A Phase 3, international, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of glepaglutide in patients with short bowel syndrome (SBS)

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5.1 Primary ObjectiveTo confirm the efficacy of glepaglutide in reducing PS volume in SBS patients.5.2 Secondary ObjectivesTo evaluate the efficacy of glepaglutide on other efficacy endpoints in patients with SBS.To evaluate the safety and...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malabsorption conditions
Study type	Interventional

Summary

ID

NL-OMON52468

Source
ToetsingOnline

Brief title
Efficacy And Safety Evaluation of Glepaglutide in treatment of SBS

Condition

- Malabsorption conditions

Synonym
Short Bowel Syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Zealand Pharma A/S
Source(s) of monetary or material Support: Sponsor Zealand Pharma A/S.

Intervention

Keyword: Glepaglutide, Parenteral Support, Short Bowel Syndrome

Outcome measures

Primary outcome

Reduction in weekly PS volume from baseline to Week 24

Secondary outcome

6.3.2 Key Secondary Endpoints

- Clinical response, defined as achieving at least 20% reduction in weekly PS volume from baseline to both Weeks 20 and 24

- Reduction in days on PS * 1 day/week from baseline to Week 24

- Reduction in weekly PS volume from baseline to Week 12

- Reduction in weekly PS volume of 100% (weaned off) at Week 24

6.3.3 Secondary Efficacy Endpoints

- Reduction of at least 20% in PS volume from baseline to both Weeks 12 and 24

- Change in fluid composite effect (FCE) from baseline to Week 24

- Reduction in calculated energy content of parenteral macronutrients from baseline to Week 24

- Reduction in number of days on PS per week from baseline to Week 24

- Reduction of at least 40% in PS volume from baseline to both Weeks 20 and 24

- PGIC improvement at Weeks 4, 12, 20, and 24

- Change in weight from baseline to week 24

6.3.4 Other Efficacy Endpoints

- Reduction in days on PS * 2 days/week from baseline to Week 24

- Reduction in days on PS * 3 days/week from baseline to Week 24

- Reduction in duration of PS infusions per week from baseline

- Concentration trough levels of glepaglutide and metabolites

- Change in plasma citrulline level from baseline to Week 24

- Change in weekly need for parenteral micronutrients (sodium, potassium,

magnesium, and calcium) from baseline to Week 24

- Change in patient-reported outcomes (SBS-I and EQ-5D-5L) from baseline to

Week 24

- Reduction in bowel movements or stoma bag emptying from baseline to Week 24

Study description

Background summary

Patients with short bowel syndrome (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, resulting in decreased absorptive capacity of the gut. 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. The malabsorption can lead to dehydration, malnutrition, and weight loss if left untreated.
Whereas less severely affected SBS patients are able to compensate for their malabsorption by increasing oral intake (hyperphagia) and adapt metabolically or pharmacologically, more severely affected patients depend upon the safe and well-adjusted provision of parenteral support of nutrients, fluids, electrolytes, vitamins, and trace elements to maintain body function, growth, homeostasis, and health. For those dependent on parenteral support (PS), it is

life-sustaining but at the same time associated with life-threatening complications. Among those are blood stream infections or sepsis, central vein thrombosis, liver damage, and renal impairment. In addition, the treatment burden of parenteral support is substantial. Often 10-18 liters of parenteral support per week are required. In addition to 10- to 12-hour over-night parenteral support 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 parenteral support 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 intestinal growth 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. This trophic effect of GLP-2 has been observed in numerous species, including humans. 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. 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.

Study objective

5.1 Primary Objective
To confirm the efficacy of glepaglutide in reducing PS volume in SBS patients.

5.2 Secondary Objectives
To evaluate the efficacy of glepaglutide on other efficacy endpoints in patients with SBS.
To evaluate the safety and tolerability of glepaglutide in patients with SBS.

Study design

This is a multicenter, placebo-controlled, randomized, parallel-group, double-blind, fixed dose, Phase 3 trial to demonstrate the superiority of once weekly and twice weekly subcutaneous (SC) injections of 10 mg glepaglutide versus placebo in stable SBS patients.
After providing informed consent and initial confirmation of eligibility during the 2-week Screening period, patients will enter a PS Optimization and Stabilization Phase before baseline measurements are performed. An individual

drinking menu will be defined by the patient and the Investigator during the Screening period and until the end of the Optimization Phase. All patients will be equipped with an electronic diary (eDiary) for recording of trial relevant data/information.
Unless otherwise specified, baseline is defined as Day 1, prior to first dosing of trial product.
PS optimization consist of 2 rounds, which limits the Optimization Phase to a maximum duration of 4 weeks (± 4 days). If optimization cannot be shown during the 4-week period, a second Optimization Phase of up to 4 weeks (± 4 days) is allowed. The last Optimization Phase visit can be combined with the first visit in the Stabilization Phase if the patient is considered optimized.

Optimization Phase
During the Optimization Phase, the Investigator may change the PS volume and content if the patient is considered unstable or not optimized. Any changes in PS volume or content will be administered according to institutional standard practice. The effect of any PS optimizations must be investigated after 2 weeks. Prior to an Optimization Phase visit, the patient must measure his/her urine over 48 hours, while adhering to the pre-defined drinking menu, and report the urine volume and oral fluid intake in the eDiary. No more than 2 rounds of PS optimization are allowed to be performed, which limits the Optimization Phase to a maximum duration of 4 weeks (± 4 days). The second Optimization Phase visit can be combined with the first visit in the Stabilization period if the patient is considered optimized.

Stabilization Phase
The Stabilization Phase has a minimum duration of 2 weeks and a maximum duration of 4 weeks (± 4 days). The last visit of the Optimization Phase can also be the first visit of the Stabilization Phase. Prior to the Stabilization Phase visit, the patient must measure his/her urine over 48 hours, while adhering to the pre-defined drinking menu, and report the urine volume and oral fluid intake in the eDiary. Patients will be evaluated every 2 weeks during the Stabilization Phase and will need to fulfill the pre-specified stability criteria before the patient can be randomized. If stability cannot be shown during the 4-week period due to unforeseen events such as infections, illness or similar, a second Stabilization Phase of up to 4 weeks (± 4 days) is allowed.
A patient will be considered stable if all the following criteria are met:
- Actual PS usage (volume and content) matches prescribed PS (± 10% deviation in volume is acceptable) and
- 48-hour urine volumes at 2 consecutive visits within a 2-week interval (± 4 days, i.e., visits should be 10 to 18 days apart) are similar (a maximum of ± 25% deviation is acceptable), while the oral fluid intake is constant (the two 48-hour oral intakes differ less than 10%) and maximum 3.5 L per day and
- Urine volume is on average * 1 L and * 2.5 L per day.

The Investigator and Medical Monitor must both agree and approve that the

patient has met the criteria to be considered stable after completing the Stabilization Phase.
The baseline PS volume (L/week) will be defined as the actual PS volume received during the 7-day period prior to Visit 1 (Day 1). The baseline daily urine volume (L per day) will be defined as the average of the last two 48-hour urine volume measures from the Stabilization Phase.

Main trial period
Visit 1 is done within 2 weeks after the last Stabilization Phase visit. If done on the same day, Visit 1 lab samples should be drawn. All eligible patients who complete the Optimization and Stabilization Phases will be randomized in a 1:1:1 manner to receive either: a) glepaglutide 10 mg twice weekly, b) glepaglutide 10 mg once weekly and placebo once weekly, or c) placebo SC for the following 24 weeks.
During the 24-week Treatment Phase, PS need will be evaluated by 48-hour balance periods involving urine measurements and during which patients will be required to keep to an individually pre-defined drinking menu (timing, volume, and content) and document this in the eDiary.
The actual volume of PS will be recorded on an ongoing basis in electronic diaries (eDiaries) by the patients. The Investigator will record the type, content, and volume of the PS being used. Once trial drug treatment is initiated, PS volume can be adjusted at trial visits (at Weeks 1, 2, 4, 8, 12, 16, 20, and 24) if the criteria for adjustment are met and according to a predefined algorithm.
Algorithm for PS volume reduction:
IF: daily urine volume of the current visit is at least 10% higher than baseline urine volume.
THEN: New PS volume (weekly) = Current PS volume (weekly) * 7 x absolute increase in daily urine volume from baseline

The Investigator may arrange unscheduled visits (preceded by a 48-hour balance period) if he or she considers the visits to be needed based on medical judgement to assess PS volume needs.
It is acknowledged that intake of oral liquids and PS might have to be changed between scheduled visits to avoid edema, especially if treatment is effective. In such cases changes to the PS is at the discretion of the Investigator and the reason needs to be documented in the eCRF.
Any changes to the content of PS are left to the discretion of the Investigator and the reason is documented in the eCRF.
After completing the Treatment Phase, all patients (patients in all 3 treatment groups) will be eligible to enter an Extension Trial and receive glepaglutide. In addition, patients who were dosed but discontinued from trial treatment due to reasons other than an unacceptable adverse event (AE) related to the trial product or withdrawal of consent may be invited to enter the Extension Trial when completing the 24-week Treatment Phase schedule. For patients not entering the Extension Trial, a Follow-up Visit will be conducted 4 weeks after

completion of the Treatment Phase.

Intervention

All patients will receive the following interventions:
- ECG
- Vital signs and physical examination
- Colonoscopy or CT/MRI
- Urine collection
- Pregnancy test (for females of childbearing potential only)
- Blood draws for safety (hematology and chemistry)
- Blood draws for citrulline, anti-drug antibodies and bone markers
- Blood draws for HIV, hepatitis B and hepatitis C testing
- Blood draws for PK
- eDiary and questionnaires
- SC injections with IP or placebo (2x per week)

Study burden and risks

4.3.1 Benefits
For the conducted dose-finding trial ZP1848-15073 testing glepaglutide in SBS patients with or without the need of parenteral support, the primary endpoint of change in wet weight of ostomy/diarrhea output (*wet weight output*) was chosen as the most directly 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 3 trial are likely to experience similar improvements in intestinal function, with reduced dependence on parenteral support as result. Trial patients completing the trial period (including those receiving placebo and patients who were dosed but discontinued from trial treatment due to reasons other than an AE related to the trial product or withdrawal of consent) will receive the opportunity to receive long-term glepaglutide treatment in an Extension Trial to the present trial.

4.3.2 Risks

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.

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 adverse events (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 in the gastrointestinal tract, there are also GLP-2 receptors in the lung, brain, and hypothalamus. 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.

Immunogenicity

Based on the current non-clinical and clinical knowledge of glepaglutide, the risk of immunogenicity (development of anti-drug antibodies [ADA]) 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 ADA will be monitored in this trial, including their glepaglutide neutralizing potential and cross-reactivity to the main glepaglutide metabolite (ZP1848 [1-34]) as well as to 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 FDA in April 2018.
Patients with severe and acute cardiac disease are excluded from trial participation.

Neoplasms
GLP-2 stimulates development of colonic adenomas in rodent models. 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 colonoscopy has been suggested for patients taking GLP-2 analogs who have residual colons. Therefore a screening colonoscopy (within 6 months prior to screening) 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. These are considered adequate precautionary measures. Neoplasms (malignant and benign) are defined as AEs of special interest (AESIs) for the trial.

Risk of underdosing
The PK results and exposure-response analyses for glepaglutide substantiates that both once weekly and twice-weekly dosing of 10 mg glepaglutide result 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.

4.4.3 Overall Benefit-risk Conclusion for the Trial
In conclusion, the benefit-risk ratio for the proposed glepaglutide treatment regimens is considered favorable for the intended trial population, and potential risks are considered appropriately handled and mitigated.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Age * 18 years and * 90 years at Screening.
* Diagnosis of SBS defined as remaining small bowel in continuity of estimated less than 200 cm [equal to 79 inches] and with the latest intestinal resection being at least 6 months prior to Screening and considered stable with regard to PS need.
* No restorative surgery planned in the trial period.
* Willing to adhere to an individual pre-defined drinking menu during 48-hours measuring intervals.
* Requiring PS at least 3 days per week and maintains a stable PS volume for at least 2 weeks. PS volume is considered stable if all of the criteria below are fulfilled:
- Actual PS usage (volume and content) matches prescribed PS (± 10% deviation

in volume is acceptable) and
- 48-hour urine volumes at 2 consecutive visits within a 2-week interval (± 4 days, i.e., visits should be 10 to 18 days apart) are similar (a maximum of ± 25% deviation is acceptable), while the oral fluid intake is constant (the two 48-hour oral intakes differ less than 10%) and maximum 3.5 L per day, and
- Urine volume is on average * 1 L per day and * 2.5 L per day

Exclusion criteria

* 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.
* 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.
* Estimated creatinine clearance (CLcr; by the Cockcroft-Gault formula) < 30 mL/min.
* Hepatic impairment defined as:
- Total bilirubin * 2 × the upper limit of normal (ULN), or
- Aspartate aminotransferase (AST) * 5 × ULN), or
- Alanine aminotransferase (ALT) * 5× ULN
* Use of GLP-1, GLP-2, human growth hormone (HGH), somatostatin, or analogs thereof, within 3 months prior to Screening.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-04-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nvt.
Generic name:	Glepaglutide

Ethics review

Approved WMO Date:	29-08-2018
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	19-10-2018
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	05-12-2018
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	17-01-2019

Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	08-01-2020
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	02-03-2020
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	30-11-2020
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	02-06-2021
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

Approved WMO Date:	05-07-2021
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	11-03-2022
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	21-03-2022
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-004394-14-NL
CCMO	NL65730.099.18