Clinical trial results:
Efficacy and safety of semaglutide 2.0 mg s.c. once-weekly compared to semaglutide 1.0 mg s.c. once-weekly in subjects with type 2 diabetes

Summary

EudraCT number	2018-004529-96
Trial protocol	SK CZ PL BG GR
Global end of trial date	09 November 2020

Results information

Result version number	v1 (current)
This version publication date	25 November 2021
First version publication date	25 November 2021

Trial information

Trial identification

Sponsor protocol code	NN9535-4506

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03989232
WHO universal trial number (UTN)	U1111-1224-5162

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsværd, Denmark, 2880
Public contact	Clinical Transparency and Medical Writing Office (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Transparency and Medical Writing Office (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.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	17 December 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 September 2020
Global end of trial reached?	Yes
Global end of trial date	09 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to establish the superior effect of semaglutide subcutaneous (s.c.) 2.0 milligrams (mg) once-weekly versus semaglutide s.c. 1.0 mg once-weekly on glycaemic control in subjects with type 2 diabetes (T2D), on a background of metformin with or without sulfonyl urea (SU) treatment.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (2016), including archiving of essential documents, and 21 CFR 312.120

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 June 2019
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	Bulgaria: 96
Country: Number of subjects enrolled	Canada: 20
Country: Number of subjects enrolled	Czechia: 15
Country: Number of subjects enrolled	Greece: 37
Country: Number of subjects enrolled	Hungary: 156
Country: Number of subjects enrolled	Japan: 50
Country: Number of subjects enrolled	Poland: 136
Country: Number of subjects enrolled	Slovakia: 92
Country: Number of subjects enrolled	Ukraine: 50
Country: Number of subjects enrolled	United States: 309
Worldwide total number of subjects	961
EEA total number of subjects	532

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	690
From 65 to 84 years	270
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 125 sites in Bulgaria (9), Canada (8), Czech Republic (4), Greece (6), Hungary (12), Japan (2), Poland (10), Slovakia (11), Ukraine (5) and the United States (58). 4 sites in the US screened but did not randomize subjects, and 3 sites were approved by the IRB/IEC but did not screen or assign any subjects to treatment.

Pre-assignment

Screening details:

Subjects with type 2 diabetes (T2D) treated with stable doses of metformin only, or metformin in combination with sulfonylurea (SU), in need of the treatment intensification were randomized 1:1 to once-weekly treatment with semaglutide 2.0 mg or once-weekly treatment with semaglutide 1.0 mg.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The first 12 weeks during escalation all the trial products were packed open-label as all subjects followed the same treatment regimen in this period. From week 13 the subject was to receive trial product which was packed open-label (which contained semaglutide), as well as trial product which was packed blinded (and contained either semaglutide or placebo). The active drug and placebo drug were visually identical.

Arms

Are arms mutually exclusive?	Yes
Arm title	Semaglutide 1.0 mg

Arm description:

Subjects received subcutaneous (s.c.) injection of semaglutide once-weekly for 40 weeks in a fixed-dose escalation regimen, with dose doubling every 4 weeks until the target dose of 1.0 mg was reached: 0.25 mg during 0-4 weeks followed by 0.5 mg during 4-8 weeks followed by 1.0 mg during 8-12 weeks and then 1.0 mg semaglutide along with s.c. injection of placebo matched to semaglutide 1.0 mg during 12-40 weeks.

Arm type	Active comparator
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:

Subjects received s.c. injection of placebo matched to semaglutide 1.0 mg during 12-40 weeks.

Investigational medicinal product name	Semaglutide B 1.34 mg/ml PDS290
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received s.c. injection of semaglutide once-weekly for 40 weeks in a fixed-dose escalation regimen, with dose doubling every 4 weeks until the target maintenance dose was reached.

Arm title	Semaglutide 2.0 mg

Arm description:

Subjects received s.c. injection of semaglutide once-weekly for 40 weeks in a fixed-dose escalation

regimen, with dose doubling every 4 weeks until the target maintenance dose of 2.0 mg was reached: 0.25 mg during 0-4 weeks followed by 0.5 mg during 4-8 weeks followed by 1.0 mg during 8-12 weeks and then 2.0 mg during 12-40 weeks.

Arm type	Experimental
Investigational medicinal product name	Semaglutide B 1.34 mg/ml PDS290
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects received s.c. injection of semaglutide once-weekly for 40 weeks in a fixed-dose escalation regimen, with dose doubling every 4 weeks until the target maintenance dose was reached.

Number of subjects in period 1	Semaglutide 1.0 mg	Semaglutide 2.0 mg
Started	481	480
Completed	471	462
Not completed	10	18
Adverse event, serious fatal	1	2
Consent withdrawn by subject	6	6
Lost to follow-up	3	10

Baseline characteristics

Reporting groups	
Reporting group title	Semaglutide 1.0 mg
Reporting group description:	
Subjects received subcutaneous (s.c.) injection of semaglutide once-weekly for 40 weeks in a fixed-dose escalation regimen, with dose doubling every 4 weeks until the target dose of 1.0 mg was reached: 0.25 mg during 0-4 weeks followed by 0.5 mg during 4-8 weeks followed by 1.0 mg during 8-12 weeks and then 1.0 mg semaglutide along with s.c. injection of placebo matched to semaglutide 1.0 mg during 12-40 weeks.	
Reporting group title	Semaglutide 2.0 mg
Reporting group description:	
Subjects received s.c. injection of semaglutide once-weekly for 40 weeks in a fixed-dose escalation regimen, with dose doubling every 4 weeks until the target maintenance dose of 2.0 mg was reached: 0.25 mg during 0-4 weeks followed by 0.5 mg during 4-8 weeks followed by 1.0 mg during 8-12 weeks and then 2.0 mg during 12-40 weeks.	

Reporting group values	Semaglutide 1.0 mg	Semaglutide 2.0 mg	Total
Number of subjects	481	480	961
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	58.2	57.9	
standard deviation	± 9.9	± 10.0	-
Gender Categorical Units: Subjects			
Female	197	201	398
Male	284	279	563

End points

End points reporting groups

Reporting group title	Semaglutide 1.0 mg

Reporting group description:

Subjects received subcutaneous (s.c.) injection of semaglutide once-weekly for 40 weeks in a fixed-dose escalation regimen, with dose doubling every 4 weeks until the target dose of 1.0 mg was reached: 0.25 mg during 0-4 weeks followed by 0.5 mg during 4-8 weeks followed by 1.0 mg during 8-12 weeks and then 1.0 mg semaglutide along with s.c. injection of placebo matched to semaglutide 1.0 mg during 12-40 weeks.

Reporting group title	Semaglutide 2.0 mg

Reporting group description:

Subjects received s.c. injection of semaglutide once-weekly for 40 weeks in a fixed-dose escalation regimen, with dose doubling every 4 weeks until the target maintenance dose of 2.0 mg was reached: 0.25 mg during 0-4 weeks followed by 0.5 mg during 4-8 weeks followed by 1.0 mg during 8-12 weeks and then 2.0 mg during 12-40 weeks.

Primary: Change in HbA1c (%-points)

End point title	Change in HbA1c (%-points)

End point description:

Change from baseline (week 0) to week 40 in glycosylated haemoglobin (HbA1c) was evaluated. Results are based on the 'on-treatment without rescue medication' observation period, which started at the date of first dose of trial product to either first initiation of rescue medication or the day of last dose of trial product plus 14 days, whichever came first; and 'In-trial' observation period which started at the date of randomisation and ended at the first of the following dates, both inclusive: follow-up visit (week 47), death, subject withdrew informed consent, last contact for subject lost to follow-up. The FAS included all randomized subjects. In below table, n=number of subjects contributed to the analysis.

End point type	Primary

End point timeframe:

From baseline (week 0) to week 40

End point values	Semaglutide 1.0 mg	Semaglutide 2.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	481	480		
Units: Percentage change of HbA1c				
arithmetic mean (standard deviation)				
On-treatment without rescue medication (n=422,423)	-2.0 (± 1.0)	-2.2 (± 1.0)		
In-trial (n=466,456)	-1.9 (± 1.0)	-2.2 (± 1.1)		

Statistical analyses

Statistical analysis title	Semaglutide 2.0 mg - Semaglutide 1.0 mg

Statistical analysis description:

Imputation of missing data was handled by multiple imputation (MI) assuming that missing data were missed at random (MAR). The imputation was performed separately within each treatment group defined by randomised treatment.

Comparison groups	Semaglutide 2.0 mg v Semaglutide 1.0 mg
Number of subjects included in analysis	961
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0003
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	-0.11

Statistical analysis title	In-trial: Semaglutide 2.0 mg - Semaglutide 1.0 mg

Statistical analysis description:

Imputation of missing data was handled by MI assuming that missing data were missed at random. The imputation was performed by imputing missing week 40 data separately within groups defined by randomised treatment and treatment status at week 40.

Comparison groups	Semaglutide 1.0 mg v Semaglutide 2.0 mg
Number of subjects included in analysis	961
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0098
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	-0.04

Secondary: Change in body weight (kg)

End point title	Change in body weight (kg)

End point description:

Change from baseline (week 0) to week 40 in body weight was evaluated. Results are based on the 'on-treatment without rescue medication' observation period, which started at the date of first dose of trial product to either first initiation of rescue medication or the day of last dose of trial product plus 14 days, whichever came first; and 'In-trial' observation period which started at the date of randomisation and ended at the first of the following dates, both inclusive: follow-up visit (week 47), death, subject withdrew informed consent, last contact for subject lost to follow-up. The FAS included all randomized subjects. In the below table, n=number of subjects contributed to the analysis

End point type	Secondary

End point timeframe:

From baseline (week 0) to week 40

End point values	Semaglutide 1.0 mg	Semaglutide 2.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	481	480		
Units: Kilogram (kg)				
arithmetic mean (standard deviation)				
On-treatment without rescue medication (n=425,434)	-6.0 (± 5.8)	-7.0 (± 5.8)		
In-trial (n=467,457)	-5.7 (± 5.9)	-6.7 (± 5.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (FPG) (mmol/l)

End point title	Change in fasting plasma glucose (FPG) (mmol/l)

End point description:

Change from baseline (week 0) to week 40 in FPG was evaluated. Results are based on the 'on-treatment without rescue medication' observation period, which started at the date of first dose of trial product to either first initiation of rescue medication or the day of last dose of trial product plus 14 days, whichever came first. The FAS included all randomized subjects. Number of subjects analyzed=number of subjects contributed to the analysis.

End point type	Secondary

End point timeframe:

From baseline (week 0) to week 40

End point values	Semaglutide 1.0 mg	Semaglutide 2.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	429		
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	-3.2 (± 2.8)	-3.4 (± 3.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body mass index (BMI) (kg/m2)

End point title	Change in body mass index (BMI) (kg/m2)

End point description:

Change from baseline (week 0) to week 40 in BMI was evaluated. Results are based on the 'on-treatment without rescue medication' observation period, which started at the date of first dose of trial product to either first initiation of rescue medication or the day of last dose of trial product plus 14 days,

whichever came first. The FAS included all randomized participants. Number of subjects analyzed=number of subjects contributed to the analysis.

End point type	Secondary

End point timeframe:

From baseline (week 0) to week 40

End point values	Semaglutide 1.0 mg	Semaglutide 2.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	425	434		
Units: Kilogram per squaremeter (Kg/m^2)				
arithmetic mean (standard deviation)	-2.1 (± 2.1)	-2.5 (± 2.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in waist circumference (cm)

End point title	Change in waist circumference (cm)

End point description:

Change from baseline (week 0) to week 40 in waist circumference was evaluated. Results are based on the 'on-treatment without rescue medication' observation period, which started at the date of first dose of trial product to either first initiation of rescue medication or the day of last dose of trial product plus 14 days, whichever came first. The FAS included all randomized subjects. Number of subjects analyzed=number of participants contributed to the analysis.

End point type	Secondary

End point timeframe:

From baseline (week 0) to week 40

End point values	Semaglutide 1.0 mg	Semaglutide 2.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	423	433		
Units: Centimeter (cm)				
arithmetic mean (standard deviation)	-5.2 (± 6.1)	-5.9 (± 6.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: HbA1c less than 7% at week 40 (yes/no)

End point title	HbA1c less than 7% at week 40 (yes/no)

End point description:

Percentage of subjects who achieved HbA1c < 7.0% is presented. Results are based on the 'on-treatment without rescue medication' observation period, which started at the date of first dose of trial product to either first initiation of rescue medication or the day of last dose of trial product plus 14 days, whichever came first. Missing HbA1c assessment at week 40 was imputed using observed data from subjects within same treatment group. The FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

At week 40

End point values	Semaglutide 1.0 mg	Semaglutide 2.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	481	480		
Units: Percentahe of subjects				
number (not applicable)	57.5	67.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Weight loss 5% or more at week 40

End point title	Weight loss 5% or more at week 40

End point description:

Percentage of subjects who achieved weight loss ≥5% is presented. Results are based on the 'on-treatment without rescue medication' observation period, which started at the date of first dose of trial product to either first initiation of rescue medication or the day of last dose of trial product plus 14 days, whichever came first. Missing body weight assessment at week 40 was imputed using observed data from subjects within same treatment group. The FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

At week 40

End point values	Semaglutide 1.0 mg	Semaglutide 2.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	481	480		
Units: Percentage of subjects				
number (not applicable)	51.3	59.2		

Statistical analyses

No statistical analyses for this end point

Secondary: HbA1c 6.5% or less at week 40 (yes/no)

End point title	HbA1c 6.5% or less at week 40 (yes/no)

End point description:

Percentage of subjects who achieved HbA1c ≤ 6.5% is presented. Results are based on the 'on-treatment without rescue medication' observation period, which started at the date of first dose of trial product to either first initiation of rescue medication or the day of last dose of trial product plus 14 days, whichever came first. Missing HbA1c assessment at week 40 was imputed using observed data from subjects within same treatment group. The FAS included all randomized participants.

End point type	Secondary

End point timeframe:

At week 40

End point values	Semaglutide 1.0 mg	Semaglutide 2.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	481	480		
Units: Percentage of subjects				
number (not applicable)	38.5	51.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Weight loss 10% or more at week 40 (yes/no)

End point title	Weight loss 10% or more at week 40 (yes/no)

End point description:

Percentage of subjects who achieved weight loss ≥10% is presented. Results are based on the 'on-treatment without rescue medication' observation period, which started at the date of first dose of trial product to either first initiation of rescue medication or the day of last dose of trial product plus 14 days, whichever came first. Missing body weight assessment at week 40 was imputed using observed data from subjects within same treatment group. The FAS included all randomized subjects.

End point type	Secondary

End point timeframe:

At week 40

End point values	Semaglutide 1.0 mg	Semaglutide 2.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	481	480		
Units: Percentage of subjects				
number (not applicable)	22.6	28.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes

End point title	Number of treatment emergent severe or blood glucose confirmed symptomatic hypoglycaemic episodes

End point description:

Hypoglycaemic episodes defined as treatment-emergent if the onset of the episode occurs within the on-treatment observation period. Severe or blood glucose (BG)-confirmed symptomatic hypoglycaemia is an episode that required assistance from another person for recovery and blood glucose-confirmed by a plasma glucose value <3.1 mmol/L (56 milligrams per deciliter (mg/dL)) with symptoms consistent with hypoglycaemia. Results are based on the 'on-treatment' observation period, which started at the date of first dose of trial product and ended at the first date of any of the following: the follow-up visit (week 47), the treatment discontinuation follow-up visit (end of treatment + 7 weeks), the date of last dose of trial product +49 days or the end-date for the 'in-trial' observation period. The SAS included all subjects exposed to at least one dose of trial product.

End point type	Secondary

End point timeframe:

From first dose to week 40

End point values	Semaglutide 1.0 mg	Semaglutide 2.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	480	479		
Units: Number of episodes	28	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in pulse rate (bpm)

End point title	Change in pulse rate (bpm)

End point description:

Change from baseline (week 0) to week 40 in pulse is presented. Results are based on the 'on-treatment' observation period, which started at the date of first dose of trial product and ended at the first date of any of the following: the follow-up visit (week 47), the treatment discontinuation follow-up visit (end of treatment + 7 weeks), the date of last dose of trial product +49 days or the end-date for the 'in-trial' observation period. The SAS included all subjects exposed to at least one dose of trial product. Number of subjects analyzed=number of subjects contributed to the analysis.

End point type	Secondary

End point timeframe:

From baseline (week 0) to week 40

End point values	Semaglutide 1.0 mg	Semaglutide 2.0 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	442		
Units: Beats per minute (bpm)				
arithmetic mean (standard deviation)	2.8 (± 10.0)	3.3 (± 9.5)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Weeks 0-47

Adverse event reporting additional description:

All presented AEs are TEAEs. A TEAE was defined as an event that had onset during the on-treatment period. Results are based on the SAS which comprised of all participants exposed to at least one dose of trial product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Semaglutide 2.0 mg

Reporting group description:

Subjects received s.c. injection of semaglutide once-weekly for 40 weeks in a fixed-dose escalation regimen, with dose doubling every 4 weeks until the target maintenance dose of 2.0 mg was reached: 0.25 mg during 0-4 weeks followed by 0.5 mg during 4-8 weeks followed by 1.0 mg during 8-12 weeks and then 2.0 mg during 12-40 weeks.

Reporting group title	Semaglutide 1.0 mg

Reporting group description:

Subjects received subcutaneous (s.c.) injection of semaglutide once-weekly for 40 weeks in a fixed-dose escalation regimen, with dose doubling every 4 weeks until the target dose of 1.0 mg was reached: 0.25 mg during 0-4 weeks followed by 0.5 mg during 4-8 weeks followed by 1.0 mg during 8-12 weeks and then 1.0 mg semaglutide along with s.c. injection of placebo matched to semaglutide 1.0 mg during 12-40 weeks.

Serious adverse events	Semaglutide 2.0 mg	Semaglutide 1.0 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 479 (4.38%)	25 / 480 (5.21%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			

subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the cervix			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dilatation			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			

subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Adenomyosis			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Smear cervix abnormal			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			

subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 479 (0.21%)	2 / 480 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 479 (0.21%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coronary artery stenosis			
subjects affected / exposed	0 / 479 (0.00%)	3 / 480 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Migraine			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuromyelitis optica spectrum disorder			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Optic ischaemic neuropathy			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	2 / 479 (0.42%)	2 / 480 (0.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis membranous			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Asymptomatic bacteriuria			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gangrene			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 479 (0.21%)	0 / 480 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 479 (0.00%)	2 / 480 (0.42%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 479 (0.00%)	2 / 480 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 479 (0.00%)	1 / 480 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Semaglutide 2.0 mg	Semaglutide 1.0 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	132 / 479 (27.56%)	126 / 480 (26.25%)	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	37 / 479 (7.72%)	32 / 480 (6.67%)	
occurrences (all)	55	40	
Nausea			
subjects affected / exposed	69 / 479 (14.41%)	70 / 480 (14.58%)	
occurrences (all)	98	98	
Diarrhoea			
subjects affected / exposed	45 / 479 (9.39%)	42 / 480 (8.75%)	
occurrences (all)	51	83	
Dyspepsia			
subjects affected / exposed	16 / 479 (3.34%)	25 / 480 (5.21%)	
occurrences (all)	17	26	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	29 / 479 (6.05%)	18 / 480 (3.75%)	
occurrences (all)	29	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 August 2019	- Updated text in Section 7.7 of the protocol, to clarify requirements for stable background medication during the trial. - Updated text in Section 9.4.3 of the protocol, to clarify that the end of treatment eye examination can be performed within 3 weeks prior to the visit; but that the results should be available at the end of treatment visit.
13 March 2020	Introduction of partial database lock.
03 July 2020	Revision of primary analysis for the treatment policy estimand; updated imputation method for missing data.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported