visit 1 and 9). After Visit 9, the patients are no longer restricted to a fixed drinking menu during the 48-hour periods, but they should instead drink an amount that reflects their preferred or habitual fluid intake. They must only drink the same fluid items as in the drinking menu and must record their intake as well as their urine output. Patients receiving PS (patients with SBS-IF) will have their PS adjusted based on an algorithm which will be used at each visit (see section 8.2.9).

A follow-up visit will be performed 4 weeks after end of treatment.

For each patient the trial period will be a maximum of 59 weeks.

4.2 Scientific Rationale for Trial Design

The purpose of the present phase 3b trial is to investigate the long-term effect on the intestinal absorption, nutritional status and the long-term safety of treatment with glepaglutide in patients with SBS.

The efficacy assessments in the ongoing phase 3 program are focused on the effects of glepaglutide on reduction of PS volume and content in patients with SBS-IF with at least 3 days of PS at baseline. The present phase 3b trial serves to investigate the direct effect of glepaglutide on absorption of fluids, nutrients, electrolytes, and trace elements in patients with SBS-II and SBS-IF.

Balance studies quantify weight, volume, as well as the content of energy, macronutrients and electrolytes of oral intake (i.e. food and fluid intake) and of the output (i.e. ostomy output, diarrhea and urine production). Balance studies are acknowledged as the "gold standard" to measure intestinal function and the methods used have been published (27). Metabolic balance study is a comprehensive method, and the laboratory of the Department of Gastroenterology and Hepatology at Rigshospitalet is one of the few centers of excellence in the world holding the equipment and expertise to perform these metabolic balance studies. The trial site has become internationally recognized for its pioneering role and its significant contribution to evidence-based treatment options within the field of intestinal failure. In a patient group as SBS, having a severe compromised intestinal absorption that may require PS, the ability to quantify intestinal absorptive function of wet weight, energy, macronutrients (carbohydrate, fat, protein), and electrolytes (sodium, potassium, calcium and magnesium), provides the clinician with options to tailor an individual nutritional and medical strategy for patients. Implementing the metabolic balance study in a clinical trial setup is a unique opportunity to test the efficacy of a medical therapy on the intestinal function. The principle of this clinical trial is to perform a "baseline" metabolic balance study leading up to the first administration of trial product. The "treatment" metabolic balance study is then repeated after a period of treatment. In this trial, the primary and key secondary endpoints will be captured after 24 weeks of treatment with glepaglutide 10 mg once-weekly.

Intestinal wet weight absorption is an important clinical outcome for patients with SBS. Efficacy on intestinal wet weight absorption and nutritional status of GLP-2 and its analogs has until this trial been limited to short-term clinical trials of 3-4 weeks treatment periods (28,29). For the first time, this trial will investigate the effect of long-term treatment with a GLP-2 analog on intestinal absorption, nutritional status and long-term safety in patients with SBS. The primary objective of the trial has therefore been chosen as the 24-week effect of glepaglutide on the absorption of fluids. Key secondary endpoint of this trial was chosen as the intestinal absorption of energy (oral intake minus fecal excretion) measured at Week 24 of treatment with glepaglutide.

The documentation of glepaglutide's effects on intestinal energy absorption obtained in this glepaglutide single-center, single-arm, fixed dose, phase 3b trial is expected to directly contribute to the regulatory filing and support the medical communication both pre- and post-launch of the product. During glepaglutide treatment, patients with SBS-IF will have less need of PS and micronutrients. The long-term effects of the reduced amount of PS on body equilibrium, body weight, body composition and other organ functions are unknown.

Patients will be screened to exclude those recently hospitalized more than twice due to SBS or related to PS, those with uncontrolled IBD, those with a history of cancer (except resected cutaneous basal or squamous cell carcinoma and in situ cervical cancer) unless it can be

documented that the patient has been in a disease-free state for at least 5 years and other disorders that may put the patient at an increased risk. Patients with any history of colon cancer are not allowed to enter the trial. Additionally, patients with a remnant colon are required to have a colonoscopy according to local standard practice performed as part of the screening procedures, and at the follow-up visit. If patients had a colonoscopy performed within the last 6 months prior to screening as part of the standard of care of the disease, results from this will be acceptable. If a remnant colon is present, but not connected to the passage of foods and thereby dormant, a colonoscopy may not be appropriate and in this case a CT scan, CCE or MRI will suffice at the discretion of the Investigator to document the absence of concerns regarding malignancy.

During treatment with trial product, patients will be carefully monitored for AEs, vital signs, and laboratory abnormalities. As no acute or non-acute AEs have been linked to the immune response to glepaglutide so far, samples for ADA will be analyzed following the last patient's last visit. Additionally, an internal Safety Committee (see Section 10.1.6) will routinely review safety data to monitor and ensure patient safety.

4.3 Justification for Dose

The selected dose for this trial is 10 mg glepaglutide once-weekly for 52 weeks. The selected dose is considered supported with respect to both safety and efficacy, as described below.

4.3.1 Safety

The safety of the proposed dose is supported by the outcome of the completed clinical trials, which showed that single SC administrations up to 20 mg and total weekly doses of 10 mg, 70 mg or 140 mg all appeared well tolerated. No safety issues were raised in these trials, which included maximum plasma concentration (C_{max}) and overall exposure levels well above those proposed for this phase 3b trial. From a safety perspective, once-weekly SC injections of 10 mg glepaglutide is therefore considered to be an appropriate dose level for testing in phase 3b.

4.3.2 Efficacy

Using the data from the glepaglutide PK trial ZP1848-16182, the average steady-state plasma concentration in the dosing interval (C_{avg}) and the associated 90% prediction interval can be calculated for 10 mg glepaglutide dosed once-weekly (based on observed data). These average plasma concentrations and associated 90% prediction intervals are shown superimposed on the exposure-response curve established for the phase 2 primary endpoint in supporting that once-weekly dosing of 10 mg glepaglutide results in glepaglutide concentrations within the therapeutically effective dose range (see Figure 2).

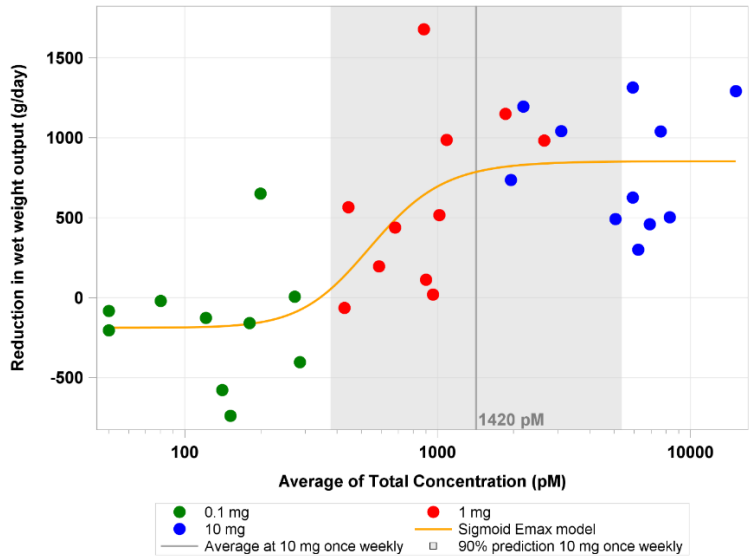


Figure 2 Exposure-Response Curve

Investigating the assumption that a minimum plasma concentration is needed to drive efficacy, the analysis predicts that a once-weekly dosing regimen of 10 mg glepaglutide would result in plasma concentrations within the therapeutically effective range for several days after dosing, but possibly falling below the therapeutically effective level during the latter phase of each weekly dosing interval. This dosing regimen is expected to result in a therapeutically relevant overall effect based on the current knowledge of biological activities related to GLP-2 receptor activation.

4.4 End of Trial Definition

A patient is considered to have completed the trial when he or she has completed trial product treatment for 52 weeks and completed both metabolic balance study periods (at Visit 1 and 9) as well as the final safety assessments at Visit 12 and completed the follow-up visit (week 56).

The end of the trial is defined as the date of the last visit (follow-up visit) of the last patient in the trial.

5 TRIAL POPULATION

The patient population selected for this trial must have SBS with intestinal insufficiency or intestinal failure. Since patients with SBS-II compensate with an increased oral intake of fluid and food, they can have as large fecal output as patients with SBS-IF. Thus, fecal output is important to assess in both patients with SBS-II and SBS-IF.

The impact of SBS on quality of life seems to depend on the degree of malabsorption and thus the need for PS: the higher the need for PS, the greater negative impact of SBS on quality of life. Hence, for the population of patients with SBS-IF there exists an unmet need for medical treatment to reduce the burden of malabsorption and PS.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Patients are eligible to be included in the trial only if all of the following criteria apply:

1. Informed consent obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2. Age ≥ 18 years and ≤ 90 years at screening.
3. Willing to comply with trial procedures, including 2 in-house visits with urine and fecal output collection.
4. Stable condition of SBS either with intestinal failure (IF) or intestinal insufficiency. For patients with SBS-IF a stable condition is defined as < 25% change in PS volume or energy content for 4 weeks prior to screening.
5. Stable body weight (<5% change in weight in the 3 months prior to screening).
6. Wet weight of fecal excretion ≥1,500 g/day demonstrated during a hospital stay prior to screening*.

*If inclusion criteria #6 cannot be met, a visit may be scheduled where fecal output collected at home by the patient or during a hospital stay can be assessed. If the wet weight of fecal excretion ≥1,500 g/day can be demonstrated, the criterion #6 is met.

5.2 Exclusion Criteria

Patients are excluded from the trial if any of the following criteria apply:

<u>General</u>

1. Current, or within 30 days prior to screening, participation in another interventional clinical trial that includes administration of an active compound.
2. Mental incapacity or language barriers which preclude adequate understanding or cooperation, or unwillingness to comply with trial requirements.
3. Previous participation in this trial. Participation is defined as having received trial product.
4. Females of childbearing potential, who are pregnant, breast-feeding, intend to become pregnant or are not using highly effective contraceptive methods. Male patients with female partners, who intend to become pregnant.

Medical history and concomitant diseases

5. More than 2 SBS-related or PS-related hospitalizations (e.g., catheter-related bacteremia/sepsis, bowel obstruction, severe water-electrolytes disturbances, etc.) within 6 months prior to screening.
6. Poorly controlled inflammatory bowel disease (IBD) that is moderately or severely active or fistula interfering with measurements or examinations required in the trial.
7. Current bowel obstruction.
8. Known radiation enteritis or significant villous atrophy, e.g., due to active celiac disease.
9. Cardiac disease defined as: decompensated heart failure (New York Heart Association [NYHA] Class III-IV), unstable angina pectoris, and/or myocardial infarction within the last 6 months prior to screening.
10. Clinically significant abnormal electrocardiogram (ECG) as judged by the Investigator.
11. Human immunodeficiency virus (HIV) positive, acute liver disease including positive results for Hepatitis B antigens (HBsAg) and Hepatitis C (HCV), or unstable chronic liver disease.
12. Any history of colon cancer. History of any other cancers (except margin-free resected cutaneous basal or squamous cell carcinoma or adequately treated in situ cervical cancer) unless disease-free state for at least 5 years.
13. Hepatic impairment defined as:
    a. Total bilirubin ≥ 2 × the upper limit of normal (ULN), or
    b. Aspartate aminotransferase (AST) ≥ 5 × ULN, or
    c. Alanine aminotransferase (ALT) ≥ 5× ULN
14. Use of GLP-1, GLP-2, human growth hormone (HGH), somatostatin, or analogs thereof, within 3 months prior to screening.
15. Known or suspected hypersensitivity to glepaglutide, its components or related products.
16. Use of dipeptidyl peptidase (DPP)-4 inhibitors within 3 months prior to screening.
17. Surgical resection of gut tissue within 6 months prior to screening.
18. Systemic immunosuppressive therapy for treatment of the gastrointestinal tract that has been introduced or has been unstable within 3 months prior to screening.
19. Unstable biological therapy (e.g. anti-TNF-α, natalizumab, etc.) within 6 months prior to screening, including significant changes in doses or switch of drug.

5.3 Lifestyle Consideration

5.3.1 Dietary Restrictions

The patients must follow an individual ‘drinking menu’ (which will be set during the screening phase) on the days of the metabolic balance study during hospital admissions (Visit 1 and Visit 9) as well as on the days of 48-hour urine collection at home prior to each visit up to and including Visit 9. The drinking menu starts on the same day as the 48-hour pre-visit urine collection, and lasts for a total of 48 hours (see Section 8.2.2).

