



Clinical trial results:

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)

Summary

| | |
|--------------------------|-------------------------|
| EudraCT number | 2017-004394-14 |
| Trial protocol | NL FR GB DE BE DK PL IT |
| Global end of trial date | 26 July 2022 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 12 June 2024 |
| First version publication date | 12 June 2024 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | ZP1848-17111 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | IND: 133151 |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Zealand Pharma A/S |
| Sponsor organisation address | Sydmarken 11, Søborg, Denmark, DK-2860 |
| Public contact | Head of clinical operations, Zealand Pharma A/S, +45 8877 3600, info@zealandpharma.com |
| Scientific contact | Head of clinical operations, Zealand Pharma A/S, +45 8877 3600, info@zealandpharma.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 14 September 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 26 July 2022 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 July 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To confirm the efficacy of glepaglutide in reducing parenteral support (PS) volume in Short Bowel Syndrome (SBS) patients.

Protection of trial subjects:

This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP) and the Declaration of Helsinki, as well as in accordance with other applicable local ethical and legal requirements. The investigator had both ethical and legal responsibility to ensure that each individual being considered for inclusion in this trial was given a full explanation of the protocol. Informed consent was obtained and documented prior to initiation of any procedures.

Background therapy:

Of the 106 patients randomized, 104 used one or more concomitant medications at the beginning of the treatment period, the most commonly used concomitant medications commenced or ongoing at the first dose date belonged to the ATC class 'Alimentary tract and metabolism'.

Evidence for comparator:

Placebo

| | |
|---|-----------------|
| Actual start date of recruitment | 04 October 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 23 |
| Country: Number of subjects enrolled | Canada: 4 |
| Country: Number of subjects enrolled | Netherlands: 4 |
| Country: Number of subjects enrolled | Poland: 27 |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | Belgium: 10 |
| Country: Number of subjects enrolled | Denmark: 8 |
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Germany: 12 |
| Worldwide total number of subjects | 106 |
| EEA total number of subjects | 70 |

Notes:

| Subjects enrolled per age group | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 81 |
| From 65 to 84 years | 25 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This trial was conducted in (number of sites that randomized patients in parenthesis) Belgium (1), Denmark (2), France (2), Germany (5), the Netherlands (1), Poland (3), Canada (3), the US (7), and the UK (5).

Pre-assignment

Screening details:

After Screening period, patients enter a PS Optimization and Stabilization Phase before randomization. During Optimization Phase, the Investigator may change PS volume and content if the patient is unstable or not optimized. During Stabilization Phase the patient need to fulfill pre-specified stability criteria before the patient can be randomized.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Treatment period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

Blinding implementation details:

Both the patient and investigator were blinded to the actual content of each vial (active or placebo). Patients were randomly assigned to trial treatments using an automatic, Interactive Response Technology (IRT).

Arms

| | |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Glepaglutide 10 mg twice weekly |

Arm description:

Patients randomized to receive twice weekly a subcutaneous injection of 10 mg Glepaglutide in patients' preferred injection site area: abdomen or thigh.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Glepaglutide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Glepaglutide 10 mg was administered twice weekly as a subcutaneous injection in patients' preferred injection site area: abdomen or thigh.

| | |
|------------------|--------------------------------|
| Arm title | Glepaglutide 10 mg once weekly |
|------------------|--------------------------------|

Arm description:

Patients randomized to receive once weekly a subcutaneous injection of 10 mg Glepaglutide and once weekly an injection with placebo in patients' preferred injection site area: abdomen or thigh.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Glepaglutide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Glepaglutide 10 mg was administered once weekly as a subcutaneous injection in patients' preferred injection site area: abdomen or thigh.

| | |
|--|------------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo was administered once weekly as a subcutaneous injection in patients' preferred injection site area: abdomen or thigh.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Patients randomized to receive twice weekly a subcutaneous injection of placebo in patients' preferred injection site area: abdomen or thigh.

| | |
|--|------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo was administered twice weekly as a subcutaneous injection in patients' preferred injection site area: abdomen or thigh.

| Number of subjects in period 1 | Glepaglutide 10 mg twice weekly | Glepaglutide 10 mg once weekly | Placebo |
|---------------------------------------|------------------------------------|-----------------------------------|---------|
| Started | 35 | 35 | 36 |
| Completed | 31 | 35 | 36 |
| Not completed | 4 | 0 | 0 |
| Consent withdrawn by subject | 2 | - | - |
| Adverse event, non-fatal | 2 | - | - |

Baseline characteristics

Reporting groups

| | |
|---|---------------------------------|
| Reporting group title | Glepaglutide 10 mg twice weekly |
| Reporting group description: Patients randomized to receive twice weekly a subcutaneous injection of 10 mg Glepaglutide in patients' preferred injection site area: abdomen or thigh. | |
| Reporting group title | Glepaglutide 10 mg once weekly |
| Reporting group description: Patients randomized to receive once weekly a subcutaneous injection of 10 mg Glepaglutide and once weekly an injection with placebo in patients' preferred injection site area: abdomen or thigh. | |
| Reporting group title | Placebo |
| Reporting group description: Patients randomized to receive twice weekly a subcutaneous injection of placebo in patients' preferred injection site area: abdomen or thigh. | |

| Reporting group values | Glepaglutide 10 mg twice weekly | Glepaglutide 10 mg once weekly | Placebo |
|---------------------------------------|---------------------------------|--------------------------------|---------|
| Number of subjects | 35 | 35 | 36 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 23 | 28 | 30 |
| From 65-84 years | 12 | 7 | 6 |
| Age continuous Units: years | | | |
| arithmetic mean | 56.9 | 54.0 | 55.0 |
| standard deviation | ± 13.4 | ± 12.0 | ± 11.8 |
| Gender categorical Units: Subjects | | | |
| Female | 19 | 18 | 30 |
| Male | 16 | 17 | 6 |

| Reporting group values | Total | | |
|---------------------------------------|-------|--|--|
| Number of subjects | 106 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 81 | | |
| From 65-84 years | 25 | | |
| Age continuous Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 67 | | |
| Male | 39 | | |

End points

End points reporting groups

| | |
|---|---------------------------------|
| Reporting group title | Glepaglutide 10 mg twice weekly |
| Reporting group description: Patients randomized to receive twice weekly a subcutaneous injection of 10 mg Glepaglutide in patients' preferred injection site area: abdomen or thigh. | |
| Reporting group title | Glepaglutide 10 mg once weekly |
| Reporting group description: Patients randomized to receive once weekly a subcutaneous injection of 10 mg Glepaglutide and once weekly an injection with placebo in patients' preferred injection site area: abdomen or thigh. | |
| Reporting group title | Placebo |
| Reporting group description: Patients randomized to receive twice weekly a subcutaneous injection of placebo in patients' preferred injection site area: abdomen or thigh. | |

Primary: Change in actual weekly PS volume from baseline to Week 24

| | |
|--|--|
| End point title | Change in actual weekly PS volume from baseline to Week 24 |
| End point description: | |
| End point type | Primary |
| End point timeframe: From baseline to Week 24 | |

| End point values | Glepaglutide 10 mg twice weekly | Glepaglutide 10 mg once weekly | Placebo | |
|--|---------------------------------|--------------------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 35 | 35 | 36 | |
| Units: number | | | | |
| least squares mean (confidence interval 95%) | | | | |
| Week 24 | -5.13 (-6.24 to -4.02) | -3.76 (-4.96 to -2.56) | -2.85 (-3.93 to -1.77) | |

Statistical analyses

| | |
|--|---|
| Statistical analysis title | Primary analysis - MI CR |
| Statistical analysis description: The primary analysis uses a restricted maximum likelihood (REML)-based repeated-measures approach to compare treatment groups with respect to the mean change from baseline in actual weekly PS volume at Week 24. The primary comparisons are the contrasts (differences in least squares means) between the glepaglutide treatment groups and the placebo group at the Week 24 visit in this mixed-effects model for repeated measures. | |
| Comparison groups | Glepaglutide 10 mg twice weekly v Placebo |

| | |
|---|-----------------------|
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0039 |
| Method | Mixed models analysis |
| Parameter estimate | Difference to Placebo |
| Point estimate | -2.28 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.83 |
| upper limit | -0.73 |

| | |
|-----------------------------------|--------------------------|
| Statistical analysis title | Primary analysis - MI CR |
|-----------------------------------|--------------------------|

Statistical analysis description:

The primary analysis uses a restricted maximum likelihood (REML)-based repeated-measures approach to compare treatment groups with respect to the mean change from baseline in actual weekly PS volume at Week 24. The primary comparisons are the contrasts (differences in least squares means) between the glepaglutide treatment groups and the placebo group at the Week 24 visit in this mixed-effects model for repeated measures.

| | |
|---|--|
| Comparison groups | Glepaglutide 10 mg once weekly v Placebo |
| Number of subjects included in analysis | 71 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.27 |
| Method | Mixed models analysis |
| Parameter estimate | Difference to Placebo |
| Point estimate | -0.91 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.52 |
| upper limit | 0.71 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs, whether serious or non-serious, were to be reported from the time a signed and dated Informed Consent Form (ICF) was obtained until the end of the post-treatment follow-up period.

Adverse event reporting additional description:

For 'Stoma complications' and related preferred terms, the denominators used in the calculation of % are based on patients with a small intestine stoma (Glepa 10 mg TW: N=17; Glepa 10 mg OW: N=20; Placebo: N=21).

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 24.1 |

Reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | Glepaglutide 10 mg twice weekly |
|-----------------------|---------------------------------|

Reporting group description:

Patients randomized to receive twice weekly a subcutaneous injection of 10 mg Glepaglutide.

| | |
|-----------------------|--------------------------------|
| Reporting group title | Glepaglutide 10 mg once weekly |
|-----------------------|--------------------------------|

Reporting group description:

Patients randomized to receive once weekly a subcutaneous injection of 10 mg Glepaglutide and once weekly a subcutaneous injection with placebo.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Patients randomized to receive twice weekly a subcutaneous injection of placebo.

| Serious adverse events | Glepaglutide 10 mg twice weekly | Glepaglutide 10 mg once weekly | Placebo |
|---|---------------------------------|--------------------------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 35 (25.71%) | 9 / 35 (25.71%) | 7 / 36 (19.44%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Stoma site haemorrhage | | | |
| subjects affected / exposed ^[1] | 1 / 17 (5.88%) | 0 / 20 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acetabulum fracture | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 35 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Alcohol poisoning | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 35 (0.00%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural pneumothorax | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 35 (0.00%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 35 (2.86%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 35 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Blood loss anaemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 35 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 35 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 2 / 35 (5.71%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site necrosis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 35 (2.86%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 35 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 35 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 35 (0.00%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 35 (2.86%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Device related sepsis | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 2 / 35 (5.71%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 35 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 35 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular device infection | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 2 / 35 (5.71%) | 2 / 36 (5.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 35 (2.86%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal viral infection | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 35 (2.86%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Product issues | | | |
| Device breakage | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 35 (0.00%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device malfunction | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 35 (0.00%) | 1 / 36 (2.78%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 35 (0.00%) | 0 / 36 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: For the 'Stoma complications' and related preferred terms, the denominators used in the calculation of % are based on patients with small intestine stoma (Glepa 10 mg TW: N=17; Glepa 10 mg OW: N=20; Placebo: N=21).

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Glepaglutide 10 mg twice weekly | Glepaglutide 10 mg once weekly | Placebo |
|---|------------------------------------|-----------------------------------|------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 30 / 35 (85.71%) | 31 / 35 (88.57%) | 24 / 36 (66.67%) |
| Investigations | | | |
| Weight decreased subjects affected / exposed | 2 / 35 (5.71%) | 1 / 35 (2.86%) | 2 / 36 (5.56%) |
| occurrences (all) | 2 | 1 | 2 |
| Aspartate aminotransferase increased subjects affected / exposed | 2 / 35 (5.71%) | 1 / 35 (2.86%) | 0 / 36 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| Stoma site oedema subjects affected / exposed ^[2] | 4 / 17 (23.53%) | 2 / 20 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 4 | 11 | 0 |
| Stoma complication subjects affected / exposed ^[3] | 1 / 17 (5.88%) | 2 / 20 (10.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Stomal hernia subjects affected / exposed ^[4] | 1 / 17 (5.88%) | 0 / 20 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Procedural pain subjects affected / exposed | 2 / 35 (5.71%) | 1 / 35 (2.86%) | 0 / 36 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |
| Fall subjects affected / exposed | 0 / 35 (0.00%) | 2 / 35 (5.71%) | 0 / 36 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Stoma site irritation subjects affected / exposed ^[5] | 0 / 17 (0.00%) | 1 / 20 (5.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Headache subjects affected / exposed | 4 / 35 (11.43%) | 2 / 35 (5.71%) | 3 / 36 (8.33%) |
| occurrences (all) | 5 | 2 | 7 |
| Dizziness subjects affected / exposed | 2 / 35 (5.71%) | 2 / 35 (5.71%) | 0 / 36 (0.00%) |
| occurrences (all) | 3 | 2 | 0 |

| | | | |
|--|-----------------|------------------|----------------|
| General disorders and administration site conditions | | | |
| Injection site reaction | | | |
| subjects affected / exposed | 9 / 35 (25.71%) | 15 / 35 (42.86%) | 0 / 36 (0.00%) |
| occurrences (all) | 135 | 114 | 0 |
| Injection site erythema | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | 6 / 35 (17.14%) | 1 / 36 (2.78%) |
| occurrences (all) | 6 | 60 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 1 / 35 (2.86%) | 1 / 36 (2.78%) |
| occurrences (all) | 4 | 1 | 2 |
| Fatigue | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 4 / 35 (11.43%) | 0 / 36 (0.00%) |
| occurrences (all) | 4 | 6 | 0 |
| Injection site pain | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 3 / 35 (8.57%) | 0 / 36 (0.00%) |
| occurrences (all) | 31 | 29 | 0 |
| Injection site induration | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 2 / 35 (5.71%) | 0 / 36 (0.00%) |
| occurrences (all) | 44 | 3 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 0 / 35 (0.00%) | 2 / 36 (5.56%) |
| occurrences (all) | 4 | 0 | 2 |
| Injection site irritation | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 0 / 35 (0.00%) | 0 / 36 (0.00%) |
| occurrences (all) | 13 | 0 | 0 |
| Feeling hot | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 35 (0.00%) | 0 / 36 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Injection site rash | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 35 (0.00%) | 0 / 36 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 35 (0.00%) | 0 / 36 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Injection site pruritus | | | |

| | | | |
|---|----------------------|-----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 3 | 4 / 35 (11.43%) 22 | 1 / 36 (2.78%) 1 |
| Complication associated with device subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 2 / 35 (5.71%) 2 | 0 / 36 (0.00%) 0 |
| Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | 0 / 35 (0.00%) 0 | 0 / 36 (0.00%) 0 |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all) | 7 / 35 (20.00%) 8 | 3 / 35 (8.57%) 3 | 1 / 36 (2.78%) 8 |
| Abdominal pain subjects affected / exposed occurrences (all) | 5 / 35 (14.29%) 8 | 6 / 35 (17.14%) 7 | 2 / 36 (5.56%) 2 |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 35 (8.57%) 5 | 6 / 35 (17.14%) 6 | 0 / 36 (0.00%) 0 |
| Abdominal discomfort subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | 0 / 35 (0.00%) 0 | 2 / 36 (5.56%) 3 |
| Dry mouth subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | 0 / 35 (0.00%) 0 | 0 / 36 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | 2 / 35 (5.71%) 2 | 1 / 36 (2.78%) 1 |
| Abdominal distension subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | 2 / 35 (5.71%) 2 | 0 / 36 (0.00%) 0 |
| Abdominal pain lower subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 2 / 35 (5.71%) 2 | 0 / 36 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|---|--|--|--|
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | 1 / 35 (2.86%) 1 | 0 / 36 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | 2 / 35 (5.71%) 3 | 1 / 36 (2.78%) 1 |
| Musculoskeletal and connective tissue disorders Muscle spasms subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Osteoporosis subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 2 / 35 (5.71%) 2 0 / 35 (0.00%) 0 1 / 35 (2.86%) 1 | 1 / 35 (2.86%) 1 1 / 35 (2.86%) 1 2 / 35 (5.71%) 2 1 / 35 (2.86%) 1 | 3 / 36 (8.33%) 3 1 / 36 (2.78%) 1 0 / 36 (0.00%) 0 3 / 36 (8.33%) 4 |
| Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Gastrointestinal bacterial overgrowth subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 1 / 35 (2.86%) 1 0 / 35 (0.00%) 0 | 0 / 35 (0.00%) 0 1 / 35 (2.86%) 1 3 / 35 (8.57%) 3 | 2 / 36 (5.56%) 2 3 / 36 (8.33%) 4 0 / 36 (0.00%) 0 |
| Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences (all) Hypomagnesaemia | 4 / 35 (11.43%) 4 | 1 / 35 (2.86%) 1 | 0 / 36 (0.00%) 0 |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 35 (0.00%) | 2 / 35 (5.71%) | 1 / 36 (2.78%) |
| occurrences (all) | 0 | 2 | 1 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 0 / 35 (0.00%) | 2 / 36 (5.56%) |
| occurrences (all) | 0 | 0 | 2 |

Notes:

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For the 'Stoma complications' and related preferred terms, the denominators used in the calculation of % are based on patients with small intestine stoma (Glepa 10 mg TW: N=17; Glepa 10 mg OW: N=20; Placebo: N=21).

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For the 'Stoma complications' and related preferred terms, the denominators used in the calculation of % are based on patients with small intestine stoma (Glepa 10 mg TW: N=17; Glepa 10 mg OW: N=20; Placebo: N=21).

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For the 'Stoma complications' and related preferred terms, the denominators used in the calculation of % are based on patients with small intestine stoma (Glepa 10 mg TW: N=17; Glepa 10 mg OW: N=20; Placebo: N=21).

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: For the 'Stoma complications' and related preferred terms, the denominators used in the calculation of % are based on patients with small intestine stoma (Glepa 10 mg TW: N=17; Glepa 10 mg OW: N=20; Placebo: N=21).

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 24 October 2018 | <p>Protocol v. 4.0</p> <ul style="list-style-type: none">• Reduction in weekly PS volume from baseline to Week 24 was changed from a key secondary endpoint to a primary endpoint• Clinical response, defined as achieving at least 20% reduction in PS volume from baseline to both Weeks 20 and 24 was changed from the primary endpoint to a key secondary endpoint• Reduction of at least 20% in PS volume from baseline to both Weeks 12 and 24 was changed from key secondary endpoint to secondary efficacy endpoint.• Changed the definition of the intention-to-treat (ITT) analysis set to include those we received at least 1 dose of investigational product• Added that patients were to measure their body weight weekly• Added the estimand section• Added that all efforts should be made to complete the assessment of actual PS volume at Week 24 in patients who could not adhere to the visit schedule• Added that a maximum of 4 week of treatment pause was allowed. After that, the patient was to be discontinued for the remainder of the trial but encouraged to attend all visits and complete all assessments.• Added lab sampling in case of suspected liver injury to unscheduled visit• Adapted the SBS characteristics and disease history based on a new reference• Added that all relevant previous treatments, including treatment with teduglutide, any other GLP-2 analogs or native GLP-2 was to be recorded in the eCRF• Added pancreatitis and cholecystitis to the list of AESIs |
| 18 September 2019 | <p>Protocol v. 5.0</p> <p>Extended the screening period from 1 week to 2 weeks</p> <ul style="list-style-type: none">• Added that a second optimization phase may be done• Added reduction in duration of PS infusions per week from baseline to other efficacy endpoints• Added FSH testing to confirm menopause• Added the Exit Interview at UK and US sites only• Added reduction in duration of PS infusions per week from baseline as another efficacy endpoint and described how the results are presented• Added that for each AESI, a time to event analysis was performed |
| 12 November 2019 | <p>Protocol v. 6.0</p> <p>Clarification on AE reporting in cases of worsening of severity or seriousness</p> |
| 05 December 2019 | <p>Protocol v. 7.0</p> <ul style="list-style-type: none">• Added change in weight from baseline to Week 24 as a secondary efficacy endpoint and described how the results are presented• Updated the trial design figure• Stated that the randomization codes will be supplied to the bioanalytical teams at Charles River (PK analyses) and Syrinx (ADA analyses). |
| 15 October 2020 | <p>Protocol v. 8.0</p> <ul style="list-style-type: none">• Added wording about blinding/unblinding of samples and that all PK and ADA samples are shipped to the laboratory. |
| 03 March 2021 | <p>Protocol v. 9.0</p> <ul style="list-style-type: none">• Added that exit interviews will be conducted at Danish, French and German sites as well as the UK and US sites• Add a longer enrollment period due to COVID-19• Changed the trial design to a group sequential design incorporating one interim analysis for efficacy/futility |

| | |
|-----------------|---|
| 27 January 2022 | Protocol v. 10.0 <ul style="list-style-type: none"> • Removed the planned interim analysis in order to stop the trial with a reduced sample size • Updated the number to patients expected • Updated the power calculation based on the reduced patient population |
|-----------------|---|

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported