A 104-Week, Multicenter, Single-Arm, Long-Term, Phase 3 Extension Trial Investigating the Safety and Efficacy of Glepaglutide in Adult Patients with Short Bowel Syndrome (SBS) Completing the EASE SBS 2 Trial

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This study has been transitioned to CTIS with ID 2024-513373-43-00 check the CTIS register for the current data. The objectives of this extension trial are to assess the long-term safety and maintenance of efficacy beyond 2 to 2.5 years of treatment...

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

Summary

ID

NL-OMON50675

Source
ToetsingOnline

Brief title
EASE SBS3

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: Extension trial, Glepaglutide, Parenteral Support, Short Bowel Syndrome

Outcome measures

Primary outcome

For all patients, changes from baseline are relative to the baseline assessment

in the lead-in trial, EASE SBS 1, if not otherwise specified.

Safety Endpoints:

Primary Endpoint:

Incidence and type of adverse events (AEs), with onset or worsening following

Visit 1

Secondary outcome

Safety Endpoints:

Secondary Endpoints:

• Incidence and type of serious adverse events (SAEs) and AEs of special

interest (AESIs) (with onset or worsening following Visit 1)

• Changes from baseline in:

- Vital signs

- Electrocardiogram

• Changes from baseline in:

- Hematology

- Biochemistry

- Urinalysis

• Immunogenicity (anti-glepaglutide antibodies, antibody reactivity to ZP18481-34, -cross reactivity to glucagon-like peptide-2 (GLP-2), glepaglutide neutralizing antibodies)

Efficacy Endpoints:

The secondary efficacy endpoints are:

• Reduction in weekly PS volume (prescribed) from baseline

• Reduction of at least 20% in weekly PS volume (prescribed) from baseline

• Reduction in days on PS >= 1 day/week from baseline

• Reduction in weekly PS volume of 100% (weaned off)

Study description

Background summary

Glepaglutide is a glucagon-like peptide (GLP) -2 which is being investigated for treatment of patients with short bowel syndrome (SBS) to improve intestinal absorption of fluids and nutrients. This trial investigates the long-term safety and efficacy of glepaglutide in adult patients with SBS. For information regarding glepaglutide, please see the current version of the Investigator's Brochure.

Study objective

This study has been transitioned to CTIS with ID 2024-513373-43-00 check the CTIS register for the current data.

The objectives of this extension trial are to assess the long-term safety and maintenance of efficacy beyond 2 to 2.5 years of treatment with glepaglutide in adult patients with SBS.

Primary Objective:
To evaluate the long-term safety of glepaglutide treatment

Secondary Objectives:
To evaluate the maintenance of response with regards to efficacy endpoints with glepaglutide 10 mg once weekly (OW)
To assess the long-term immunogenicity of glepaglutide and its impact on pharmacokinetics (PK), safety, and efficacy maintenance

Study design

This is an open-label, multicenter, single-arm, phase 3 extension trial investigating glepaglutide 10 mg administered OW by an auto-injector (AI) in adult patients with SBS completing the EASE SBS 2 trial.
Patients receiving OW or twice weekly (TW) glepaglutide in the EASE SBS 2 trial will receive glepaglutide 10 mg OW in this extension trial.
Treatment in addition to glepaglutide will be according to standard of care.
Pauses in trial drug are allowed.
Relevant data collected during the lead-in pivotal trial ZP1848-17111 (Efficacy and Safety Evaluation of Glepaglutide in Treatment of SBS 1 [EASE SBS 1]), and data from the last visit of EASE SBS 2 trial will be transferred to this trial.
The Investigator will record in the electronic case report form (eCRF) the type, content, and volume of the prescribed parenteral support (PS) on an ongoing basis. Changes to the prescribed volume and content of PS during the 104-week treatment phase are left to the discretion of the Investigator based on institutional practice. The changes and the reason for changes in volume/content should be documented in the eCRF. The Investigator may arrange unscheduled visits during the trial to assess patient safety and PS volume/content needs. Intake of enteral liquid/food will be according to clinical practice per Investigator clinical judgment.
Following exposure to glepaglutide OW or TW for 2 or 2.5 years in the lead-in trial EASE SBS 1 and the extension trial EASE SBS 2, the treatment for this extension trial is glepaglutide 10 mg OW, administered by AI in addition to standard of care. Duration of treatment is 104 weeks. If deterioration in PS needs is observed, the dose of glepaglutide may be increased to 10 mg TW as judged by the Investigator. The reason for TW dosing must be entered in the eCRF.

Intervention

All patients will undergo the following interventions:
- ECG
- Vital signs, including weight
- Physical examination (full physical examination at Visit 1; SBS symptom-driven at all other visits)
- Colonoscopy or CT/MRI (In case a remnant colon is not connected to the passage of foods and thereby dormant, a CT-scan or MRI (if standard of care at site) will suffice at the discretion of the investigator.)
- Urine collection
- Pregnancy test for females of childbearing potential3
- Blood draws for safety (hematology and biochemistry)
- Blood draws for Citrulline
- Blood draws for PK
- Blood draws for anti-drug antibodies
- Administration of IP via auto-injector

Study burden and risks

Benefits:
The completed dose-finding phase 2 trial ZP1848-15073 tested glepaglutide in patients with SBS 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, improved macronutrient absorption was seen for the 1 mg/day and 10 mg/day glepaglutide dose level, 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. Patients receiving glepaglutide treatment in this extension trial are likely to experience maintenance of intestinal function, with reduced dependence on PS as a result.

Risks:
Overal 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 Wistar 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 be 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 be 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 a 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 extension 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). 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 injection site reactions, 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 in 2 patients in the 0.1 mg glepaglutide dose group and 8 events reported in 6 patients in the 10.0 mg glepaglutide dose group, 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. So far, clinically significant off-intestinal targeted effects resulting from these additional receptor sites have not been seen.
Studies with 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 pharmacokinetics (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, reactivity to the main glepaglutide metabolite (ZP18481-34) as well as potential crossreactivity 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 effects at the intended dose level, on which grounds a waiver for a dedicated thorough QT study was granted by the Food and Drug Administration in April 2018.

Neoplasms:
GLP-2 and GLP-2 analogs stimulate development of colonic adenomas in rodent models. Increases in plasma citrulline concentrations as seen with GLP-2 analog treatment indicate an intestinotrophic effect with increases in enterocyte mass and intestinal surface area. Consequently, it cannot be excluded that treatment with glepaglutide could 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 patien

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

The patient must meet both of the following inclusion criteria:
1. Signed informed consent
2. Completed the full treatment period of the extension trial EASE SBS 2

Exclusion criteria

The patient must be excluded from this trial if any of the following criteria are met:
1. Any condition, disease, or circumstance that in the Investigator*s opinion would put the patient at any undue risk, prevent completion of the trial, or confound the planned assessments of the trial.

2. Not having a colonoscopy performed at EOT in EASE SBS 2 (for patients with remnant colon).
Note: The results of the colonoscopy must not give rise to any safety concerns. A colonoscopy performed within 6 months prior to EOT and not giving rise to any safety concerns is accepted. For patients with a remnant colon, which is not connected to the passage of foods and is thereby dormant, a computerized tomography (CT) scan or magnetic resonance imaging (MRI) will suffice at the discretion of the Investigator.
3. Use of GLP-1, GLP-2, human growth hormone (HGH), dipeptidyl peptidase-4 (DPP-4) inhibitors, somatostatin, or analogs thereof within 3 months. Note: Prior use of glepaglutide trial drug is allowed.
4. Females of childbearing potential, who are pregnant, breast-feeding, intend to become pregnant, or are not using highly effective contraceptive methods.
5. Committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.
6. An employee of the sponsor or Investigator or otherwise dependent on them.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-04-2022
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Glepaglutide
Generic name:	-

Ethics review

Approved WMO Date:	13-10-2021
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	13-12-2021
Application type:	First submission
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	17-05-2022
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	23-05-2022
Application type:	Amendment
Review commission:	RTPO, Regionale Toetsingscie Patientgebonden Onderzoek (Leeuwarden)
Approved WMO Date:	18-09-2023
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
EU-CTR	CTIS2024-513373-43-00
EudraCT	EUCTR2020-005502-25-NL
CCMO	NL79050.099.21