Fasting is required for blood sampling for citrulline, cholesterol and triglycerides (see Section 8.2.13). Fasting is defined as no intake of food or drinks, except water, for at least 10 hours (±1 hour) (since app. 22:00h) the day before the blood sampling. PS administration is allowed.

For other laboratory tests, fasting is optional.

5.3.2 Smoking

Smoking is not permitted the last 2 hours prior to blood sampling for citrulline (see Section 8.2.13).

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently assigned to trial intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reason(s), eligibility criteria, and any SAE. A screen failure rate of 10% is expected.

Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.5 Dosing Criteria

The first dose of trial product must only be administered after the baseline metabolic balance study as well as all other baseline assessments are completed at Visit 1.

To be eligible for dosing, all inclusion criteria must be met and none of the exclusion criteria.

Re-sampling is not allowed if the patient has failed any of dosing criteria related to laboratory parameters. However, in case of technical issues (e.g. hemolysed or lost), re-sampling is allowed for the affected parameters.

6 TREATMENTS

6.1 Treatment Administered

The trial product for the trial is described in Table 5.

Table 5 Trial Product

Trial Product Name	Glepaglutide 20 mg/mL
Dose Formulation	Solution for injection
Unit Dose Strength	10 mg/0.5mL
Dosage Level	10 mg once-weekly
Route of Administration	SC injection
Sourcing	By Sponsor
Packaging and Labeling	Trial product will be provided in single-use autoinjectors containing 0.5 mL of 20 mg/mL glepaglutide (clear, essentially colorless solution). Each autoinjector and box will be labeled in accordance with Annex 13, country and trial requirements.
Storage	Store in refrigerator between 2°C – 8°C. Protect from light

Additional details regarding the trial product can be found in the trial materials manual.
Each dispensing unit/pen is uniquely numbered with a dispensing unit number.

6.1.1 Trial product administration

Patients must choose their preferred injection site area; either on their abdomen or their thigh(s). Unless otherwise agreed with the Investigator, patients must use this selected injection site area during the entire trial. The specific injection site must be rotated for each weekly injection such that the injections are administered at least 5 cm away from the last injection administered, and still within the same injection site area, i.e., abdomen or thigh. It is acceptable to inject in one thigh or both thighs during the treatment period. Only patients eligible for treatment must use trial product and only delegated site staff must dispense or administer trial product. No trial product may be dispensed to any person not enrolled in the trial.

6.2 Handling/Storage/Accountability

6.2.1 Handling and Storage

The Sponsor will provide trial product for each patient for the duration of his/her participation in the trial. The Investigator, or designee will dispense trial product at each dispensing visit. A sufficient quantity of trial product will be dispensed to assure that the patient has sufficient trial product supply to last at least until the next scheduled drug dispensing visit. The Investigator, or designee must ensure that no patient uses expired trial product at any time.

Patients will be familiarized with the handling and use of the autoinjector prior to the first administration of trial product, and as needed at the site. The Investigator must document that Instructions for use are given to the patient verbally, and in writing at all dispensing visits (as specified in the flowchart).

The Investigator must maintain an accurate record of the shipment and dispensing of trial product.

The Investigator or designee must instruct the patient in what to return at next visit to the clinic.

All returned (used and unused), expired or damaged trial products (for technical complaint samples, see section 8.4.8) must be stored separately from non-allocated trial products and can be done at room temperature. No temperature monitoring is required.

In case the Investigator, the site staff, or the monitor suspect that the trial drug is defective or potentially defective, the Sponsor should be contacted immediately.

6.2.2 Accountability

The Investigator must ensure that a designated person receives trial product deliveries from the Sponsor or designee and that all such deliveries are:

- Recorded
- Handled and stored safely and properly
- Returned to sponsor or designee, as required

The Investigator or designee must keep drug inventory and accountability logs of which a copy must be given to the Sponsor at the end of the trial. An accurate record of the date and amount of trial product dispensed to and returned from each patient must be available for inspection at any time. The inventory log will include details of the trial product received and dispensed to the patient. All used and unused autoinjectors and the dispensing cartons must be kept and returned to the monitor who will perform reconciliation of delivery records and accountability logs. Discrepancies between the amount of trial drug received, dispensed and returned will be verified.

Patients should be instructed to bring all their trial product including the dispensing cartons to each scheduled trial visit. Investigator or delegated staff must perform drug accountability with the patient at every visit to the clinic. Returned trial product (used or unused autoinjectors and the dispensing cartons) must be stored separately from non-allocated trial product.

The Investigator must not destroy any used or unused trial product supplies. At the conclusion of the trial (or by agreement with Sponsor during the trial if storage capacity at site is limited) the Investigator will return all used and unused trial drug and the dispensing cartons to the Sponsor.

6.3 Measures to Minimize Bias: Randomization and Blinding

This is a single-arm, fixed dose trial and all patients will receive the same treatment. No randomization and blinding will be performed.

The primary and key secondary endpoints are addressing the absorptive capacity of the intestines and are thus objective. They are derived from laboratory measurements of the input and output during the balance studies. To minimize bias on the wet weight absorption, fluid intake during the balance study is restricted to a drinking menu.

Adjustment of PS for patients with SBS-IF, will be done according to an algorithm that takes the urine output at baseline and during the 48h periods along with the current PS into account. This will limit the bias of the open-label design.

6.4 Treatment Compliance

6.4.1 Drug Treatment Compliance

Throughout the trial, the Investigator will remind the patients to follow the trial procedures and requirements to encourage patient compliance.

During the trial, patients will mainly self-administer trial product at home. The first dose will be administered at the trial site.

Patients are requested to enter details regarding trial product administration (including date and time of the day as well as dispensing unit number) and injection site area used (i.e., abdomen, thigh) in the diary and transcribed to the eCRF.

Patients are to record PS use (including bag name, volume and infusion date) in the diary on an ongoing basis, and must be checked and transcribed into the eCRF at every visit by the Investigator.

When patients self-administer trial product at home, compliance with trial product administration will be assessed and documented in source documents at each visit where information is available. If any suspicion of non-compliance arises, the site must start a dialogue with the patient, re-emphasizing the importance of compliance, uncover barriers to compliance, and re-train the patient, if needed. This dialogue must be documented. Compliance will be assessed by cross-checking the following sources and comparing these to the expected use:

- Drug accountability information; visual inspection of returned autoinjectors
- Review of patient diaries

The Investigator must ensure that patients who temporarily discontinue treatment with trial product due to safety concerns, e.g. admission to hospital, are resuming treatment safely to avoid dehydration.

Missed Doses of Trial Drug

Patients should not omit planned doses. Patients who miss a scheduled dose of trial product should be instructed to administer the missed dose as soon as they become aware of the mistake; however, 2 doses should not be administered the same day.

6.4.2 Compliance with 48-hour Drinking Menu

Compliance to the drinking menu in association with the at-home 48-hour urine collection prior to each visit (up to and including Visit 9) will be assessed by review of patient diaries, where the patients will record their fluid intake (see Section 8.2.2).

6.5 Concomitant Therapy

Medications commonly used to treat SBS symptoms including anti-diarrhea agents are allowed during trial participation; however, changes (start, stop, new brands, or dose changes) should be kept to a minimum and the Medical Monitor be informed on the indication for the change via reporting in the eCRF.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) other than the trial product that the patient has taken within 7 days

prior to and including the screening visit, or receives during the trial must be recorded along with:

- Trade name or generic name
- Indication
- Dates of administration including start and stop dates
- Dose (total daily), unit and route of administration

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE, then this must be reported according to Section 8.4.

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

6.6 Prohibited Medication

GLP-1 analogs, GLP-2 analogs (teduglutide), HGH, DPP-4 inhibitors, and somatostatins are not allowed to be used by patients during the course of the trial.

Medications commonly used to treat SBS symptoms including anti-diarrhea agents are allowed during trial participation; however, changes (start, stop, new brands, or dose changes) should be kept to a minimum and the reason for the change should be recorded in in eCRF. Any changes to concomitant medications must be documented in the eCRF.

6.7 Dose Modification

Not applicable.

6.8 Treatment After the End of the Trial

When discontinuing trial product (Visit 12), the patient should be treated according to the standard of care at the discretion of the Investigator or treating physician.

7 DISCONTINUATION OF TRIAL PRODUCT AND PATIENT WITHDRAWAL

7.1 Discontinuation of Trial Treatment

Treatment of a patient may be discontinued at any time during the trial at the discretion of the Investigator for safety reasons. However, the patient can still continue, and should be encouraged to stay in the trial if assessed safe according to the Investigator.

Efforts must be made so that patients continue to attend and complete all scheduled visit procedures to the extent possible. Patients should stay in the trial regardless of compliance with trial drug, assessments, or visit schedule. The Investigators should make a special effort to ensure that all patients complete the assessment for the primary and key secondary endpoints.

Patients must be educated about the continued scientific importance of their data, even if they discontinue trial product.

A patient must be discontinued from trial treatment if:

1. Any safety concerns or AEs that in the opinion of the Investigator might place the patient at unacceptable risk, including any deterioration of a patient's health state, especially in terms of the frequency and volume of total PS.
2. Any malignancy.
3. Increased liver values, defined as:
    a. ALT or AST >3 times baseline value lasting more than 2 weeks*, or
    b. ALT or AST >5 × ULN and total bilirubin >2 x ULN*, or
    c. ALT or AST >5 × ULN and international normalized ratio (INR) >1.5*, or
    d. ALT or AST >5 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)*

    * where no other etiology exists.
4. Pregnancy or intention to become pregnant.
5. The patient requires treatment with prohibited medications (see Section 6.6).

Patients can be discontinued from trial treatment if:

- A patient was enrolled despite it was later identified that some of the inclusion or exclusion criteria were violated. The Investigator must discuss with the Sponsor's Medical Monitor if it is safe for the patient to continue the trial treatment. If a patient prematurely discontinues trial treatment, the primary reason must be specified in the eCRF. If the patient continues in the trial without trial treatment, the intent should be to follow the patient to the extent possible according to the planned visit schedule and assessments with the purpose of following the safety and efficacy of the patients. Reason for visits not having been performed must be documented.

7.2 Patient Withdrawal from the Trial

A patient may withdraw from the trial at any time at his/her own request (withdrawal of consent). The patient's request to withdraw from the trial must always be respected. A patient may be withdrawn at any time at the discretion of the Investigator for safety reasons.

A patient must be withdrawn if any of the following applies:

- Withdrawal of informed consent
- Safety concerns or AEs that in the opinion of the Investigator might place the patient at unacceptable risk for further participation in this trial or would likely make the patient unable to carry out the full trial
- Sponsor closure of the trial
- Pregnancy or intention of becoming pregnant

IMPORTANT: Efforts must be made to have the patients to attend the Week 52 end of treatment visit (EoT) and the Week 56 follow-up visit (FU) where all general, safety, and laboratory assessments should be performed as detailed in the flowchart (see section 1.2).

Final drug accountability must be performed even if the patient is not able to come to the site.

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such withdrawal.

If a patient withdraws from the trial, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site trial records.

Although a patient is not obliged to give his/her reason(s) for withdrawing, the Investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the 'end of trial' form in the eCRF.

All data collected from a withdrawn patient prior to withdrawal and during the final visit will be included in the analyses of the trial data. Although a patient is not obliged to give his/her reason(s) for withdrawing consent, the Investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights. An end of trial form must be completed and final drug accountability done even when patients are not able to come for a trial visit. Only patients who withdraw their consent will be considered as withdrawn from the trial.

7.2.1 Replacement of Patients

Patients who discontinue trial product or withdraw from the trial will not be replaced.

7.3 Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the trial site.

8 TRIAL ASSESSMENTS AND PROCEDURES

- The following sections describe the trial assessments and procedures, while their timing is summarized in the flowchart (see Section 1.2).
- Informed consent must be obtained before any trial-related activity, see Section 10.1.4.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all inclusion criteria and none of the exclusion criteria.
- The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reason for screen failure, as applicable.
- At screening, patients will be provided with a patient card stating that they are participating in a trial and giving contact details of relevant site staff that can be contacted in case of emergency.
- Adherence to the trial design requirements, including those specified in the flowchart, is essential and required for trial conduct.
- Patients will be provided with patient diaries to register administrations of trial product, PS use (SBS-IF only) as well as fluid intake and urinary output during 48-hour periods prior to site visits.
- Review of patient diaries, PRO questionnaires, ECG, laboratory reports etc. must be documented either on the documents or in the patient's source documents. If clarification of entries or discrepancies in the patient diary or PRO questionnaires is needed, the patient must be questioned, and a conclusion made in the patient's source documents. Care must be taken not to bias the patient.
- During the trial, blood samples will be collected from all patients for efficacy, safety, PK and ADA assessments. The total blood volume drawn per patient amounts to a maximum of approximately 530 mL, including all assessments described in Sections 8.2 and 8.3. The samples are collected over a period of approximately 59 weeks (1 year and 1.5 months).
- Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 (see section 10.2) for further details on laboratory samples.

8.1 Demographics and Other Baseline Characteristics

8.1.1 Demographics

Demographic information to be collected includes date of birth, gender, race, and ethnicity.

8.1.2 SBS Characteristics and History

Information about the patient’s SBS includes the following characteristics:

- The underlying cause of SBS
- Date of diagnosis of underlying disease
- Date of SBS diagnosis

- Remaining bowel sections [30]; whether patient has a colon-in-continuity (jejuno-colic anastomosis/SBS anatomical group 2, jejuno-ileo-colic anastomosis/SBS anatomical group 3, or other), an end-jejunostomy/SBS anatomical group 1, ileostomy/SBS anatomical group 1, or colostomy, presence of ileocecal valve, the surgery dates and reason(s) for resection, this includes the most recent resection
- Bowel lengths; length of the remnant small bowel, the remnant colon in percent (according to Cummings classification [31])
- Severity of SBS based on the ESPEN Functional and Clinical Classification of Chronic Intestinal Failure (8)
- Date that the patient started PS, if applicable

8.1.3 Body Weight and Height

Body weight (kg with 1 decimal accuracy) will be measured at all visits. Height (cm) will be measured at screening only.

Weight will be measured on a calibrated scale. Patients should wear light clothing and no shoes. Stoma bags should be emptied prior to the measurement.

Patients should be encouraged to measure their body weight at home weekly to detect potential signs of fluid retention early (before edema becomes readily visible). If the weight changes, patients should be instructed to call the site for guidance.

8.1.4 Medical History/Concomitant Illness

Medical history information to be collected includes all ongoing conditions and relevant/significant medical history (including all major hospitalizations and surgeries).

Details of whether the patient suffered from any of the following will be recorded: Encephalopathy, ascites, cholestasis, steatosis, and/or cirrhosis. If yes, the outcome / histopathologic diagnosis and date of histopathologic diagnosis will be recorded.

Concomitant illness must also be captured and noted as to relatedness to SBS.

The patient's history of drug and/or alcohol abuse, information on tobacco smoking (never smoker (<100 cigarettes or equivalent /lifetime), current smoker, or former smoker) and current alcohol use will also be captured.

8.1.5 Concomitant Medication

All prescription and non-prescription medications taken within 7 days prior to and including the screening visit will be recorded in the eCRF. Any changes to concomitant medications that occur throughout the trial will be recorded (see Section 6.5).

All relevant previous treatments, including treatment with teduglutide, any other GLP-2 analogs or native GLP-2 are recorded in the eCRF.

8.1.6 Colonoscopy

Patients with a remnant colon are required to have a colonoscopy as part of the screening procedures and the follow-up visit (Week 56). Colonoscopy results must be available for Visit 1. Colonoscopies performed up to 6 months prior to screening are acceptable. If a remnant colon is

present, but a colonoscopy may not be appropriate, a CT scan, CCE or MRI will suffice at the discretion of the Investigator.

8.1.7 COVID-19 Management

The COVID-19 pandemic is expected to exist during the conduct of the trial. In case the situation worsens, the following mitigating actions may be implemented, as applicable:

- Site visits (Visit 2 and forward) can be converted to phone/video calls to obtain and record information about:
    - AEs
    - Body weight (patient´s home scale is acceptable)
    - Procedures and changes to concomitant medication
    - Urine and blood samples for safety assessments (may be collected at a local community laboratory, patient´s general practitioner or by a home nurse at the Investigator´s discretion)
    - Pregnancy, planned pregnancy and missed menstruation, if any. For females of childbearing potential a pregnancy urine dipstick kit will be shipped to patient's home from the site.
    - Adherence to PS regimen in the diary (see Section 6.4.1) as per standard practice (including volume, and content) and modify weekly PS volume and schedule in accordance with section 8.2.9 in the protocol.

- PROs**:**
    - Copies of PGIC, SBS-I and EQ-5D-5L questionnaires can be sent to the patients for completion, including the standard instructions for how to complete, date, and sign. The instructions include among other things the following notes; It is important the SBS-I is completed by the patient without assistance of family members.
    - Patients should:
        - Fill in the PROs and complete the questionnaires on the same day as the remote visit is scheduled, but prior to the site visit call.
        - Send a copy of completed PROs to site for review and entry into eCRF.
        - Bring original documents to site at next possible visit. These documents will be source data to be verified at that point. If source data is lost, then copies received will suffice.

- Trial product can be sent directly from the site to the patient's home
- Visit 9 can be postponed, until on-site visit is possible again. After 24 weeks of treatment, the patient will be in a stable treatment, and postponing the visits is not expected to affect the assessments
- The EoT visit can be postponed (time window can be extended up to + 8 weeks)

Deviations from the protocol caused by circumstances related to the pandemic will be documented. Handling of data affected by the pandemic situation will, if applicable, be addressed in the statistical analysis plan.

8.2 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the flowchart (Section 1.2). Assessment of the primary and key secondary endpoints will be based on metabolic balance studies, described in Section 8.2.1. During the metabolic balance studies, as well as before trial visits, the patients will adhere to an individual fixed drinking menu, described in Section 8.2.2, associated with measurements of urine volume, described in Section 8.2.3.

8.2.1 Metabolic Balance Study

The metabolic balance study measures the total intake and output of energy, macronutrients (lipids, carbohydrates, proteins [nitrogen as a marker]) and micronutrients. The oral diet intake (i.e. food and fluids) are assessed by duplicate meals and liquids by quantification of weight, volume, as well as the content of energy, macronutrients and electrolytes. During the metabolic balance study, the patients will collect duplicate portions of all intake solid and liquid in buckets covering 24-hour periods. Likewise, all output (i.e. ostomy output, diarrhea and urine production) will be collected and quantified. The content of the buckets will be weighed, processed into dry matter by laboratory techniques and subsequently analyzed at the site's local laboratory.

Before the metabolic balance study is started, a fixed drinking menu will be set which will be followed for the metabolic balance study at Visits 1 and 9 (see Section 8.2.2).

The 48-hour metabolic balance study will start at 8:00 in the morning. If the patient receives PS at baseline, the 48 hours should preferably cover a day on PS (first day) and a day off PS.

The procedure for the metabolic balance study is listed below:

- The laboratory technician will inform the patient about collection of diet and liquid intake, urine and feces and hand out bottles and buckets that will be used for the collection.
- The collection will be performed for 48 hours.
- The patient will collect oral diet intake corresponding to the type and amount ingested. Wrapping paper, plum stones, chicken bones and similar will not be collected.
- Each day, bottles and buckets will be picked up by the laboratory technician.

Table 6 specifies the samples collected.

Table 6 Sample Collection during Metabolic Balance Study

Sample	To be collected in	Handling and storage
Urine	Bottle	No special handling or precautions
Feces	Bucket	Feces will be stored in a freezer
Oral liquid intake	Bottle	No special handling or precautions
Oral food intake	Bucket	No special handling or precautions

The content of the bottles/buckets will be weighed, processed into dry matter by laboratory techniques and subsequently analyzed at the laboratory. Details of the techniques used are published (32).

The analyses performed on the collected material are presented in Table 7.

Table 7 Analyzes on Collected Material in Metabolic Balance Study

Analysis	Samples	Method
Weight/volume	Urine, feces, food an liquid	Weight/measuring cylinder
Energy content	Feces, food and liquid	Bomb calorimetry
Fat (aliphatic compounds)	Feces, food and liquid	Titration
Carbohydrates	Feces, food and liquid	Englyst's method (33)
Nitrogen (as a marker of protein)	Urine, feces, food and liquid	Kjeldahl's method (34)
Sodium and potassium	Feces, food and liquid	Flame photometry
Calcium and magnesium	Feces, food and liquid	Atomic absorptiometry
Sodium, potassium, calcium, magnesium, urea, creatinine	Urine	• Sodium (potentiometri) • Potassium (potentiometri) • Calcium (calculated as a product of the urine calcium concentration and 24h urine volume) • Magnesium (calculated as a product of the urine magnesium concentration and 24h urine volume) • Urea (calculated as a product of the urine carbamide concentration and 24h urine volume) • Creatinine (absorption photometry)

8.2.2 Fixed Fluid Intake

The oral liquid intake should be kept constant during the metabolic balance study, ensuring that potential changes in any output measurements are not caused by changes in liquid intake. Therefore, during the screening phase, patients will be instructed to in detail documenting their 24-hour fluid intake, specifying sort (water, tea, milk, coffee etc.), amount (mL) and time of intake.

The patients must follow their drinking menu on metabolic balance study days during hospital admissions (Visit 1 and Visit 9) and during the 48-hour pre-visit urine collection periods at home prior to each visit, excluding Visit 1 and 9. As stated above, the drinking menu starts on the same day/time as the 48-hour pre-visit urine collection, and lasts for a total of 48 hours. After Visit 9, the patients are no longer restricted to a fixed drinking menu during the 48-hour periods, but they should instead drink an amount that reflects their preferred or habitual fluid intake. They must only drink the same fluid items as in the drinking menu and must record their intake as well as their urine output.

Solid oral food intake is unrestricted and may be varied according to the patients' own choice.

8.2.3 48-hour Urine Volume

Urine volume will be recorded by the patient in his or her patient diary during the defined 48-hour measurement periods prior to a trial visit and transcribed to the eCRF. During this time the patient must adhere to the individually predefined drinking menu (up to Visit 9, see Section 8.2.2). The patient will be provided with urine measuring cups.

The 48-hour urine volume measurements should occur as close as possible to and within 7 days of the coming site visit. For patients with SBS-IF the measurements should be timed with the PS schedule. Patients on PS 7 days weekly must perform the 48-hour measurement on 2 consecutive

days on PS. Patients on PS 1-6 days weekly must record the 48-hour measurement at 1 day on PS and 1 day off starting on the day on PS.

See Table 8 for further clarity. The grey boxes indicate the possible 48-hour urine measurement periods. If more than 1 interval is available anyone of them can be chosen.

The patient should perform the 48-hour measurement on the same days of the week during each period as long as the PS regimen remains the same. The selected days will be recorded in the patient diary. If the PS regimen changes during the trial, a new schedule for 48-hour measurement can be chosen.

Table 8 Timing of 48-hour periods and balance studies

PS days/ Week	48-hour measurement	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
7 days	2 days on PS	1	2	3	4	5	6	7
6 days	1 day on PS + 1 day off PS	1	2	3	4	5		6
5 days	1 day on PS + 1 day off PS	1		2	3	4		5
4 days	1 day on PS + 1 day off PS	1		2		3	4	
3 days	1 day on PS + 1 day off PS	1		2		3		
2 days	1 day on PS + 1 day off PS	1				2		
1 day	1 day on PS + 1 day off PS	1						
0 days	2 days off PS							

8.2.4 Patient Diary

Patients will be required to complete diaries throughout the course of the trial. Patients will record the following:

- Details regarding trial product administration, including date and time of the day as well as injection site area used, i.e. abdomen or thigh
- PS use (SBS-IF only) including bag name, volume and infusion date on an ongoing basis
- Urine volume and oral fluid intake will be recorded by the patient during the defined 48-hour periods prior to a trial visit
    - The patient should perform the 48-hour measurement on the same days of the week during each period as long as the PS regimen remains the same. The selected days will be recorded in the patient diary.
- If the PS regimen changes during the trial, a new schedule for 48-hour measurement can be chosen and recorded in the patient diary

The Investigator (or designee) must review the patient´s diary entries routinely throughout the entire trial period. If clarification of entries or discrepancies in the diary is needed, the patient must be questioned, and a conclusion made in the patient's medical record and in the diary. Care must be taken not to bias the patient.

8.2.5 Absorption of Wet Weight/Fluids

During both 48-hour metabolic balance studies (Visit 1 and Visit 9), the duplicate meal and liquid intake and the total excretion of stomal output and/or diarrhea will be collected and weighed. Absorption of wet weight/fluids is calculated as oral intake (liquid and solid) minus fecal output. Absolute intestinal wet weight absorption (g/day) = oral wet weight intake (liquid and solid) – fecal wet weight output. Changes from baseline to Week 24 (Visit 9) will be measured.

8.2.6 Absorption of Energy

During both 48-hour metabolic balance studies (Visit 1 and Visit 9) the processed dry matter for the duplicate meal and all liquid intake and the fecal output will be analyzed for energy content by bomb calorimetry. Absorption of energy is measured as oral intake (liquid and solid) minus fecal output. Changes from baseline to Week 24 (Visit 9) will be measured.

8.2.7 Absorption of Macronutrients

During both 48-hour metabolic balance studies (Visit 1 and Visit 9), the processed dry matter for the duplicate meal and all liquid intake and the fecal output will be analyzed for macronutrients: fat by titration, carbohydrate by Englyst's method (33) and nitrogen by Kjeldahl's method (34). Energy will be assessed by bomb calorimetry. Absorption of macronutrients is measured as oral intake (liquid and solid) minus fecal output. Changes from baseline to Week 24 (Visit 9) will be measured.

8.2.8 Absorption of Electrolytes

During both 48-hour metabolic balance studies (Visit 1 and Visit 9), the homogenized wet weight of the duplicate meal and all liquid intake and the fecal output will be analyzed for electrolytes. Absorption of electrolytes is measured as oral intake (liquid and solid) minus fecal output. Changes from baseline to Week 24 (Visit 9) will be measured.

8.2.9 Weekly PS Volume (SBS-IF Only)

During the trial, PS volume and content will be regulated according to changes in urine output, weight change and clinical symptoms of fluid overload. During the second part of the trial, this will be based on a 48-hour measurement without a fixed drinking menu. Changes from baseline to Week 12 (Visit 6), Week 24 (Visit 9) and Week 52 (Visit 12) will be measured.

Requirement for PS volume reduction:

IF: daily urine volume of the current visit is at least 10% higher than baseline urine volume.

Quantity of PS volume reduction:

THEN: New PS volume (weekly) = Current PS volume (weekly) – 7 x absolute increase in daily urine volume.

Example:

Patient received so far 10 L of PS per week. The urine output has increased from 1300 mL per day to 1500 mL per day. Hence, the urine output has increased by more than 10% and PS volume should be reduced. The new weekly PS volume should be 8.6 L (10 L – 7 x 200 mL).

PS volume and content may be changed for safety reasons, e.g. if clinical signs of laboratory values support this or in case of clinical signs of fluid overload, as judged by the Investigator.

In cases where a patient may not have been fully compliant with the adherence to the prescribed PS volume, the drinking menu, and/or may have missed a urine measurement (e.g., in case the patient has missed to report a urine measurement during the 48-hour measurement period), the Investigator may still perform adjustments to the new PS volume at the Investigators discretion, in order to best match the needs of the patient and in adherence with the algorithm stated above. In that case, the reason for the change must be documented in the eCRF.

The patients should be instructed to contact the clinical site in case urine production falls below normal and if their clinical status changes.

Increasing PS volume:

Increasing PS volume should be considered if laboratory parameters indicate safety concerns. If the average urine production falls below 1 L per day, the Investigator should consider increasing PS volume.

If PS is not adjusted according to the algorithm (within ±200mL/day) a reason for not adhering to the algorithm must be provided in the eCRF.

8.2.10 Weekly PS Macronutrients and Electrolytes (SBS-IF Only)

Changes to the content of PS are left to the discretion of the Investigator and the reason is documented in the eCRF. Changes from baseline to Week 12 (Visit 6) and Week 24 (Visit 9) will be measured. This only applies for patients with SBS-IF.

8.2.11 Body Weight

For both 48-hour metabolic balance studies an average of the two 24-hour days will be calculated. Changes from baseline to Week 12 (Visit 6), Week 24 (Visit 9) and Week 52 (Visit 12) will be measured. See also Section 8.1.3.

8.2.12 Body Composition by DEXA

A DEXA scan shows the distribution of total body fat, lean body mass and bone mineral content and thus, also contributes as a safety assessment to determine if patients accumulate fluid as edema. DEXA is a low dose x-ray assessment equivalent to 1/10 of the dose of a regular x-ray examination of the thorax. Patients are exposed to less than 0.0005 mSv per scan. During the whole trial (4 DEXA-scans), the radiation dose is comparable to one day of natural background radiation (35). The radiation a patient is exposed to is considered low and is not associated with any known risk. A full DEXA scan takes approximately 20 minutes.

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.

Changes from baseline to Week 12 (Visit 6), Week 24 (Visit 9) and Week 52 (Visit 12) will be measured.

8.2.13 Citrulline

Samples for measurement of Lith-Hep plasma citrulline should be taken in the morning after at least 10 hours (±1 hour) of oral fasting. Smoking is not permitted the last 2 hours prior to blood sampling. Samples will be taken prior to first dose of trial product at Visit 1 and prior to

administration of trial product at other visits (if dosing occurs on the visit day). Details are provided in the laboratory manual. The samples will be stored at the trial site until shipment for analysis by special laboratory Klinische Chemisch Laboratorium, Nijmegen, Holland. Samples will be destroyed after analysis.

Changes from baseline to Week 12 (Visit 6), Week 24 (Visit 9) and Week 52 (Visit 12) will be measured.

8.2.14 Aldosterone

Blood samples for measurement of plasma aldosterone will be drawn prior to first dose of trial product at Visit 1 and prior to administration of trial product at other visits (if dosing occurs on the visit day). Details are provided in the laboratory manual. Analysis will be performed at the local laboratory at the trial site. Samples will be destroyed after analysis.

Changes from baseline to Week 12 (Visit 6), Week 24 (Visit 9) and Week 52 (Visit 12) will be measured.

8.2.15 Hemoglobin A1c

Blood samples for measurement of hemoglobin A1c (HbA1c) will be drawn prior to first dose of trial product at Visit 1 and prior to administration of trial product at other visits (if dosing occurs on the visit day).[1] Details are provided in the laboratory manual. Analysis will be performed at the local laboratory at the trial site. Samples will be destroyed after analysis.

Changes from baseline to Week 4 (Visit 4), Week 12 (Visit 6), Week 24 (Visit 9) and Week 52 (Visit 12) will be measured.

8.2.16 eGFR, Creatinine Clearance and Liver Function Tests

eGFR will be calculated by modification of diet in renal disease (MDRD) formula based on the patient's creatinine level, age, body size and gender. Creatinine levels are measured as part of the safety laboratory tests (see Section 8.3.5).

Liver function will be assessed based on levels of ALT, AST, alkaline phosphatase (ALP), albumin and bilirubin. Levels are measured as part of the safety laboratory tests (see Section 8.3.5).

Changes from baseline to Week 12 (Visit 6) and Week 24 (Visit 9) and Week 52 (Visit 12) will be measured.

8.2.17 Patient Reported Outcomes

The PGIC, SBS-I and EQ-5D-5L (36). PROs will be used to investigate the effects of treatment on health-related quality of life.

Questionnaires must be completed in paper format at site visits, see Table 1, prior to any other trial-related assessment. The PROs will be completed by the patient without assistance of site personnel.

- When all 3 questionnaires are to be completed at a visit, patients are recommended to first complete the PGIC followed by the SBS-I and the EQ-SD-5L.

[1] Blood samples for analyses of HbA1c will only be collected for patients who reach Week 4 after protocol amendment #2 has become effective.

- When only the SBS-I and EQ-5D-5L are to be completed at a visit, it is recommended that the SBS-I is completed first.

The PROs must not be completed at home before the patient attends the visit (however, see also COVID-19 Management, section 8.1.7). Patients will be instructed to complete the PROs in a private area without influence from site personnel or accompanied by family or friends. No one is allowed to answer or interpret items for the patient. The Investigator or a delegated site personnel is allowed to read items/answers options to the patient aloud if the patient is unable to read. The Investigator or delegated site personnel will instruct the patient to complete every item in the PROs and explain that there are no right or wrong answers. The Investigator or a delegated site personnel will instruct the patient to give the best answer they can and explain that all responses will remain confidential.

Immediately after completion, the PROs will be reviewed by the Investigator (or designee) for completeness and potential AEs. When reviewing the PROs for AEs the Investigator should not influence nor question the patient on the content of their response to PRO questions. Review of the PROs must be documented. If entries are missing in the PROs, the patient should be asked to answer all questions. Care should be taken not to bias the patient.

The Investigator and/or delegated site personnel will receive training and instruction in completion of the PROs prior to the conduct of the trial.

8.2.18 Microbiome Composition

Fecal samples may be analyzed for microbe abundance using 16 rDNA sequencing. Absolute abundance, using spike-in bacteria, will allow for absolute values that will be compared between patients at baseline and after 24 weeks of treatment. Samples will be analyzed at Clinical Microbiomics, Copenhagen.

8.2.19 Weekly PS Macronutrients and Electrolytes: Change from baseline to Week 52 (SBS-IF Only)

Changes to the content of PS are left to the discretion of the Investigator and the reason is documented in the eCRF. Changes from baseline to Week 52 will be measured. This only applies for patients with SBS-IF.

8.2.20 Weekly Days on PS (SBS-IF Only)

The changes from baseline of weekly days on PS and the weekly average administration time to Week 12, 24 and 52 will be measured. This only applies for patients with SBS-IF.

8.2.21 Fluid Composite Effect

The fluid composite effect has been defined as parenteral volume + oral fluid volume - urine volume. Changes from baseline to Week 12 (Visit 6), Week 24 (Visit 9) and Week 52 (Visit 12) will be measured.

8.2.22 Urine Output (SBS-II Only)

During the baseline and treatment metabolic balance study (Visit 1 and Visit 9), and at home before V2-V8 and V10-V12, the total urinary output for 48 hours will be measured. This will be performed under a fixed drinking menu (see Section 8.2.2). Changes from baseline to Week 12 (Visit 6) and Week 24 (Visit 9) will be calculated. Likewise, changes in 48-hour urine output

from Week 24 (Visit 9) to Week 52 (Visit 12) will be measured. This will be performed without a fixed drinking menu (see Section 8.2.2). This only applies for patients with SBS-II.

8.2.23 Drinking Volume During 48-hour Periods

The drinking volume during the 48-hour periods will be recorded. Changes from Week 24 (Visit 9) to Week 52 (Visit 12) will be measured.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the flowchart (see Section 1.2).

Safety will be assessed by the following parameters:

- Body weight
- Physical examination
- Vital signs
- ECGs
- Clinical laboratory tests (hematology, biochemistry and urinalysis)
- Immunogenicity
- AEs

8.3.1 Body Weight

Body weight (kg) will be measured at every visit (see Section 8.1.3 and 8.2.11).

8.3.2 Physical Examinations

At screening, patients will undergo a full physical examination, consisting of the following: General Appearance, Skin and mucosae, Head, Ears, Eyes, Nose and Throat incl. thyroid gland, Heart, Lung, Chest (incl. breast), Abdomen (incl. genitourinary system), Nervous System, Lymph Nodes, and Musculoskeletal. Abnormalities on physical examination will be recorded in the patient's medical notes and in the eCRF. Clinically significant changes from baseline examination that are noted during follow-up will be recorded as an AE.

During the treatment phase, an abbreviated physical examination, driven by SBS (e.g. edema), will be performed. The body systems included in these exams will be based on Investigator judgment and/or patient symptoms.

8.3.3 Vital Signs

The following vital signs will be collected: body temperature (ºC) (measured according to the site's usual procedure), pulse rate (beats/min), and seated diastolic and systolic blood pressure (mm Hg). During the treatment period visits, vital signs will be collected prior to injection of trial product, if the visit is scheduled on a dosing day.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions. Blood pressure and pulse rate measurements will be performed with a completely automated device. Manual techniques must be used only if an automated device is not available. Clinically significant changes from baseline examination that are noted during follow-up will be recorded as an AE.

8.3.4 Electrocardiograms

A 12-lead ECG will be performed. During the treatment phase, ECG will be obtained prior to dosing of trial product if trial product is administered on the same day.

ECG parameters (heart rate, PR, QRS, QT, QTcF, RR) and any abnormality will be recorded and described in the eCRF including the Investigator's assessment of clinical significance ('abnormal, not clinically significant' or 'abnormal, clinically significant'). Any clinically significant deterioration of a pre-existing condition as well as any new clinically significant findings will be recorded as AEs.

Additional ECGs will be performed for cause as needed to evaluate AEs.

8.3.5 Clinical Safety Laboratory Assessments

All laboratory assessments, as defined in Appendix 2: Clinical Laboratory Tests, must be conducted in accordance with the laboratory manual and the protocol flowchart.

All samples should be taken prior to dosing of trial product if trial product is administered on the same day.

Safety laboratory tests include hematology, biochemistry and urinalysis. All parameters assessed are listed in Appendix 2: Clinical Laboratory Tests.

Urinalysis will be performed during the Metabolic Balance Study (Visit 1 and 9), see Table 2 and Table 7, and at every trial visit by urine dipstick, see Appendix 2: Clinical Laboratory Tests.

In addition, screening tests will be performed to confirm the HIV, Hepatitis B and C status (if positivity is confirmed, the patient will be excluded from participation in the trial).

Serum pregnancy tests (human chorionic gonadotropin [hCG]) will be performed at screening, Visit 1 and Visit 4 to Visit 12 and the FU visit for women of childbearing potential, and follicle-stimulating hormone (FSH) will be assessed at screening as needed in women of non-childbearing potential (to confirm menopause).

The Investigator must review the laboratory reports, document this review, and record any clinically relevant changes occurring during the trial as the AEs. The laboratory reports must be filed with the source documents.

All laboratory tests with values considered clinically significantly abnormal during participation in the trial should be repeated until the values return to normal or baseline, or are no longer considered clinically significant by the Investigator or Medical Monitor.

In case of suspected liver injury based on increased ALT, AST, ALP, or total bilirubin, the tests should be repeated at 48-72 hours for evaluation of the event course/confirmation (see Section 8.4.6). When drug-induced liver injury (DILI) is suspected based on the transferases values, the liver functionality needs to be evaluated by the bilirubin and INR for confirmation/information of DILI.

IMPORTANT: If a generalized hypersensitivity reaction is suspected and assessed as possibly or probably related to IMP dosing, additional blood samples should be taken to further characterize the reaction. If possible, blood samples should be taken within 4 hours after the event for the measurement of tryptase and ADA, and again approximately 2-4 weeks later (or at next planned visit) to determine tryptase baseline levels. In addition, samples should be taken for ADA according to trial protocol: In case of treatment discontinuation, at the EOT and FU visits. If

treatment is continued/re-initiated, an ADA sample should be taken pre-dose 2-4 weeks after the reaction (or at the next planned visit).

8.3.6 Immunogenicity Assessments

Serum samples will be obtained to determine the presence of ADA and the ADA titer. Samples will be taken before initiation of the first 48-hour metabolic balance study, prior to first dose of trial product at Visit 1 (Week 0) and prior to administration of trial product (if dosing occurs on the visit day) at other selected visits, i.e. Week 4, 12, 24, 52, and Week 56 at follow-up. Details are provided in the laboratory manual.

In the event that a patient permanently discontinues treatment early, the patient will be asked to come for a site visit for ADA sampling at end of treatment and approximately 4 weeks after treatment discontinuation, so that a potential ADA response can be characterized and results related to the clinical picture.

The serum samples will be analyzed using a tiered approach (screening, confirmation, and titration of confirmed anti-glepaglutide-antibody positive samples), followed by characterization of ADA-positive samples for *in vitro* glepaglutide-neutralizing potential and reactivity to the major metabolite ($ZP1848_{1-34}$), and cross-reaction with GLP-2.

All ADA samples will be retained at the special laboratory Syrinx Bioanalytics Oy, Finland, or long-term storage facility at MLM Medical Labs GmbH, Germany, until drug approval by FDA and/or the European Medicines Agency (EMA) or 15 years after end of trial at maximum. The retained ADA samples may be used for further confirmation and characterization of detected ADAs if required by health authorities or for safety reasons.

8.4 Adverse Events and Serious Adverse Events

Timely, accurate, and complete reporting and analysis of safety information from clinical trials are crucial for the protection of patients. Investigator and Sponsor are mandated by regulatory agencies worldwide to report the safety information.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the trial intervention or trial procedures, or that caused the patient to discontinue the trial (see Section 7).

See further guidance in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting.

8.4.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs, whether serious or non-serious, must be collected from the time a signed and dated informed consent form is obtained until the follow-up visit.

Patients will be observed for any signs or symptoms and asked about their condition by open questions, such as “How have you been feeling since you were last asked?” at each contact with the trial site. Patients will also be encouraged to spontaneously inform the Investigator of any signs or symptoms occurring at any other time during the trial.

All AEs, regardless of seriousness, severity, or presumed relationship to trial product, must be recorded and evaluated by the Investigator. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. If no diagnosis can be made, the Investigator

should record each sign and symptom as individual AEs. Investigators must record their opinion concerning the relationship of the AE to the trial product. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

- All AEs will be reported in the eCRF.
- AE information should as a minimum include the following:
    - Date and time of onset.
    - Date and time of Investigators first information about the AE.
    - Seriousness.
    - Severity.
    - Causal relationship with trial product.
    - Measures taken due to AE.
    - Interruption or discontinuation of treatment with trial product.
    - Date of resolution and final outcome.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).[1]

All SAEs will be recorded and reported to Pharmalex immediately and under no circumstance should this exceed **24 hours**, as indicated in Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting. The Investigator will submit any updated information on SAEs to Pharmalex within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the trial participation. However, if the Investigator learns of any SAE, including a death, at any time after a patient has been discharged from the trial, and he/she considers the event to be reasonably related to the trial intervention or trial participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3 (Appendix 3).

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs including AESIs (as defined in Section 8.4.6) will be followed up until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.3). As the case for initial AEs/SAEs, follow-up information is reported in the eCRF. Follow-up questions to Investigators regarding SAEs are queried directly by Pharmalex to the Investigator. Further information on follow-up procedures is provided in Section 10.3 (Appendix 3).

Follow-up information must be reported according to the following:

[1] The most current version at the beginning of the trial.

- **SAEs**: All SAEs must be followed until the outcome of the events is "recovered/resolved", "recovered/resolved with sequelae", or "fatal", and until all queries have been resolved. Cases of chronic conditions, cancer, or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when the patient has completed the follow-up period and is expected by the Investigator to recover.

The SAE follow-up information should only include new (e.g., corrections or additional) information and must be reported **within 24 hours** of the Investigator's first knowledge of the information. This is also the case for previous non-serious AEs which subsequently become SAEs.

- **Non-serious AEs**: Non-serious AEs must be followed until the outcome of the event is "recovering/resolving", "recovered/resolved", or "recovered/resolved with sequelae" or until the end of the follow-up period stated in the protocol, whichever comes first, and until all queries related to these AEs have been resolved. Cases of chronic conditions, cancer, or AEs ongoing at time of death (where death is due to another AE) may be closed with the outcome of "recovering/resolving" or "not recovered/not resolved". Cases can be closed with the outcome of "recovering/resolving" when patient has completed the follow-up period and is expected by the Investigator to recover.

The Investigator must ensure that the worst-case severity and seriousness of an event is kept throughout the trial, i.e. if the severity of an AE changes over time then it should be reported as a single AE with worst-case severity. A worsening of an unresolved AE must be reported as follow-up with re-assessment of severity and/or seriousness of the event.

If an AE is resolved and re-appears later then it should be reported as a new AE.

Queries or follow-up requests must be responded within 14 calendar days from the date of receipt of the request, unless otherwise specified in the follow-up request.

8.4.4 Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a trial intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a trial intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Independent Ethics Committees (IEC), and Investigators.

For all trials, except those utilizing medical devices, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file

it along with the Investigator's Brochure and will notify the IEC, if appropriate according to local requirements.

8.4.5 Pregnancy

Pregnancy during the trial should be avoided and the patients must be instructed in highly effective contraception as per local guidelines (see Contraception Guidance in Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information), and to use this throughout the trial through 4 weeks after receiving the last dose of trial product.

Pregnancy information for female patients and female partners of male patients will be collected after the start of trial treatment and until the follow-up visit.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4 (Appendix 4).

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

If a patient becomes pregnant during the trial, the patient should be withdrawn from trial (see Section 7.2).

8.4.6 Adverse Events of Special Interest

In this trial the following events are to be regarded as AESIs, should they occur:

- Neoplasms (malignant and benign)
- Suspicion of liver injury
- Pancreatitis
- Cholecystitis

If the event is reported as an SAE, the timelines for SAE reporting apply. If the event is reported as a non-serious AE, it should be reported in the dedicated eCRF page within 2 working days (if at all possible) of Investigator's first knowledge.

The event-specific information that needs to be captured in addition to the standard AE information is presented below:

Neoplasms:

Information on histopathology (date of examination and results), imaging (if imaging is performed), TNM staging, history of cancer (the patient's and family), treatment received for this event, and an event narrative. Copies of images (if performed) should be stored at site. A retrospective imaging review may be performed if deemed necessary.

Suspicion of Liver Injury:

Suspicion of liver injury* is defined as:

- ALT or AST increasing more than 3 times from baseline value, or
- ALT or AST > 5 × ULN and total bilirubin > 2 x ULN, or
- ALT or AST > 5 × ULN and INR > 1.5.

* In that case, the tests should be repeated at 48-72 hours for evaluation of the event course/confirmation. Furthermore, additional information needs to be provided by the site, e.g.

physical examination, information on alcohol consumption, concomitant therapy (including herbals).

Narrative of the event should include:

- Clinical signs and symptoms and how they developed over time. Aspects like e.g. abdominal pain, nausea, vomiting, jaundice, fever, rash, abdominal tenderness, hepatomegaly, splenomegaly, blood pressure, peripheral edema, jugular venous distension, signs of ascites, recent weight gain should be considered and described.
- Information on relevant medical history, alcohol consumption, and relevant concomitant therapy (including herbals).
- Lab tests (at local lab, if needed): as a minimum ALT, AST, Bilirubin (direct and total) and INR. Other tests may be warranted as clinically indicated.
- Imaging diagnostic (ultrasound/CT scan/MRI/Other imaging modality). Copies of images (if performed) should be stored at site.
- Biopsy results (if performed).

Pancreatitis:

Narrative of the event should include:

- Clinical signs and symptoms and how they developed over time. Aspects like pain (character of the pain including the anatomical region (e.g. sudden and in center abdomen) +/- irradiating pain in the back), tenderness of the abdomen, diarrhea, indigestion, fever, jaundice) should be considered and described.
- Information on relevant medical history, alcohol consumption, and relevant concomitant therapy (including herbals).
- Lab tests (at local lab, if needed): pancreatic and liver function tests, including lipase, amylase, ALT, AST, bilirubin, and ALP. Other tests may be warranted as clinically indicated.
- Imaging diagnostic (ultrasound/CT scan/MRI/Other imaging modality). Copies of images (if performed) should be stored at site.
- Biopsy results (if performed).

Cholecystitis:

Narrative of the event should include:

- Clinical signs and symptoms and how they developed over time. Aspects like pain (character of the pain including the anatomical region (e.g. sudden, after a large meal, in upper right or center abdomen) +/- irradiating pain to right shoulder or back), tenderness of the abdomen, nausea, vomiting, and fever should be considered and described.
- Information on relevant medical history, alcohol consumption, and relevant concomitant therapy (including herbals).
- Lab tests (at local lab, if needed): liver function tests, including ALT, AST, bilirubin, and ALP. Other tests may be warranted as clinically indicated.
- Imaging diagnostic (ultrasound/X-Ray/CT scan/MRI/Other imaging modality). Details like presence of gall bladder stones and common bile duct diameter should be reported, if available.

8.4.7 Other Important Events

The following events must always be reported to Pharmalex according to SAE timelines, regardless of whether the event is non-serious or serious:

- Suspicion of transmission of infectious agents via the trial product.
- Overdose of the trial product.
- Medication error involving the trial product.
- Inadvertent or accidental exposure to the trial product.

Note: Medication errors are defined as all unintended failures (e.g. wrong kit, missing dose, not taking the full amount, etc.) to administer the investigational product correctly that either:

- Lead to harm to the patient
- Have the potential to lead to harm to the patient

Other important events must be recorded in the eCRF.

8.4.8 Technical Complaints

Technical complaints on trial products and technical issues with the device will be reported by the Investigator via the eCRF.

8.4.9 Precautions

Normal precautions taken for a human trial, including the provision of emergency equipment, will be taken during this trial. Qualified and well-trained physicians and medical staff will instruct the patients. During a patient's participation in the trial, the Investigator should ensure that adequate medical care is provided to the patients for any AEs, including clinically significant laboratory values related to the trial. The Investigator should inform the patient when medical care is needed for intercurrent illnesses of which the Investigator becomes aware.

For further information on safety precautions for glepaglutide, refer to the current version of the Investigator's Brochure.

8.5 Treatment of Overdose

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the patient for any AE/SAE and laboratory abnormalities for at least 14 days. In case of AEs/SAEs, these should be followed up until resolution, stabilization or until the event is otherwise explained, or the subject is lost to follow-up as described in section 8.4.3.
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the patient.

8.6 Pharmacokinetics

PK parameters will be assessed as an exploratory endpoint.

Blood samples for assessment of PK will be taken according to Table 3 , and prior to administration of trial product at other visits (if dosing occurs on the visit day). Details are provided in the laboratory manual. The actual date and time of each sample will be recorded. The PK sampling schedule is set in order to be able to correlate PK values of glepaglutide to ADA data and to obtain sufficient information from the dosing regimen tested. Results will not be revealed to the site. PK samples will be shipped for analysis to Charles River Laboratories, UK. Samples will be destroyed after completion of the final clinical trial report.

8.7 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this trial.

8.8 Genetics

Genetics are not evaluated in this trial.

8.9 Biomarkers

Biomarkers are not evaluated in this trial.

8.10 Health Economics

Health Economics parameters are not evaluated in this trial.

8.11 Unscheduled Visits

If required an unscheduled visits can be performed, including, but not limited to, any of the following:

- PS volume adjustments
- Lab sampling: In case of suspected liver injury based on increased ALT, AST, ALP, or total bilirubin, the tests should be repeated at 48-72 hours for evaluation of the event course/confirmation
- Additional trial product dispensing and/or to replace trial product to ensure that no patient use expired trial product at any time

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The primary statistical null hypothesis H_0 is defined as

H_0: $mean$ 24-week change in Wet Weight Absorption = 0

With the alternative hypothesis being defined as

H_a: $mean$ 24-week change in Wet Weight Absorption ≠ 0

For the key secondary endpoint the corresponding null hypothesis 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 primary and secondary hypotheses, supplementary analyzes will be performed that analyze the primary hypotheses for the SBS-II and SBS-IF patients separately. The supplementary analyzes will however not be part of the testing strategy.

9.2 Sample Size Determination

Sample size is planned based on both, feasibility considerations and statistical considerations. Sample size should be such that there is sufficient power to reject at least the primary null hypothesis (primary endpoint). In the phase 2 trial, ZP1848-15073, after three weeks of treatment, the pooled 1 and 10 mg/day treatment groups displayed a mean (SD) change from baseline in absorption of wet weight fluids of 719 g/day (340 g/day), corresponding to an effect size (mean divided by standard deviation) of 2.11. Calculations based on a one-sample t-test (alpha= 0,05, two-sided) reveal 90% power for a statistically significant test result of the primary null hypothesis, if an effect size of 2.11 can be assumed and 5 patients are analyzed. The effect size is the true population mean of the 24 week change in wet weight absorption divided by its standard deviation.

In the same trial, the change from baseline in the intestinal energy absorption was 391 KJ/day (1374 KJ/day), corresponding to an effect size of 0.28.While achieving statistical significance for the key secondary endpoint in addition to the primary endpoint is aimed for, a sample size providing high power for the key secondary endpoint is not considered feasible, should a similar variability have to be expected for the present study. It seems, however, reasonable to assume that the variability of results for the key secondary endpoint will be lower after 24 weeks compared to after 3 weeks. Should the reduced variability lead to an effect size of around 1.15, then the below table shows that 90% power can be achieved with 10 patients in the analysis, and 80% power can be achieved with 8 patients in the analysis. Even a less extensive reduction in variability can still lead to a reasonable power with 8 to 10 patients in the analysis.

Table 9 Power calculation of a One-Sample t-test for different effect sizes

Number Of Patients	Effect Size		Power (%)
8	1,156		80
8	1,2		82
8	1,3		88
8	1,342		90
8	1,4		92
10	0,996		80
10	1,0		80
10	1,1		87
10	1,155		90
10	1,2		92

Taken together, the sample size will be as follows: Aiming for at least 8 patients in the full analysis set (i.e. patients assigned to trial treatment who received at least one dose), 2 more patients will be allocated to treatment. This means patients will be screened until 10 eligible patients (eligible with respect to inclusion and exclusion criteria) are enrolled and allocated to treatment. Patients with SBS-II and SBS-IF will be included in the trial, with an aim of an equal distribution between the two.

9.3 Analysis Sets

The analysis of efficacy will be performed based on the full analysis set (primary confirmatory analysis) and based on the per-protocol analysis set (supportive analysis). The analysis of safety will be based on the safety analysis set. The analysis are defined in Table 10 :

Table 10 Analysis Sets

Analysis Set	Description
Full analysis set (FAS)	The FAS comprises all patients assigned to trial treatment who received at least one dose of trial product.
Per-protocol analysis set	The per-protocol analysis set comprises all FAS patients without major protocol deviations. Criteria for exclusion from the per-protocol analysis set will be listed in the statistical analysis plan (SAP). Final judgment on exclusion from the per-protocol analysis set will be made prior to database lock. The per-protocol analysis set will be used for supplementary analyzes of the primary and key secondary efficacy endpoints.
Safety analysis set (SAS)	The SAS comprises all patients who received at least one dose of trial product.

9.4 Statistical Analyzes

The statistical analysis plan (SAP) will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyzes described in this section. This section is a summary of the planned statistical analyzes of the most important endpoints including primary and key secondary endpoints. Any changes from the methods planned in the SAP will be justified in the clinical trial report (CTR).

9.4.1 General Considerations

Statistical analyzes will be performed after end of trial, when the database has been locked. The results will be included in the CTR.

The primary analysis will be based on observed data, missing data will not be replaced. Sensitivity analyses with regard to the handling of missing data may be described in the SAP.

In general, data will be summarized using descriptive statistics: Continuous data will be summarized by presenting the number of non-missing observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical data will be summarized by presenting the number of patients and percentage for each category. Listings of individual patient data will be presented.

9.4.2 Demographics and Baseline Characteristics

Demographic data, SBS history, medical history/concomitant illness and other baseline data will be summarized in terms of descriptive statistics.

9.4.3 Primary Endpoint - Absorption of Wet Weight/Fluids

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

The primary analysis will use a one-sample t-test (two-sided alpha= 0.05) to analyze the mean change from baseline in absorption of wet weight/fluids to Week 24. The null hypothesis to be tested is defined in Section 9.1. The primary analysis will include all FAS patients, a descriptive analysis will also be provided separately for patient with SBS-II and patient with SBS-IF.

The primary estimand for the primary endpoint is defined according to the intention-to-treat principle as follows: The population will be the FAS DB, 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.

More details will be described in the SAP. This may include definition of an estimand with handling of intercurrent events according to the hypothetical strategy.

9.4.4 Secondary Endpoints

The key secondary endpoint change from baseline to Week 24 in absorption of energy (measured by bomb calorimetry and based on 48 hour metabolic balance studies) will be analyzed using the same approach as for the primary endpoint. According to the hierarchical testing procedure a statistical test in the confirmatory sense will only be performed in case the test for the primary endpoint was statistically significant.

The other secondary endpoints (changes from baseline for absorption of individuals macronutrients, absorption of electrolytes, weekly PS volume [SBS-IF only], and weekly PS macronutrients and electrolytes [SBS-IF only]) will be analyzed descriptively.

9.4.4.1 Absorption of Energy (Key Secondary Endpoint)

Change from baseline to Week 24 measured by 48-hour metabolic balance studies. Energy absorption is measured by bomb calorimetry.

9.4.4.2 Absorption of Individual Macronutrients

Change from baseline to Week 24 measured by 48-hour metabolic balance studies.

9.4.4.3 Absorption of Electrolytes

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

9.4.4.4 Weekly PS Volume (SBS-IF Only)

Change from baseline to Week 12 and Week 24.

9.4.4.5 Weekly PS Macronutrients and Electrolytes (SBS-IF Only)

Change from baseline to Week 12 and Week 24.

9.4.5 Exploratory Endpoints

For details on analyzes of exploratory endpoints, please refer to the SAP.

9.4.6 Other Safety Analyzes

All safety analyzes will be made on the SAS. The standard safety assessments (AEs [only treatment-emergent AEs will be tabulated, whereas non-TE AEs will be listed], safety laboratory parameters, vital signs, etc.) will be reported descriptively; including any notable changes of clinical interest in laboratory parameters. Treatment-emergent AEs are defined as AEs with onset date on or after the day of first administration of trial product.

9.4.7 Other Analyses

No formal statistical interim analysis is planned. Safety data may need to be summarized for regulatory purposes while the study is ongoing.

9.5 Interim Analyzes

An interim analysis may be conducted during the course of the trial.

9.6 Data Monitoring Committee (DMC)

No Data Monitoring Committee will be established in this clinical trial.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

- This trial will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki (37) and applicable ICH Good Clinical Practice Guidelines (38)
    - Applicable laws and regulations
- The protocol, protocol amendments, informed consent form (ICF), Investigator's Brochure, and other relevant documents must be submitted to an IEC by the Investigator and reviewed and approved by the IEC before the trial is initiated.
- Any amendments to the protocol will require IEC approval before implementation of changes made to the trial design, except for changes necessary to eliminate an immediate hazard to trial patients.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the trial to the IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IEC
    - Notifying the IEC of SAEs or other significant safety findings as required by IEC procedures
    - Providing oversight of the conduct of the trial at the site and adherence to requirements of 21 CFR, ICH guidelines, the IEC, European regulation 536/2014 for clinical studies, and all other applicable local regulations

10.1.2 Financial Disclosure

The Investigator and Sub-Investigators will provide Sponsor with sufficient, accurate financial information as requested to allow Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the trial and 1 year after completion of the trial.

10.1.3 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance coverage in accordance with all legal requirements. The civil liability of the Investigator, the person instructed by him or her and the hospital, practice, or institute in which they are employees and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of carrying out this trial are governed by the applicable law. The Sponsor will arrange for liability insurance if trial patients should be injured due to the participation in the trial and will provide that Sponsor is legally liable for that. Excluded from the insurance cover are injuries to health and deteriorations of illnesses already in existence which would have occurred or continued to exist even if the trial patient had not taken part in the clinical trial.

The insurance cover is jeopardized if the trial patient fails to report immediately to the Investigator or responsible physician any injury to health, which might have resulted from participation in the clinical trial, or if he/she undergoes any other medical treatment without their consent before the clinical trial has been completely finished insofar as the individual trial patient is concerned. Any injury to health, which might have occurred as a result of participation in the clinical trial, must be reported by the trial patient to the Investigator without delay. The Investigator is obliged to make such a report in any case.

10.1.4 Informed Consent Process

- The Investigator or his representative will explain the nature of the trial to the patient and answer all questions regarding the trial.
- The Investigator must ensure the patient ample time to come to a decision whether or not to participate in the trial.
- Patients must be informed that their participation is voluntary and that the patient may withdraw from the trial at any time and for any reason.
- Patients must be informed about their privacy rights.
- Patients will be required to sign and date a statement of informed consent that meets the requirements of local regulations, Declaration of Helsinki (37), ICH guidelines (38), and the IEC or site.
- The medical record must include a statement that written informed consent was obtained before any trial-related activity and the date when the written consent was obtained. The authorized person obtaining the informed consent must also sign and date the ICF before any trial-related activity.
- The responsibility of seeking informed consent must remain with the Investigator, but the Investigator may delegate the task to a medically qualified person, in accordance with local requirements.
- Patients must be re-consented to the most current version of the ICF during their participation in the trial.
- A copy of the ICF must be provided to the patient.

10.1.5 Data Protection

- Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient must be informed that his/her personal trial-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.
- The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IEC members, and by inspectors from regulatory authorities.

10.1.6 Committees Structure

Internal Safety Committee

An internal Sponsor Safety Committee is constituted to perform ongoing safety surveillance of clinical trials with glepaglutide, including this trial.

If safety signals or concerns are observed, whether based on reported SAEs, review of all AEs and laboratory parameters reported or any other notification of significant findings, the Safety Committee will respond appropriately to protect the safety of the patients.

The Safety Committee meets quarterly and additionally on an ad-hoc basis, as needed, and will call upon external expertise when judged needed.

10.1.7 Dissemination of Clinical Trial Data

Information of the trial will be disclosed at clinicaltrials.gov before the first patient enters into the trial. It will also be disclosed according to other applicable requirements, such as those of the International Committee of Medical Journal Editors (ICMJE) (39), the FDA Amendment Act (FDAAA)(40), European Commission Requirements (41,42) and other relevant recommendations or regulations. If a patient requests to be included in the trial via a Sponsor e-mail contact at these web sites, Sponsor disclose the Investigator's contact details to the patient.

A CTR describing the conduct of the trial and the results obtained, will be prepared by the Sponsor or delegate. A summarizing report will be submitted to the applicable Competent Authority (CA) and IEC within 12 months after completion of the trial.

Trial results (positive, negative or inconclusive) will be reported in the European Clinical Trials Database per applicable regulations within 12 months after completion of the trial. Trial completion is defined as the date of the last visit (follow-up visit) of the last patient in the trial.

The primary completion date (PCD) is the last assessment of the primary endpoint, and is for this trial last patient first treatment (LPFT) + 24 weeks, corresponding to Visit 9. If the last patient is withdrawn early, the PCD is considered the date when the last patient would have completed Visit 9. The PCD determines the deadline for results disclosure at clinicaltrials.gov according to FDAAA.

10.1.8 Data Quality Assurance

10.1.8.1 Case Report Forms

- KLIFO A/S is responsible for the data management of this trial including quality checking of the data.
- All patient data relating to the trial will be recorded in an eCRF. The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- Patients will record data in paper diaries and PROs which subsequently will be transferred to the eCRF by the site.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The following will be provided as paper CRFs:
    - Pregnancy forms.

- The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF is temporarily unavailable:
    - SAE forms
    - Technical complaint forms (also to be used to report complaints on trial product not yet allocated to a patient)
- Corrections to the eCRF data may be made by the Investigator or the Investigator's delegated staff. An audit trail will be maintained in the eCRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the Investigator's delegated staff after the date when the Investigator signed the eCRF, the eCRF must be signed and dated again by the Investigator.
- The Investigator must ensure that data is recorded in the eCRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Sponsor for data verification and validation purposes.

10.1.8.2 Monitoring

The Investigator must permit trial-related monitoring, Audits, IEC review, and Regulatory Agency Inspections, be available during Audits and Inspections for Interviews and provide direct access to source data documents (original documents), data and records. Direct access includes permission to examine, analyze, verify and reproduce any record(s) and report(s) that are important to the evaluation of the trial. If the electronic medical record does not have a visible audit trail, the Investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g. by telephone).

Trial monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; to monitor drug accountability, and that the trial is being conducted in accordance with the currently approved protocol and any other trial agreements, ICH GCP (E6 R2) (38), and all applicable regulatory requirements.

Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan and Medical Monitoring Plan.

Records and documents, including signed ICFs, pertaining to the conduct of this trial must be retained by the Investigator according to relevant legislation after the completion of the trial, and no less than 25 years after trial completion. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

10.1.8.3 Protocol Compliance

Deviations from the protocol should be avoided. If deviations do occur, the Investigator must inform the monitor without delay and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the eCRF or via listings from the trial database.

10.1.9 Source Documents

- All data entered in the eCRF must be verifiable in source documentation other than the eCRF.
- The originals of the completed diaries and PROs must not be removed from the site.
- Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records. Also, current medical records must be available.
- It must be possible to verify the patient's medical history in source documents, such as the patient's medical record.
- The Investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.
- Definition of what constitutes source data can be found in a source document agreement at the site. There will only be one source document defined at any time for any data element.

10.1.10 Trial and Site Start and Closure

The trial start date is the date on which the clinical trial will be open for recruitment of patients.

The Sponsor designee reserves the right to close the trial site or terminate the trial at any time for any reason at the sole discretion of the Sponsor. The trial site will be closed upon trial completion. The trial site is considered closed when all required documents and trial supplies have been collected and a trial site closure visit has been performed.

The Investigator may initiate trial site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a trial site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of patients by the Investigator
- Discontinuation of further trial intervention development

If the trial is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigator, the IEC, the regulatory authorities, and any contract research organization(s) used

in the trial of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the patients and should assure appropriate patient therapy and/or follow-up.

The trial will be prematurely terminated at any time in the emergence of any safety information that could significantly affect continuation of the trial, i.e. AEs or other safety information that are considered unacceptable taken the indication into account and resulting in an unacceptable benefit-risk ratio.

If, after the termination of the trial, the benefit-risk analysis changes, the new evaluation must be provided to the IEC in case it has an impact on the planned follow-up of patients who have participated in the trial. If it has an impact, the actions needed to inform and protect the patients should be described.

10.1.11 Responsibilities

The Investigator is accountable for the conduct of the trial at his/her site and must ensure adequate supervision of the conduct of the trial at the site. If any tasks are delegated, the Investigator is responsible for supervising any individual or party to whom the Investigator delegates trial-related duties and functions conducted at the trial site. The Investigator must maintain a log of appropriately qualified persons to whom he has delegated specified trial-related duties and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated. The Investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the trial. It is the Investigator's responsibility to supervise the conduct of the trial and to protect the rights, safety, and well-being of the patients.

A qualified physician, who is an Investigator or a sub-Investigator for the trial, must be responsible for all trial-related medical decisions.

The Investigator is responsible for filing essential documents (i.e. those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced) in the Investigator trial master file. The documents, including the patient identification code list must be kept in a secure locked facility so that no unauthorized persons can get access to the data.

The Investigator will take all necessary technical and organizational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The Investigator will prevent any unauthorized access to data or any other processing of data against applicable law. The Investigator must be able to provide the necessary information or otherwise demonstrate to Sponsor that such technical and organizational safety measures have been taken.

During any period of unavailability, the Investigator must delegate responsibility for medical care of patients to a specific qualified physician who will be readily available to patients during that time.

If the Investigator is no longer able to fulfill the role as Investigator (e.g. if he moves or retires), a new Investigator will be appointed in consultation with the Sponsor.

The Investigator and other site personnel must have sufficient English skills according to their assigned task(s).

10.1.12 Publication Policy

The site (Institution) reserves the right to publish all findings related to the project; provided, however, that Institution, Institution or Investigator shall notify Zealand Pharma of any such publication at least 30 day prior to submission for publication to allow Zealand Pharma to ensure against inadvertent disclosure of unprotected trial drug discoveries or confidential information. Zealand Pharma shall be entitled to receive in any such publication an acknowledgement of its contribution to the project. In addition, Institution, or Investigator shall delay any such publication, at the request of Zealand Pharma, for up to 90 days to permit Zealand Pharma to prepare and file one or more patent applications relating to the subject matter of such publication.

Institution shall undertake to use its best efforts to ensure that the findings of the project are made public through publications in scientific journals or scientific conferences. Institution shall undertake to use its best efforts to ensure that each publication that it seeks to publish in connection with the project complies with applicable international standards, including the requirements for financial disclosures, if applicable.

Upon Institution's publication of any findings relating to project, Zealand Pharma shall have the right to use the published information without any restrictions; provided that Zealand Pharma shall do so only with appropriate references. Upon publication Zealand Pharma shall not be liable to pay any royalties for the use or re-publication of this information.

The Sponsor will comply with the requirements for publication of trial results.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

No confidential information shall be disclosed to others without prior written consent from Sponsor. Such information shall not be used except in the performance of this trial.

10.2 Appendix 2: Clinical Laboratory Tests

- The analyses detailed in Table 11 will be performed at a local laboratory at the trial site.
- Samples for the safety laboratory assessments* will be destroyed after analyzes.
- The Investigator must review all laboratory results for concomitant illnesses and AEs.

Table 11 Laboratory Assessments

Laboratory Assessments	Parameters	Time For Assessment

Hematology*	• Hemoglobin
	• Hematocrit
	• Red blood cell count
	• White blood cell count with Differential:
	  ○ Neutrophils
	  ○ Lymphocytes
	  ○ Monocytes
	  ○ Eosinophils
	  ○ Basophils
	• Platelet Count
		All trial visits (screening, Visit 1-12 and follow-up)

Biochemistry*	• Sodium • Potassium • Chloride • Bicarbonate • Blood Urea Nitrogen • Creatinine • Creatinine Clearance (estimated) • Glucose • Calcium • Phosphorous • ALP • ALT • AST • INR • Gamma-glutamyl transferase (GGT) • Lactic dehydrogenase • Conjugated bilirubin • Unconjugated bilirubin • Total bilirubin • Total protein • Albumin • Amylase • Uric acid • C-reactive protein	All trial visits (screening, Visit 1-12 and follow-up)
	• HbA1c	Visits 1, 4, 6, 9, 12 and follow-up
	• Cholesterol, measured orally fasting • Triglycerides, measured orally fasting • Magnesium • Zinc	Visits 1, 9 and 12 only
Other analyses	• Aldosterone • Citrulline • ADA	Visits 1, 4, 6, 9, 12 and follow-up
	• PK	See Table 3
Urinalysis (by dipstick)*	• Blood • Glucose • Leukocytes • pH • Protein	All trial visits (screening, Visit 1-12 and follow-up)
Urinalysis*	• Sodium	Visit 1 and 9 MBS only

	• Potassium • Calcium • Magnesium • Urea • Creatinine	
Pregnancy testing	• Serum human chorionic gonadotropin (hCG) pregnancy test (women of childbearing potential only)	Screening and visits 1, 4, 5, 6, 7, 8, 9, 10, 11, 12 and follow-up
Screening tests	• FSH; as needed in women of non-childbearing potential to confirm menopause • HIV type 1 and 2 antibodies • Hepatitis B surface antigen (HBsAg) • Hepatitis C virus antibody (HCV)	Screening only

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a clinical trial patient administered a medicinal (investigational or non-investigational) product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a product, whether or not related to the product.

AEs include:

- A clinically significant worsening of a concomitant illness.
- A clinical laboratory AE: a clinical abnormality which is clinically significant, i.e., any abnormality that suggests a disease and/or organ toxicity and is of a severity that requires active management. Active management includes active treatment or further investigations, e.g., change of dose or more frequent follow-up due to the abnormality.

The following should **not** be considered as AEs:

- Pre-existing conditions, including those found as a result of screening procedures (pre-existing conditions should be reported as medical history or concomitant illness).
- Pre-planned procedure, unless the condition for which the procedure was planned has worsened from the first trial-related activity after the patient has signed the informed consent.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose fulfills any of the following criteria:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Otherwise medically important:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to Pharmalex in lieu of completion of the AE/SAE eCRF page. All SAEs will be recorded and reported to Pharmalex immediately and under no circumstance should this exceed 24 hours. Sponsor is informed by Pharmalex.
- There may be instances when copies of medical records for certain cases are requested by Pharmalex. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Pharmalex.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

The Investigator will assess severity for each event reported during the trial and assign it to one of the following categories:

- **Mild:** No or transient symptoms, no interference with the patient's daily activities.
- **Moderate**: Marked symptoms, moderate interference with the patient's daily activities.
- **Severe:** Considerable interference with the patient's daily activities, which the patient finds unacceptable. A severe reaction does not necessarily deem the AE as serious and an SAE are not always severe in nature.

Assessment of Causality

- The Investigator is obligated to assess the relationship between trial intervention and each occurrence of each AE/SAE according to the following definitions:
  - **Probably:** Good reason and sufficient documentation to assume a causal relationship.
  - **Possibly:** A causal relationship is conceivable and cannot be dismissed.
  - **Unlikely:** The event is most likely related to etiology other than the product.
  - **Not related:** No relationship to product.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to trial intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure in his assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to Pharmalex. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Pharmalex.
- The Investigator may change his opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Assessment of Outcome

The Investigator must judge outcome of the AE by the following terms:

- **Recovered/resolved:** The patient has fully recovered, or by medical or surgical treatment, the condition has returned to the level observed at the first trial-related activity after the patient signed the informed consent.
- **Recovering/resolving:** The condition is improving and the patient is expected to recover from the event. This term is only applicable if the patient has completed the trial or has died from another AE.
- **Recovered/resolved with sequelae:** The patient has recovered from the condition, but with lasting effect due to a disease, injury, treatment, or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved**: The condition of the patient has not improved and the symptoms are unchanged, or the outcome is not known.
- **Fatal:** This term is only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AEs in a patient before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae", or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.
- **Unknown**: This term is only applicable if the patient is lost to follow-up.

Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Pharmalex to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. The SAE follow-up information should only include new (e.g., corrections or additional) information and must be reported to Pharmalex **within 24 hours** of the Investigator's first knowledge of the information. This is also the case for previous non-serious AEs which subsequently become SAEs. • If a patient dies during participation in the trial or during a recognized follow-up period, the Investigator will provide Pharmalex with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed eCRF.

10.3.4 Reporting of SAEs

SAE Reporting to Pharmalex via the eCRF
• The primary mechanism for reporting an SAE to Pharmalex will be the eCRF. • If the electronic system is unavailable, then the site will use the SAE paper form (see below) in order to report the event **within 24 hours**. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the trial is completed, the eCRF will be taken off-line to prevent the entry of new data or changes to existing data. • If the trial site receives a report of a new SAE from a trial patient or receives updated data on a previously reported SAE after the eCRF has been taken off-line, then the site can report this information on a paper SAE form (see next section). Reporting to Pharmalex via Paper CRF (in case of eCRF unavailability). • SAE paper forms must be forwarded to Pharmalex. • Email transmission of the SAE paper form is the preferred method to transmit this information to Pharmalex. • Contact details for Pharmalex are: Phone: +45 74 44 19 36 Email: PV-nordic@pharmalex.com

10.4 Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of trial intervention, additional evaluation should be considered.

Females in the Following Categories Are Not Considered WOCBP

1. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Females with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining trial entry.

   Note: Documentation can come from the site personnel's: review of the patient's medical records, medical examination, or medical history interview.
2. Postmenopausal female
   - A postmenopausal state is defined as amenorrhea for 12 months without an alternative medical cause.
   - A high FSH level (>25,8 IU/L) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the trial. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before trial enrollment.

Contraception Guidance:

Female patients:

Highly effective contraception is defined as:

- Having a male partner who is sterile (vasectomized or orchiectomized) prior to the female patient's entry into the trial and is the sole sexual partner for that female patient.
- Use of intrauterine devices.
- Use of intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Use of hormonal contraceptives containing combined estrogen and progestogen associated with inhibition of ovulation (intravaginal, transdermal).

- Use of progestogen-only hormonal contraception associated with inhibition of ovulation (injectable, implantable).
- True abstinence: When this is in line with the preferred and usual lifestyle of the patient (period abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).

Male patients:

Male patients who are not sterilized or infertile must use condom throughout the trial through 4 weeks after receiving the last trial product dose. If their partner is a female of childbearing potential, she must use highly effective contraception (as detailed above) throughout the trial through 4 weeks after last dose.

Collection of Pregnancy Information

Female patients who become pregnant

- The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this trial.
- Female patients must be instructed to notify the Investigator immediately if she becomes pregnant or if she suspects she might be pregnant during the trial.
- All initial reports of pregnancy in female patients must be reported to PharmaLex by the trial site personnel within 24 hours of knowledge of the event using the appropriate pregnancy form.
- The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24-hours of learning of a patient's pregnancy.
- The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate, and the information will be forwarded to the Sponsor. Follow-up will not be required for longer than 1 month beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion [occurring at <22 weeks gestational age], stillbirth [occurring at >22 weeks gestational age], fetal death, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be reported using the SAE form.
- Any post-trial pregnancy related SAE considered reasonably related to the trial intervention by the Investigator will be reported to the Sponsor as described in Section 8.4.1. While the Investigator is not obligated to actively seek this information in former trial patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the trial will discontinue trial intervention.

Male patients with partners who become pregnant

- Because the effect of the trial product on sperm is unknown, the Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this trial. This information will include medical history in relation to previous pregnancy(ies) and birth(s), if applicable, relevant medical history, and information on present pregnancy.
- Male patients must be instructed to notify the Investigator immediately if his partner becomes pregnant or suspects to be pregnant.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to PharmaLex within 24-hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 1 month following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.5 Appendix 5: Abbreviations

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
CA	competent authority
CCE	colon capsule endoscopy
CL_{cr}	creatinine clearance
C_{max}	maximum plasma concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CT	computerized tomography
CTR	clinical trial report
DEXA	dual-energy x-ray absorptiometry
DILI	drug-induced liver injury
DMC	data monitoring committee
DPP	dipeptidyl peptidase
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EoT	end of treatment
FAS	full analysis set
FDA	US Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FU	follow-up
GGT	gamma-glutamyl transferase

GLP-2	glucagon-like peptide 2
HbA1c	hemoglobin A1c
HGH	human growth hormone
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
INR	international normalized ratio
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NOAEL	no observed adverse-effect level
NYHA	New York Heart Association
PCD	primary completion date
PGIC	patient's global impression of change
PK	pharmacokinetics
PRO	patient reported outcome
PS	parenteral support
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SBS	short bowel syndrome
SBS-I	SBS impact scale (a disease specific PRO questionnaire developed by Sponsor)
SBS-IF	short bowel syndrome with intestinal failure
SBS-II	short bowel syndrome with intestinal insufficiency
SC	subcutaneous
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
ULN	upper limit of normal
WOCBP	woman of childbearing potential

11 REFERENCES

1. Buchman AL, Scolapio J, Fryer J. AGA technical review on short bowel syndrome and intestinal transplantation. Gastroenterology 2003 Apr;124(4):1111–34.
2. Jeppesen PB, Arends J, Baxter J, Bozzetti F, Peláez RB, Cuerda C. Spectrum of short bowel syndrome in adults: intestinal insufficiency to intestinal failure. JPEN J Parenter Enteral Nutr 2014 May;38(1 Suppl 1):8S-13S.
3. Pironi L, Arends J, Baxter J, Bozzetti F, Peláez RB, Cuerda C, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. Clin Nutr 2015 Apr;34(2):171–80.
4. Ladefoged K. Hessov I, Jarnum S. Nutrition in short-bowel syndrome. Scand J Gastroenterol Suppl 1996;216:122–31.
5. Jeppesen PB, Pertkiewicz M, Forbes A, Pironi L, Gabe SM, Joly F, et al. Quality of life in patients with short bowel syndrome treated with the new glucagon-like peptide-2 analogue teduglutide - analyses from a randomised, placebo-controlled study. Clin Nutr 2013 Oct;32(5):713–21.
6. O'Keefe SJ, Buchman AL, Fishbein TM, Jeejeebhoy KN, Jeppesen PB, Shaffer J. Short bowel syndrome and intestinal failure: Consensus definitions and overview. Clin Gastroenterol Hepatol 2006 Jan;4(5):6–10.
7. Tee CT, Wallis K, Gabe SM. Emerging treatment options for short bowel syndrome: potential role of teduglutide. Clin Exp Gastroenterol 2011;4:189-96.
8. Pironi L, Arends J, Bozzetti F, Cuerda C, Gillanders L, Jeppesen PB, et al. ESPEN guidelines on chronic intestinal failure in adults. Clin Nutr 2016 Apr;35(2):247-307.
9. Forbes A. Parenteral nutrition. Curr Opin Gastroenterol 2005 Mar;21(2):192-6.
10. Goulet O, Joly F, Corriol O, Colomb-Jung V. Some new insights in intestinal failure-associated liver disease. Curr Opin Organ Transplant 2009 Jun;14(3):256-61.
11. Lauverjat M, Aissa H, Vanhems A P, Bouletreau P, Fouque D, Chambrier C. Chronic dehydration may impair renal function in patients with chronic intestinal failure on long-term parenteral nutrition. Clin Nutr 2006 Feb;25(1):75-81.
12. Drucker DJ, Ehrlich P, Asa SL, Brubaker PL. Induction of intestinal epithelial proliferation by glucagon-like peptide 2. Proc Natl Acad Sci U S A. 1996 Jul 23;93(15):7911-6.
13. Wallis K, Walters JR, Forbes A. Review article: glucagon-like peptide 2 - current applications and future directions. Aliment Pharmacol Ther 2007 Feb 15;25(4):365-72.
14. Meier JJ, Nauck MA, Pott A, Heinze K, Goetze O, Bulut K, et al. Glucagon-like peptide 2 stimulates glucagon secretion, enhances lipid absorption, and inhibits gastric acid secretion in humans. Gastroenterology 2006 Jan;130(1):44-54.
15. Benjamin MA, McKay DM, Yang PC, Cameron H, Perdue MH. Glucagon-like peptide-2 enhances intestinal epithelial barrier function of both transcellular and paracellular pathways in the mouse. Gut 2000 Jul;47(1):112-9.
16. Wøjdemann M, Wettergren A, Sternby B, Holst JJ, Larsen S, Rehfeld JF, et al.

Inhibition of human gastric lipase secretion by glucagon-like peptide-1. Dig Dis Sci 1998 Apr;43(4):799-805.
17. Au A, Gupta A, Schembri P, Cheeseman CI. Rapid insertion of GLUT2 into the rat jejunal brush-border membrane promoted by glucagon-like peptide 2. Biochem J 2002 Oct 1;367(Pt 1):247-54.
18. Cheeseman CI. Upregulation of SGLT-1 transport activity in rat jejunum induced by GLP-2 infusion in vivo. Am J Physiol 1997 Dec;273(6):R1965-71.
19. Guan X, Stoll B, Lu X, Tappenden KA, Holst JJ, Hartmann B, et al. GLP-2-mediated up-regulation of intestinal blood flow and glucose uptake is nitric oxide-dependent in TPN-fed piglet. Gastroenterology 2003 Jul;125(1):136-47.
20. Grasso P. and Golberg L. (1966)- Subcutaneous sarcoma as an index of carcinogenic potency Food and Cosmetics Toxicology, Vol. 4, 297-320.
21. Hooson J., Grasso P., and Gangolli S. D. (1973) - Injection Site Tumours and Preceding Pathological Changes in rats Treated Subcutaneously with Surfactants and Carcinogens Br J Cancer. Mar; 27(3): 230–244.
22. Yusta B, Huang L, Munroe D, Wolff G, Fantaske R, Sharma S. Enteroendocrine localization of GLP-2 receptor expression in humans and rodents. Gastroenterology 2000 Sep;119(3):744-55.
23. NPS. GATTEX (teduglutide [rDNA origin]), for injection, for subcutaneous use. Packag. Inser., 2012.
24. Armstron D el al. Colon polyps in patients with short bowl syndrome before and after teduglutide: Post hoc analysis of the STEPS study series. Clinical Nutrition 39 (2020) 1774e1777
25. Pevny S, Pape UF, Elezkurtai S, et al. De novo development of distal jejunal and duodenal adenomas after 41 months of teduglutide treatment in a patient with short-bowl syndrome: A case report.
26. Thulesen J, Hartmann B, Hare KJ, Kissow H, Ørskov C, Holst JJ, et al. Glucagon-like peptide 2 (GLP-2) accelerates the growth of colonic neoplasms in mice. Gut 2004 Aug;53(8).
27. Jeppesen PB. Intestinal insufficiency and failure. Dan Med Bull 2003 Aug;50(3):238-61.
28. Jeppesen PB, Hartmann B, Thulesen J, Graff J, Lohmann J, Hansen BS, et al. Glucagon-like peptide 2 improves nutrient absorption and nutritional status in short-bowel patients with no colon. Gastroenterology 2001 Mar;120(4):806-15.
29. Naimi RM, Hvistendahl M, Enevoldsen LH, Madsen JL, Fuglsang S, Poulsen SS. Glepaglutide, a novel long-acting glucagon-like peptide-2 analogue, for patients with short bowel syndrome: a randomised phase 2 trial. Lancet Gastroenterol Hepatol 2019 May;4(5):354-363.
30. Messing B, Crenn P, Beau P, Boutron-Ruault MC, Rambaud JC, Matuchansky C. Long-term survival and parenteral nutrition dependence in adult patients with the short bowel syndrome. Gastroenterology 1999 Nov;117(5):1043-50.
31. Cummings JH, James WP, Wiggins HS. Role of the colon in ileal-resection diarroea. Lancet 973 Feb 17;1(7799):344-7.
32. Jeppesen PB. Intestinal insufficiency and failure. Lægeforeningens Forl 2003.

33. Englyst HN, Cummings JH. Non-starch polysaccharides (dietary fiber) and resistant starch. Adv Exp Med Biol 1990;270:205-25.
34. AOAC. AOAC official methods of analysis. Arlingt. AOAC Inc. 1984.
35. Albanese CV, Diessel E, Genant HK. Clinical applications of body composition measurements using DXA. J Clin Densitom 2003 Summer;6(2):75-85.
36. Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: Past, present and future. Appl Health Econ Health Policy 2017 Apr;15(2):127-37.
37. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. October 2013.
38. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R2), Step 4 version. 09 Nov 2016.
39. International Committee of Medical Journal Editors. Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals; current version available at www.icmje.org.
40. U.S. Department of Health and Human Services, Food and Drug Administration. Food and Drug Administration Amendments Act of 2007 as amended by the Final Rule "Clinical Trials Registration and Results Information Submission". 21 September 2016.
41. The European Parliament and the Council of the European Council. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. 2001.
42. The European Parliament and the Council of the European Council. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, article 57. 30 April 2004.