Clinical trial results:
Efficacy and safety of subcutaneous semaglutide 2.4 mg once-weekly in subjects with obesity and prediabetes (STEP 10)

Summary

EudraCT number	2020-002939-29
Trial protocol	FI DK ES
Global end of trial date	14 July 2023

Results information

Result version number	v1 (current)
This version publication date	26 June 2024
First version publication date	26 June 2024

Trial information

Trial identification

Sponsor protocol code	NN9536-4734

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05040971
WHO universal trial number (UTN)	U1111-1253-1956

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Alle, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Office (2834), 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	01 September 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm the superiority of semaglutide s.c. 2.4 mg once-weekly versus semaglutide placebo, both as adjuncts to a reduced-calorie diet and increased physical activity in subjects with obesity and prediabetes, on body weight and reversal to normoglycemia.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Oct 2013) and International Council for Harmonisation (ICH) Good Clinical Practice, including archiving of essential documents (May 1996) and European Standard (EN) International Organization for Standardization (ISO) 14155 Part 1 and 2 and Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) 312.120.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 September 2021
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	Canada: 75
Country: Number of subjects enrolled	Denmark: 23
Country: Number of subjects enrolled	Spain: 32
Country: Number of subjects enrolled	Finland: 32
Country: Number of subjects enrolled	United Kingdom: 45
Worldwide total number of subjects	207
EEA total number of subjects	87

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)	176
From 65 to 84 years	30
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 30 sites in 5 countries as follows: Canada (15 sites), Denmark (2 sites), Finland (2 sites), Spain (3 sites) and United Kingdom (8 sites).

Pre-assignment

Screening details:

Trial has Main phase (52-week treatment period: 16 weeks dose escalation, 36 weeks maintenance dose) & Extension phase (28-week off-treatment for body weight, glycaemic & cardiovascular assessment). Subjects were randomized 2:1 to receive semaglutide 2.4mg or placebo as an adjunct to a reduced-calorie diet and increased physical activity.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Semaglutide 2.4 mg

Arm description:

Subjects received once-weekly subcutaneous (s.c) injection of 0.25 milligram (mg) Semaglutide administered using a DV3396 pen-injector followed by a fixed-dose escalation regimen, with dose increase every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week) until the maintenance dose of 2.4 mg after 16 weeks. Treatment was continued on the maintenance dose of 2.4 mg Semaglutide once weekly for an additional 36 weeks until week 52. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.

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

Dosage and administration details:

Once-weekly subcutaneous injection of semaglutide was administered for 16 weeks with escalating doses for every 4 weeks (0.25 mg, 0.5 mg, 1.0 mg, and 1.7 mg) followed by a maintenance period of 52 weeks with a dose of 2.4 mg.

Arm title	Placebo

Arm description:

Subjects received once-weekly subcutaneous (s.c) injection of 0.25 milligram (mg) placebo matched to 2.4 mg Semaglutide administered using a DV3396 pen-injector followed by a fixed-dose escalation regimen, with dose increase every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week) until the maintenance dose of 2.4 mg after 16 weeks. Treatment was continued on the maintenance dose of 2.4 mg placebo matched to 2.4 mg Semaglutide once weekly for an additional 36 weeks until week 52. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.

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:

Once-weekly subcutaneous injection of semaglutide placebo was administered for 16 weeks with escalating doses for every 4 weeks (0.25 mg, 0.5 mg, 1.0 mg, and 1.7 mg) followed by a maintenance period of 52 weeks with a dose of 2.4 mg.

Number of subjects in period 1	Semaglutide 2.4 mg	Placebo
Started	138	69
Full analysis set (FAS)	138	69
Safety analysis set (SAS)	138	69
Completed	128	64
Not completed	10	5
Adverse event, serious fatal	2	-
Consent withdrawn by subject	-	2
Lost to follow-up	8	3

Baseline characteristics

Reporting groups	
Reporting group title	Semaglutide 2.4 mg
Reporting group description:	
Subjects received once-weekly subcutaneous (s.c) injection of 0.25 milligram (mg) Semaglutide administered using a DV3396 pen-injector followed by a fixed-dose escalation regimen, with dose increase every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week) until the maintenance dose of 2.4 mg after 16 weeks. Treatment was continued on the maintenance dose of 2.4 mg Semaglutide once weekly for an additional 36 weeks until week 52. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.	
Reporting group title	Placebo
Reporting group description:	
Subjects received once-weekly subcutaneous (s.c) injection of 0.25 milligram (mg) placebo matched to 2.4 mg Semaglutide administered using a DV3396 pen-injector followed by a fixed-dose escalation regimen, with dose increase every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week) until the maintenance dose of 2.4 mg after 16 weeks. Treatment was continued on the maintenance dose of 2.4 mg placebo matched to 2.4 mg Semaglutide once weekly for an additional 36 weeks until week 52. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.	

Reporting group values	Semaglutide 2.4 mg	Placebo	Total
Number of subjects	138	69	207
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	120	56	176
From 65-84 years	17	13	30
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	53	53	
standard deviation	± 11	± 11	-
Gender Categorical Units: Subjects			
Female	100	47	147
Male	38	22	60

End points

End points reporting groups

Reporting group title	Semaglutide 2.4 mg

Reporting group description:

Subjects received once-weekly subcutaneous (s.c) injection of 0.25 milligram (mg) Semaglutide administered using a DV3396 pen-injector followed by a fixed-dose escalation regimen, with dose increase every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week) until the maintenance dose of 2.4 mg after 16 weeks. Treatment was continued on the maintenance dose of 2.4 mg Semaglutide once weekly for an additional 36 weeks until week 52. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.

Reporting group title	Placebo

Reporting group description:

Subjects received once-weekly subcutaneous (s.c) injection of 0.25 milligram (mg) placebo matched to 2.4 mg Semaglutide administered using a DV3396 pen-injector followed by a fixed-dose escalation regimen, with dose increase every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week) until the maintenance dose of 2.4 mg after 16 weeks. Treatment was continued on the maintenance dose of 2.4 mg placebo matched to 2.4 mg Semaglutide once weekly for an additional 36 weeks until week 52. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.

Primary: Change in body weight

End point title	Change in body weight

End point description:

Change in body weight from randomisation (week 0) to end of treatment (week 52) is presented. The endpoint was evaluated based on the data from both in-trial and on-treatment observation periods. In-trial observation period was defined as the time period where the subject was assessed in the study. The in-trial observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive): End of trial visit, withdrawal of consent, last contact with subjects (for subjects lost to follow-up), death. On-treatment: The time period where subjects were treated with study product. FAS included all randomised subjects. 'Number of subjects analysed' = subjects with available data. n= number of subjects evaluated per each arm respectively for this outcome measure.

End point type	Primary

End point timeframe:

From randomisation (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	66		
Units: Percentage (%) of body weight				
arithmetic mean (standard deviation)				
In-trial (n= 129, 66)	-14.4 (± 7.9)	-2.7 (± 4.3)		
On-treatment (n= 117, 60)	-15.4 (± 7.2)	-2.6 (± 4.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

All responses prior to first discontinuation of treatment (or initiation of other anti-obesity medication or bariatric surgery) were included in a mixed model for repeated measurements with randomised treatment as factor and baseline body weight as covariate, all nested within visit.

Comparison groups	Semaglutide 2.4 mg v Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-13.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.2
upper limit	-11.4

Notes:

[1] - Hypothetical estimand: Total number of subjects included in statistical analysis is 166. The number given here is auto-calculated by the system.

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 52 responses were analysed using an analysis of covariance model (ANCOVA) with randomised treatment as factor and baseline body weight as covariate.

Comparison groups	Semaglutide 2.4 mg v Placebo
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-11.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.97
upper limit	-9.42

Notes:

[2] - Treatment policy estimand

Primary: Change to normoglycemia (Normoglycemia is defined as having both HbA1c below 6.0% (below 42 mmol/mol) and FPG below 5.5 mmol/L (below 99 mg/dL)

End point title	Change to normoglycemia (Normoglycemia is defined as having both HbA1c below 6.0% (below 42 mmol/mol) and FPG below 5.5 mmol/L (below 99 mg/dL)

End point description:

Number of subjects in glycaemic categories, "normoglycaemia, pre-diabetes and type 2 diabetes" at Week 52 are presented. These categories were set as per the following criteria: 1) Normoglycaemia: glycosylated haemoglobin (HbA1c) lesser than (<) 6.0 percentage (%) and fasting plasma glucose (FPG) lesser than (<) 5.5 millimoles per liter (mmol/L). 2) Pre-diabetes: 6.0% lesser than or equal (≤) HbA1c lesser than (<) 6.5% or 5.5 mmol/L lesser than or equal (≤) FPG lesser than (<) 7.0 mmol/L or non-verified type 2 diabetes. 3) Type 2 diabetes: HbA1c greater than or equal (≥) 6.5% or FPG greater than or equal (≥) 7.0 mmol/L. Type 2 diabetes needs to verified with a retest within 4 weeks. FAS included

all randomised subjects. 'Number of subjects analysed' = subjects with available data. n= number of subjects evaluated per each arm respectively for this outcome measure.

End point type	Primary

End point timeframe:

From randomisation (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	64		
Units: Subjects				
In-trial: Normoglycemia (n= 127, 64)	103	9		
In-trial: Pre-diabetes (n= 127, 64)	23	53		
In-trial: Type 2 diabetes (n= 127, 64)	1	2		
On-treatment: Normoglycemia (n= 115, 60)	97	8		
On-treatment: Pre-diabetes (n= 115, 60)	18	51		
On-treatment: Type 2 diabetes (n= 115, 60)	0	1		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 52 responses were analysed using a logistic regression model with randomised treatment as factor and baseline glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG) as covariates.

Comparison groups	Semaglutide 2.4 mg v Placebo
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	19.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	8.68
upper limit	45.21

Notes:

[3] - Treatment policy estimand: Total number of subjects included in statistical analysis is 190. The number given here is auto-calculated by the system.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

All responses prior to first discontinuation of treatment (or initiation of other anti-obesity medication or bariatric surgery) were included in a mixed model for repeated measurements with randomised treatment as factor and baseline glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG) as covariates.

Comparison groups	Semaglutide 2.4 mg v Placebo
Number of subjects included in analysis	191
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.0001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	43.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	18.03
upper limit	104.8

Notes:

[4] - Hypothetical estimand: Total number of subjects included in statistical analysis is 165. The number given here is auto-calculated by the system.

Secondary: Change in HbA1c

End point title	Change in HbA1c

End point description:

Change in glycosylated haemoglobin (HbA1c) from randomisation (week 0) to end of treatment (week 52) is presented. The endpoint was evaluated based on the data from in-trial observation period which was defined as the time period where the subject was assessed in the study. The in-trial observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive): End of trial visit, withdrawal of consent, last contact with subjects (for subjects lost to follow-up), death. FAS included all randomised subjects. 'Number of subjects analysed' = subjects with available data.

End point type	Secondary

End point timeframe:

From randomisation (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	63		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)	-0.4 (± 0.3)	0.1 (± 0.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in FPG

End point title	Change in FPG

End point description:

Change in fasting plasma glucose (FPG) from randomisation (week 0) to end of treatment (week 52) is presented. The endpoint was evaluated based on the data from in-trial observation period which was defined as the time period where the subject was assessed in the study. The in-trial observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive): End of trial visit, withdrawal of consent, last contact with subjects (for subjects lost to follow-

up), death. FAS included all randomised subjects. 'Number of subjects analysed' = subjects with available data.

End point type	Secondary

End point timeframe:

From randomisation (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	63		
Units: millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)	-0.8 (± 0.6)	-0.3 (± 0.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in waist circumference

End point title	Change in waist circumference

End point description:

Change in waist circumference from randomisation (week 0) to end of treatment (week 52) is presented. The endpoint was evaluated based on the data from in-trial observation period which was defined as the time period where the subject was assessed in the study. The in-trial observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive): End of trial visit, withdrawal of consent, last contact with subjects (for subjects lost to follow-up), death. FAS included all randomised subjects. 'Number of subjects analysed' = subjects with available data.

End point type	Secondary

End point timeframe:

From randomisation (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	66		
Units: centimeter (cm)				
arithmetic mean (standard deviation)	-11.6 (± 8.7)	-2.8 (± 5.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in systolic blood pressure

End point title	Change in systolic blood pressure

End point description:

Change in systolic blood pressure from randomisation (week 0) to end of treatment (week 52) is presented. The endpoint was evaluated based on the data from in-trial observation period which was defined as the time period where the subject was assessed in the study. The in-trial observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive): End of trial visit, withdrawal of consent, last contact with subjects (for subjects lost to follow-up), death. FAS included all randomised subjects. 'Number of subjects analysed' = subjects with available data.

End point type	Secondary

End point timeframe:

From randomisation (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	66		
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)	-9 (± 13)	-1 (± 13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in triglycerides

End point title	Change in triglycerides

End point description:

Change in triglycerides (measured in mmol/L) from randomisation (week 0) to end of treatment (week 52) is presented as ratio to baseline. The endpoint was evaluated based on the data from in-trial observation period which was defined as the time period where the subject was assessed in the study. The in-trial observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive): End of trial visit, withdrawal of consent, last contact with subjects (for subjects lost to follow-up), death. FAS included all randomised subjects. 'Number of subjects analysed' = subjects with available data.

End point type	Secondary

End point timeframe:

From randomisation (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	62		
Units: Ratio of triglycerides				
geometric mean (geometric coefficient of variation)	0.80 (± 36.4)	0.96 (± 30.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in total cholesterol

End point title	Change in total cholesterol

End point description:

Change in total cholesterol (measured in mmol/L) from randomisation (week 0) to end of treatment (week 52) is presented as ratio to baseline. The endpoint was evaluated based on the data from in-trial observation period which was defined as the time period where the subject was assessed in the study. The in-trial observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive): End of trial visit, withdrawal of consent, last contact with subjects (for subjects lost to follow-up), death. FAS included all randomised subjects. 'Number of subjects analysed' = subjects with available data.

End point type	Secondary

End point timeframe:

From randomisation (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	127	63		
Units: Ratio of total cholesterol				
geometric mean (geometric coefficient of variation)	0.94 (± 16.1)	1.01 (± 15.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in High density lipoprotein (HDL) cholesterol

End point title	Change in High density lipoprotein (HDL) cholesterol

End point description:

Change in high density lipoprotein (HDL) cholesterol (measured in mmol/L) from randomisation (week 0) to end of treatment (week 52) is presented as ratio to baseline. The endpoint was evaluated based on the data from in-trial observation period which was defined as the time period where the subject was assessed in the study. The in-trial observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive): End of trial visit, withdrawal of consent, last contact with subjects (for subjects lost to follow-up), death. FAS included all randomised subjects. 'Number of subjects analysed' = subjects with available data.

End point type	Secondary

End point timeframe:

From randomisation (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	61		
Units: Ratio of HDL cholesterol				
geometric mean (geometric coefficient of variation)	1.02 (± 12.4)	0.99 (± 11.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in low density lipoprotein (LDL) cholesterol

End point title	Change in low density lipoprotein (LDL) cholesterol

End point description:

Change in low density lipoprotein (LDL) cholesterol (measured in mmol/L) from randomisation (week 0) to end of treatment (week 52) is presented as ratio to baseline. The endpoint was evaluated based on the data from in-trial observation period which was defined as the time period where the subject was assessed in the study. The in-trial observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive): End of trial visit, withdrawal of consent, last contact with subjects (for subjects lost to follow-up), death. FAS included all randomised subjects. 'Number of subjects analysed' = subjects with available data.

End point type	Secondary

End point timeframe:

From randomisation (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	61		
Units: Ratio of LDL cholesterol				
geometric mean (geometric coefficient of variation)	0.93 (± 26.6)	1.03 (± 23.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in very low density lipoprotein (VLDL) cholesterol

End point title	Change in very low density lipoprotein (VLDL) cholesterol

End point description:

Change in very low density lipoprotein (VLDL) cholesterol (measured in mmol/L) from randomisation (week 0) to end of treatment (week 52) is presented as ratio to baseline. The endpoint was evaluated based on the data from in-trial observation period which was defined as the time period where the subject was assessed in the study. The in-trial observation period for a subject begins on the date of randomisation and ends at the first of the following dates (both inclusive): End of trial visit, withdrawal of consent, last contact with subjects (for subjects lost to follow-up), death. FAS included all randomised subjects. 'Number of subjects analysed' = subjects with available data.

End point type	Secondary

End point timeframe:

From randomisation (week 0) to end of treatment (week 52)

End point values	Semaglutide 2.4 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	62		
Units: Ratio of VLDL cholesterol				
geometric mean (geometric coefficient of variation)	0.80 (± 36.5)	0.96 (± 30.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation (week 0) to week 57

Adverse event reporting additional description:

All the presented adverse events are treatment emergent adverse events (TEAEs). TEAEs: events that had onset date during on-treatment period, time period in which subjects was considered exposed to trial product. SAS during on-treatment included all subjects randomly assigned to treatment who took at least one dose of study product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received once-weekly subcutaneous (s.c) injection of 0.25 milligram (mg) placebo matched to 2.4 mg Semaglutide administered using a DV3396 pen-injector followed by a fixed-dose escalation regimen, with dose increase every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week) until the maintenance dose of 2.4 mg after 16 weeks. Treatment was continued on the maintenance dose of 2.4 mg placebo matched to 2.4 mg Semaglutide once weekly for an additional 36 weeks until week 52. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.

Reporting group title	Semaglutide 2.4 mg

Reporting group description:

Subjects received once-weekly subcutaneous (s.c) injection of 0.25 milligram (mg) Semaglutide administered using a DV3396 pen-injector followed by a fixed-dose escalation regimen, with dose increase every 4 weeks (to doses of 0.5, 1.0, 1.7 and 2.4 mg/week) until the maintenance dose of 2.4 mg after 16 weeks. Treatment was continued on the maintenance dose of 2.4 mg Semaglutide once weekly for an additional 36 weeks until week 52. The treatment was an adjunct to a reduced-calorie diet and increased physical activity.

Serious adverse events	Placebo	Semaglutide 2.4 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 69 (8.70%)	12 / 138 (8.70%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anaplastic thyroid cancer			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Bladder neoplasm			

subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Concussion			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 69 (1.45%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 69 (1.45%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 69 (1.45%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Angina pectoris			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 69 (1.45%)	0 / 138 (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 pain			
subjects affected / exposed	1 / 69 (1.45%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 69 (0.00%)	2 / 138 (1.45%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectocele			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Embedded device			
subjects affected / exposed	1 / 69 (1.45%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Endophthalmitis			
subjects affected / exposed	1 / 69 (1.45%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Submandibular abscess			
subjects affected / exposed	1 / 69 (1.45%)	0 / 138 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal disease			
subjects affected / exposed	0 / 69 (0.00%)	1 / 138 (0.72%)	
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	Placebo	Semaglutide 2.4 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 69 (43.48%)	93 / 138 (67.39%)	
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 69 (7.25%)	6 / 138 (4.35%)	
occurrences (all)	6	8	
Dizziness			
subjects affected / exposed	1 / 69 (1.45%)	7 / 138 (5.07%)	
occurrences (all)	1	7	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	4 / 69 (5.80%)	7 / 138 (5.07%)	
occurrences (all)	4	8	
Constipation			
subjects affected / exposed	0 / 69 (0.00%)	25 / 138 (18.12%)	
occurrences (all)	0	29	
Diarrhoea			
subjects affected / exposed	7 / 69 (10.14%)	17 / 138 (12.32%)	
occurrences (all)	7	31	
Vomiting			
subjects affected / exposed	1 / 69 (1.45%)	16 / 138 (11.59%)	
occurrences (all)	1	27	
Dyspepsia			
subjects affected / exposed	3 / 69 (4.35%)	12 / 138 (8.70%)	
occurrences (all)	4	21	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 69 (0.00%)	7 / 138 (5.07%)	
occurrences (all)	0	8	
Nausea			
subjects affected / exposed	3 / 69 (4.35%)	40 / 138 (28.99%)	
occurrences (all)	3	50	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	2 / 69 (2.90%)	7 / 138 (5.07%)	
occurrences (all)	2	7	
COVID-19			

subjects affected / exposed occurrences (all)	21 / 69 (30.43%) 21	48 / 138 (34.78%) 55	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 1 / 69 (1.45%) 1	 11 / 138 (7.97%) 11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 July 2021	Reporting of serious adverse events (SAEs) in the extension phase. Update of time frame for evaluation of treatment intensity of antihypertensive and lipid-lowering medication. Inclusion of assumption on unequal variances in the primary analysis of change in body weight.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported