



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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	Glepaglutide 10 mg twice weekly
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Reporting group description:

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

Reporting group title	Glepaglutide 10 mg once weekly
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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
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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	1 / 35 (2.86%)	4 / 35 (11.43%)	1 / 36 (2.78%)
occurrences (all)	3	22	1
Complication associated with device			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	7 / 35 (20.00%)	3 / 35 (8.57%)	1 / 36 (2.78%)
occurrences (all)	8	3	8
Abdominal pain			
subjects affected / exposed	5 / 35 (14.29%)	6 / 35 (17.14%)	2 / 36 (5.56%)
occurrences (all)	8	7	2
Vomiting			
subjects affected / exposed	3 / 35 (8.57%)	6 / 35 (17.14%)	0 / 36 (0.00%)
occurrences (all)	5	6	0
Abdominal discomfort			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	2 / 36 (5.56%)
occurrences (all)	2	0	3
Dry mouth			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
Diarrhoea			
subjects affected / exposed	1 / 35 (2.86%)	2 / 35 (5.71%)	1 / 36 (2.78%)
occurrences (all)	1	2	1
Abdominal distension			
subjects affected / exposed	1 / 35 (2.86%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	1	2	0
Abdominal pain lower			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	0	2	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
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported