

**Clinical trial results:****Investigation of efficacy and safety of three dose levels of subcutaneous semaglutide once daily versus placebo in subjects with non-alcoholic steatohepatitis****Summary**

EudraCT number	2016-000685-39
Trial protocol	GB GR BG FI SE NL AT BE FR ES DK
Global end of trial date	19 March 2020

Results information

Result version number	v1 (current)
This version publication date	01 April 2021
First version publication date	01 April 2021

Trial information**Trial identification**

Sponsor protocol code	NN9931-4296
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02970942
WHO universal trial number (UTN)	U1111-1179-7464
Other trial identifiers	Japanese registration number: 25-1634

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (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	15 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	13 February 2020
Global end of trial reached?	Yes
Global end of trial date	19 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to compare the effect of semaglutide subcutaneous (s.c.) once daily versus placebo on histological resolution of non-alcoholic steatohepatitis (NASH).

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (Fortaleza, Brazil, 2013) International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice (June 1996), including archiving of essential documents, and 21 United States Code of Federal Regulations (CFR) 312.120.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 November 2016
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	Australia: 4
Country: Number of subjects enrolled	Austria: 5
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Bulgaria: 15
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	United Kingdom: 28
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Japan: 41
Country: Number of subjects enrolled	Netherlands: 7
Country: Number of subjects enrolled	Russian Federation: 49
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United States: 91
Worldwide total number of subjects	320
EEA total number of subjects	82

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)	262
From 65 to 84 years	58
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Trial was conducted at 114 sites in 16 countries (number of sites that screened subjects/randomised subjects):Australia(4/3);Austria(3/3);Belgium(4/4);Bulgaria(2/2);Canada(9/7);Denmark(2/2);Finland(1/1);France(8/6);Greece(5/5);Japan(13/12);Netherlands(7/5);Russian Federation(25/17);Spain(6/5);Sweden(3/2); United

Pre-assignment

Screening details:

Subjects were randomised in a 3:3:3:1:1:1 ratio to receive once-daily semaglutide or placebo subcutaneously. After randomisation, the subjects entered a dose-escalation period, with increase in dose every 4 weeks until the target dose was reached.

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Semaglutide 0.1 mg

Arm description:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 milligrams (mg) of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.1 mg was reached: 0.05 mg (week 1 to week 4) and 0.1 mg (week 5 to week 72).

Arm type	Experimental
Investigational medicinal product name	Semaglutide B 1 mg/ml NovoPen4
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.1 mg was reached: 0.05 mg (week 1 to week 4) and 0.1 mg (week 5 to week 72).

Arm title	Semaglutide 0.2 mg
------------------	--------------------

Arm description:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.2 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8) and 0.2 mg (week 9 to week 72).

Arm type	Experimental
Investigational medicinal product name	Semaglutide B 1 mg/ml NovoPen4
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.2 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8) and 0.2 mg (week 9 to week 72).

Arm title	Semaglutide 0.4 mg
Arm description: Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.4 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8), 0.2 mg (week 9 to week 12), 0.3 mg (week 13 to week 16) and 0.4 mg (week 17 to week 72).	
Arm type	Experimental
Investigational medicinal product name	Semaglutide B 1 mg/ml NovoPen4
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.4 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8), 0.2 mg (week 9 to week 12), 0.3 mg (week 13 to week 16) and 0.4 mg (week 17 to week 72).

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

Arm description:

Subjects were to receive once daily s.c. injection of placebo matched to semaglutide (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg or 0.4 mg) for 72 weeks.

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

Dosage and administration details:

Subjects were to receive once daily s.c. injection of placebo matched to semaglutide (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg or 0.4 mg) for 72 weeks.

Number of subjects in period 1	Semaglutide 0.1 mg	Semaglutide 0.2 mg	Semaglutide 0.4 mg
Started	80	78	82
Completed	76	72	77
Not completed	4	6	5
Death	-	1	-
Withdrawal by Subject	3	5	3
Lost to follow-up	1	-	2

Number of subjects in period 1	Placebo
Started	80
Completed	77
Not completed	3
Death	-
Withdrawal by Subject	2
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	Semaglutide 0.1 mg
Reporting group description:	
Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 milligrams (mg) of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.1 mg was reached: 0.05 mg (week 1 to week 4) and 0.1 mg (week 5 to week 72).	
Reporting group title	Semaglutide 0.2 mg
Reporting group description:	
Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.2 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8) and 0.2 mg (week 9 to week 72).	
Reporting group title	Semaglutide 0.4 mg
Reporting group description:	
Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.4 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8), 0.2 mg (week 9 to week 12), 0.3 mg (week 13 to week 16) and 0.4 mg (week 17 to week 72).	
Reporting group title	Placebo
Reporting group description:	
Subjects were to receive once daily s.c. injection of placebo matched to semaglutide (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg or 0.4 mg) for 72 weeks.	

Reporting group values	Semaglutide 0.1 mg	Semaglutide 0.2 mg	Semaglutide 0.4 mg
Number of subjects	80	78	82
Age Categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	55.2	58.1	54.3
standard deviation	± 10.9	± 9.9	± 10.2
Gender Categorical Units: Subjects			
Female	51	52	47
Male	29	26	35

Reporting group values	Placebo	Total	
Number of subjects	80	320	
Age Categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	52.4	-	
standard deviation	± 10.8		
Gender Categorical Units: Subjects			
Female	44	194	

Male	36	126	
------	----	-----	--

End points

End points reporting groups

Reporting group title	Semaglutide 0.1 mg
Reporting group description:	
Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 milligrams (mg) of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.1 mg was reached: 0.05 mg (week 1 to week 4) and 0.1 mg (week 5 to week 72).	
Reporting group title	Semaglutide 0.2 mg
Reporting group description:	
Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.2 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8) and 0.2 mg (week 9 to week 72).	
Reporting group title	Semaglutide 0.4 mg
Reporting group description:	
Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.4 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8), 0.2 mg (week 9 to week 12), 0.3 mg (week 13 to week 16) and 0.4 mg (week 17 to week 72).	
Reporting group title	Placebo
Reporting group description:	
Subjects were to receive once daily s.c. injection of placebo matched to semaglutide (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg or 0.4 mg) for 72 weeks.	

Primary: NASH resolution without worsening of fibrosis (yes/no)

End point title	NASH resolution without worsening of fibrosis (yes/no)
End point description:	
NASH resolution defined as lobular inflammation of 0 or 1; hepatocellular ballooning reduced to 0; both criteria were necessary conditions. Hepatocellular ballooning range 0-2; lobular inflammation ranges from 0-3, with higher scores indicating more severe hepatocellular ballooning or lobular inflammation. Worsening of fibrosis defined by an increase in fibrosis at least one stage of Kleiner fibrosis classification: fibrosis stages range 0-4, with higher scores indicating greater fibrosis (0=None,4=Cirrhosis). Full analysis set included all randomised subjects. Number of subjects analysed = Number of subjects with fibrosis stage 2 or 3 at baseline who contributed to the analysis. In below table, 'Yes' infers percentage of subjects who achieved NASH resolution without worsening of fibrosis and 'No' infers vice-versa; 'Missing' refers to percentage of subjects with data missing due to different reasons (lost to follow-up, withdrawal).	
End point type	Primary
End point timeframe:	
After 72 weeks	

End point values	Semaglutide 0.1 mg	Semaglutide 0.2 mg	Semaglutide 0.4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	59	56	58
Units: Percentage of subjects				
number (not applicable)				
Yes	40.4	35.6	58.9	17.2
No	54.4	47.5	30.4	74.1
Missing	5.3	16.9	10.7	8.6

Statistical analyses

Statistical analysis title	Semaglutide 0.1 mg versus Placebo
Statistical analysis description: The common odds ratio was estimated together with 95% confidence interval using the Mantel-Haenszel estimator associated with the Cochran-Mantel-Haenszel test.	
Comparison groups	Semaglutide 0.1 mg v Placebo
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	t-test, 2-sided
Parameter estimate	Odds ratio (OR)
Point estimate	3.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.29
upper limit	8.86

Statistical analysis title	Semaglutide 0.2 mg versus Placebo
Statistical analysis description: The common odds ratio was estimated together with 95% confidence interval using the Mantel-Haenszel estimator associated with the Cochran-Mantel-Haenszel test.	
Comparison groups	Semaglutide 0.2 mg v Placebo
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0359
Method	t-test, 2-sided
Parameter estimate	Odds ratio (OR)
Point estimate	2.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	7.56

Statistical analysis title	Semaglutide 0.4 mg versus Placebo
-----------------------------------	-----------------------------------

Statistical analysis description:

The common odds ratio was estimated together with 95% confidence interval using the Mantel-Haenszel

estimator associated with the Cochran-Mantel-Haenszel test.

Comparison groups	Semaglutide 0.4 mg v Placebo
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Odds ratio (OR)
Point estimate	6.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.6
upper limit	17.63

Secondary: At least one stage of liver fibrosis improvement with no worsening of NASH (yes/no) (worsening defined as an increase of at least one stage of either lobular inflammation or hepatocyte ballooning according to NASH clinical research network (CRN) criteria)

End point title	At least one stage of liver fibrosis improvement with no worsening of NASH (yes/no) (worsening defined as an increase of at least one stage of either lobular inflammation or hepatocyte ballooning according to NASH clinical research network (CRN) criteria)
-----------------	---

End point description:

Worsening of fibrosis defined by an increase in fibrosis at least one stage of Kleiner fibrosis classification: fibrosis stages range from 0-4, higher scores indicate greater fibrosis (0=None, 4=Cirrhosis). Full analysis set included all randomised subjects. Number of subjects analysed = Number of subjects with fibrosis stage 2 or 3 at baseline who contributed to the analysis. In below table, 'Yes' infers percentage of subjects who achieved at least one stage of fibrosis improvement with no worsening of NASH; 'No' infers vice-versa; 'Missing' refers to percentage of subjects with data missing due to different reasons (lost to follow-up, withdrawal).

End point type	Secondary
----------------	-----------

End point timeframe:

After 72 weeks

End point values	Semaglutide 0.1 mg	Semaglutide 0.2 mg	Semaglutide 0.4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	57	59	56	58
Units: Percentage of subjects				
number (not applicable)				
Yes	49.1	32.2	42.9	32.8
No	45.6	50.8	46.4	58.6
Missing	5.3	16.9	10.7	8.6

Statistical analyses

No statistical analyses for this end point

Secondary: Change in non-alcoholic fatty liver disease (NAFLD) activity score (NAS) (0-8)

End point title	Change in non-alcoholic fatty liver disease (NAFLD) activity score (NAS) (0-8)
-----------------	--

End point description:

Percentage of subjects who had worsened, improved or had no change in total NAS from baseline to week 72 is presented. Worsening is defined as an increase of at least 1 in the NAS; Improvement is defined as a decrease of at least 1 in the NAS; while no change corresponds to no change in NAS from baseline to week 72. NAS is calculated as the sum of scores for steatosis (0 to 3), lobular inflammation (0 to 3), and hepatocyte ballooning (0 to 2). Therefore, it is assessed on a scale of 0-8, with higher scores indicating more severe disease. The endpoint was evaluated based on the data from in-trial period which started on the date of the randomisation visit and ended on the first of the following dates (both inclusive): 1) follow-up visit (Week 79); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. Full analysis set included all randomised subjects.

End point type	Secondary
----------------	-----------

End point timeframe:

From baseline to week 72

End point values	Semaglutide 0.1 mg	Semaglutide 0.2 mg	Semaglutide 0.4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	78	82	80
Units: Percentage of subjects number (not applicable)				
Improvement	71.3	79.5	82.9	43.8
Worsening	7.5	2.6	3.7	16.3
No change	13.8	5.1	1.2	27.5
Missing	7.5	12.8	12.2	12.5

Statistical analyses

No statistical analyses for this end point

Secondary: Change in stage of fibrosis according to the Kleiner fibrosis classification (0-4)

End point title	Change in stage of fibrosis according to the Kleiner fibrosis classification (0-4)
-----------------	--

End point description:

Percentage of subjects who had improved, worsened, or had no change in fibrosis stage from baseline to week 72 is presented. The degree of fibrosis is described by the Kleiner fibrosis staging system, ranging from F0 (absence of fibrosis), F1 (portal/perisinusoidal fibrosis), F2 (perisinusoidal and portal/periportal fibrosis), F3 (septal or bridging fibrosis) through F4 (cirrhosis). The endpoint was evaluated based on the data from in-trial period which started on the date of the randomisation visit and ended on the first of the following dates (both inclusive): 1) follow-up visit (Week 79); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. Full analysis set included all randomised subjects.

End point type	Secondary
----------------	-----------

End point timeframe:

From baseline to week 72

End point values	Semaglutide 0.1 mg	Semaglutide 0.2 mg	Semaglutide 0.4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	78	82	80
Units: Percentage of subjects number (not applicable)				
Improvement	46.3	32.1	42.7	31.3
Worsening	10.0	7.7	4.9	18.8
No change	36.3	42.3	36.6	37.5
Missing	7.5	17.9	15.9	12.5

Statistical analyses

No statistical analyses for this end point

Secondary: Change in activity component of steatosis-activity-fibrosis (SAF) score (0-4)

End point title	Change in activity component of steatosis-activity-fibrosis (SAF) score (0-4)
-----------------	---

End point description:

Percentage of subjects who had improved, worsened, or had no change in the activity component of the SAF score from baseline to week 72 is presented. The activity component of the SAF score is defined as the unweighted sum of hepatocyte ballooning (0 to 2) and lobular inflammation (0 to 3). The definition of the lobular inflammation score is modified in this calculation so that the scores 2 and 3 on the original scale are merged to a score 2. The possible range of the sum is thus 0 to 4. For all scores, a higher value indicates a more severe state of disease. The endpoint was evaluated based on the data from in-trial period which started on the date of the randomisation visit and ended on the first of the following dates (both inclusive): 1) follow-up visit (Week 79); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. Full analysis set included all randomised subjects.

End point type	Secondary
----------------	-----------

End point timeframe:

From baseline to week 72

End point values	Semaglutide 0.1 mg	Semaglutide 0.2 mg	Semaglutide 0.4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	80	78	82	80
Units: Percentage of subjects number (not applicable)				
Improvement	62.5	71.8	72.0	42.5
Worsening	7.5	3.8	1.2	11.3
No change	22.5	11.5	14.6	33.8
Missing	7.5	12.8	12.2	12.5

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (FPG)

End point title | Change in fasting plasma glucose (FPG)

End point description:

Change in FPG from baseline to week 72 is presented. The endpoint was evaluated based on the data from in-trial period which started on the date of the randomisation visit and ended on the first of the following dates (both inclusive): 1) follow-up visit (Week 79); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. Full analysis set included all randomised subjects. Number of subjects analyzed = Number of subjects with type 2 diabetes who contributed to the analysis.

End point type | Secondary

End point timeframe:

From baseline to week 72

End point values	Semaglutide 0.1 mg	Semaglutide 0.2 mg	Semaglutide 0.4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	45	44	47	48
Units: Millimoles per liter				
arithmetic mean (standard deviation)	-1.39 (± 2.53)	-2.17 (± 1.82)	-2.09 (± 2.68)	-0.34 (± 2.72)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in glycosylated haemoglobin A1c (HbA1c)

End point title | Change in glycosylated haemoglobin A1c (HbA1c)

End point description:

Change in HbA1c from baseline to week 72 is presented. The endpoint was evaluated based on the data from in-trial period which started on the date of the randomisation visit and ended on the first of the following dates (both inclusive): 1) follow-up visit (Week 79); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. Full analysis set included all randomised subjects. Number of subjects analyzed = Number of subjects with type 2 diabetes who contributed to the analysis.

End point type | Secondary

End point timeframe:

From baseline to week 72

End point values	Semaglutide 0.1 mg	Semaglutide 0.2 mg	Semaglutide 0.4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	46	45	47	47
Units: Percentage point of HbA1c				
arithmetic mean (standard deviation)	-0.7 (± 1.1)	-1.2 (± 0.9)	-1.2 (± 1.0)	-0.0 (± 1.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Change in serum enhanced liver fibrosis (ELF)

End point title	Change in serum enhanced liver fibrosis (ELF)
End point description:	Change in ELF from baseline to week 72 is presented. The endpoint was evaluated based on the data from in-trial period which started on the date of the randomisation visit and ended on the first of the following dates (both inclusive): 1) follow-up visit (Week 79); 2) withdrawal of consent; 3) last contact with subject (for subjects lost to follow-up); 4) death. Full analysis set included all randomised subjects. Number of subjects analyzed = Number of subjects who contributed to the analysis.
End point type	Secondary
End point timeframe:	From baseline to week 72

End point values	Semaglutide 0.1 mg	Semaglutide 0.2 mg	Semaglutide 0.4 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	76	70	76	75
Units: Change in ELF score				
arithmetic mean (standard deviation)	-0.4 (± 0.7)	-0.4 (± 0.8)	-0.6 (± 0.8)	0.1 (± 0.7)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From week 0 to week 79

Results are based on safety analysis set which included all subjects who received at least one dose of randomised treatment. All adverse events reported here are treatment emergent adverse events (TEAEs).

Adverse event reporting additional description:

TEAE was defined as an event that had onset date during on-treatment period (for AEs), which started from date of first administration of trial product and ended on date of whatever came first: 1) last dose of trial product + 49 days (7 half lives of semaglutide); 2) end of the in-trial period.

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

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	22.1
--------------------	------

Reporting groups

Reporting group title	Semaglutide 0.1 mg
-----------------------	--------------------

Reporting group description:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.1 mg was reached: 0.05 mg (week 1 to week 4) and 0.1 mg (week 5 to week 72).

Reporting group title	Semaglutide 0.2 mg
-----------------------	--------------------

Reporting group description:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.2 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8) and 0.2 mg (week 9 to week 72).

Reporting group title	Semaglutide 0.4 mg
-----------------------	--------------------

Reporting group description:

Subjects were to receive once daily s.c. injection of semaglutide for 72 weeks. Subjects initially received 0.05 mg of semaglutide and the dose was then escalated once in 4 weeks until the target dose of 0.4 mg was reached: 0.05 mg (week 1 to week 4), 0.1 mg (week 5 to week 8), 0.2 mg (week 9 to week 12), 0.3 mg (week 13 to week 16) and 0.4 mg (week 17 to week 72).

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

Reporting group description:

Subjects were to receive once daily s.c. injection of placebo matched to semaglutide (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg or 0.4 mg) for 72 weeks.

Serious adverse events	Semaglutide 0.1 mg	Semaglutide 0.2 mg	Semaglutide 0.4 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 80 (15.00%)	15 / 78 (19.23%)	12 / 81 (14.81%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholesteatoma			

subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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
Neurilemmoma benign			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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
Peripheral T-cell lymphoma unspecified			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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
Uterine leiomyoma			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	0 / 81 (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
Ovarian cyst			
subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	0 / 81 (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
Uterine polyp			
subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	0 / 81 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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
Atelectasis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	0 / 81 (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
Pleural effusion			
subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	0 / 81 (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
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	0 / 81 (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
Major depression			

subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	0 / 81 (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
Suicidal ideation			
subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Diabetic neuropathy			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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
Epilepsy			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lumbosacral radiculopathy			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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
Transient epileptic amnesia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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 disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			

subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	0 / 81 (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
Constipation			
subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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 polyp haemorrhage			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Megacolon			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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
Nausea			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			

subjects affected / exposed	1 / 80 (1.25%)	1 / 78 (1.28%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 80 (0.00%)	2 / 78 (2.56%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus urinary			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot deformity			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteoarthritis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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			
Anal abscess			
subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	0 / 81 (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
Cellulitis			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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
Cystitis escherichia			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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
Diverticulitis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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
Gastroenteritis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis E			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	0 / 81 (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
Urosepsis			
subjects affected / exposed	0 / 80 (0.00%)	1 / 78 (1.28%)	0 / 81 (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
Metabolism and nutrition disorders			
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 80 (0.00%)	0 / 78 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 80 (1.25%)	1 / 78 (1.28%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 80 (1.25%)	0 / 78 (0.00%)	0 / 81 (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

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 80 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholesteatoma			

subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endometrial adenocarcinoma			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neurilemmoma benign			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral T-cell lymphoma unspecified			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ovarian cyst			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Uterine polyp			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Atelectasis			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Major depression			

subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haematoma			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ventricular tachycardia			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Diabetic neuropathy			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Lumbosacral radiculopathy			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient epileptic amnesia			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis ischaemic			

subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Megacolon			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			

subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Calculus urinary			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Foot deformity			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Osteoarthritis			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystitis escherichia			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diverticulitis			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatitis E			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			

subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	0 / 80 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Semaglutide 0.1 mg	Semaglutide 0.2 mg	Semaglutide 0.4 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 80 (76.25%)	64 / 78 (82.05%)	63 / 81 (77.78%)
Investigations			
Lipase increased			
subjects affected / exposed	4 / 80 (5.00%)	7 / 78 (8.97%)	1 / 81 (1.23%)
occurrences (all)	5	8	3
Injury, poisoning and procedural			

complications			
Procedural pain			
subjects affected / exposed	6 / 80 (7.50%)	2 / 78 (2.56%)	2 / 81 (2.47%)
occurrences (all)	7	2	2
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 80 (3.75%)	3 / 78 (3.85%)	3 / 81 (3.70%)
occurrences (all)	3	3	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 80 (7.50%)	6 / 78 (7.69%)	8 / 81 (9.88%)
occurrences (all)	8	8	10
Headache			
subjects affected / exposed	7 / 80 (8.75%)	10 / 78 (12.82%)	10 / 81 (12.35%)
occurrences (all)	11	13	13
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 80 (8.75%)	8 / 78 (10.26%)	7 / 81 (8.64%)
occurrences (all)	7	8	8
Injection site bruising			
subjects affected / exposed	1 / 80 (1.25%)	5 / 78 (6.41%)	3 / 81 (3.70%)
occurrences (all)	1	10	4
Pyrexia			
subjects affected / exposed	1 / 80 (1.25%)	4 / 78 (5.13%)	1 / 81 (1.23%)
occurrences (all)	1	4	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 80 (1.25%)	8 / 78 (10.26%)	4 / 81 (4.94%)
occurrences (all)	1	9	7
Abdominal pain			
subjects affected / exposed	9 / 80 (11.25%)	8 / 78 (10.26%)	6 / 81 (7.41%)
occurrences (all)	10	9	7
Abdominal pain upper			
subjects affected / exposed	5 / 80 (6.25%)	6 / 78 (7.69%)	8 / 81 (9.88%)
occurrences (all)	5	7	10
Constipation			

subjects affected / exposed occurrences (all)	12 / 80 (15.00%) 14	17 / 78 (21.79%) 22	18 / 81 (22.22%) 20
Diarrhoea subjects affected / exposed occurrences (all)	23 / 80 (28.75%) 31	22 / 78 (28.21%) 30	16 / 81 (19.75%) 21
Dyspepsia subjects affected / exposed occurrences (all)	4 / 80 (5.00%) 4	9 / 78 (11.54%) 11	4 / 81 (4.94%) 5
Eructation subjects affected / exposed occurrences (all)	5 / 80 (6.25%) 6	6 / 78 (7.69%) 6	1 / 81 (1.23%) 1
Flatulence subjects affected / exposed occurrences (all)	2 / 80 (2.50%) 2	5 / 78 (6.41%) 5	3 / 81 (3.70%) 3
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	3 / 80 (3.75%) 3	4 / 78 (5.13%) 5	5 / 81 (6.17%) 6
Large intestine polyp subjects affected / exposed occurrences (all)	1 / 80 (1.25%) 1	4 / 78 (5.13%) 4	3 / 81 (3.70%) 3
Nausea subjects affected / exposed occurrences (all)	24 / 80 (30.00%) 32	29 / 78 (37.18%) 39	33 / 81 (40.74%) 49
Vomiting subjects affected / exposed occurrences (all)	14 / 80 (17.50%) 21	17 / 78 (21.79%) 26	12 / 81 (14.81%) 29
Respiratory, thoracic and mediastinal disorders Respiratory disorder subjects affected / exposed occurrences (all)	1 / 80 (1.25%) 1	0 / 78 (0.00%) 0	1 / 81 (1.23%) 1
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 80 (1.25%) 1	1 / 78 (1.28%) 1	4 / 81 (4.94%) 5
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	0 / 80 (0.00%)	4 / 78 (5.13%)	8 / 81 (9.88%)
occurrences (all)	0	4	8
Back pain			
subjects affected / exposed	7 / 80 (8.75%)	5 / 78 (6.41%)	10 / 81 (12.35%)
occurrences (all)	10	5	10
Muscle spasms			
subjects affected / exposed	1 / 80 (1.25%)	1 / 78 (1.28%)	3 / 81 (3.70%)
occurrences (all)	1	1	3
Pain in extremity			
subjects affected / exposed	1 / 80 (1.25%)	1 / 78 (1.28%)	2 / 81 (2.47%)
occurrences (all)	1	1	2
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	4 / 80 (5.00%)	2 / 78 (2.56%)	1 / 81 (1.23%)
occurrences (all)	4	2	1
Influenza			
subjects affected / exposed	7 / 80 (8.75%)	1 / 78 (1.28%)	3 / 81 (3.70%)
occurrences (all)	7	1	4
Nasopharyngitis			
subjects affected / exposed	11 / 80 (13.75%)	15 / 78 (19.23%)	10 / 81 (12.35%)
occurrences (all)	15	21	11
Sinusitis			
subjects affected / exposed	4 / 80 (5.00%)	7 / 78 (8.97%)	2 / 81 (2.47%)
occurrences (all)	4	8	4
Upper respiratory tract infection			
subjects affected / exposed	4 / 80 (5.00%)	6 / 78 (7.69%)	3 / 81 (3.70%)
occurrences (all)	4	8	4
Urinary tract infection			
subjects affected / exposed	5 / 80 (6.25%)	2 / 78 (2.56%)	7 / 81 (8.64%)
occurrences (all)	7	2	9
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 80 (20.00%)	18 / 78 (23.08%)	18 / 81 (22.22%)
occurrences (all)	18	18	22
Diabetes mellitus			

subjects affected / exposed occurrences (all)	0 / 80 (0.00%) 0	1 / 78 (1.28%) 1	0 / 81 (0.00%) 0
Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 80 (1.25%) 1	2 / 78 (2.56%) 3	3 / 81 (3.70%) 6

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events subjects affected / exposed	55 / 80 (68.75%)		
Investigations Lipase increased subjects affected / exposed occurrences (all)	0 / 80 (0.00%) 0		
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	2 / 80 (2.50%) 2		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	4 / 80 (5.00%) 4		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	6 / 80 (7.50%) 7 8 / 80 (10.00%) 10		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Injection site bruising subjects affected / exposed occurrences (all) Pyrexia	7 / 80 (8.75%) 7 2 / 80 (2.50%) 2		

subjects affected / exposed occurrences (all)	1 / 80 (1.25%) 1		
Gastrointestinal disorders			
Abdominal distension subjects affected / exposed occurrences (all)	4 / 80 (5.00%) 5		
Abdominal pain subjects affected / exposed occurrences (all)	3 / 80 (3.75%) 4		
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 80 (3.75%) 4		
Constipation subjects affected / exposed occurrences (all)	10 / 80 (12.50%) 11		
Diarrhoea subjects affected / exposed occurrences (all)	11 / 80 (13.75%) 16		
Dyspepsia subjects affected / exposed occurrences (all)	5 / 80 (6.25%) 7		
Eructation subjects affected / exposed occurrences (all)	0 / 80 (0.00%) 0		
Flatulence subjects affected / exposed occurrences (all)	0 / 80 (0.00%) 0		
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	2 / 80 (2.50%) 2		
Large intestine polyp subjects affected / exposed occurrences (all)	0 / 80 (0.00%) 0		
Nausea subjects affected / exposed occurrences (all)	9 / 80 (11.25%) 10		

Vomiting subjects affected / exposed occurrences (all)	2 / 80 (2.50%) 3		
Respiratory, thoracic and mediastinal disorders Respiratory disorder subjects affected / exposed occurrences (all)	4 / 80 (5.00%) 5		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	5 / 80 (6.25%) 5		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	7 / 80 (8.75%) 7 6 / 80 (7.50%) 6 4 / 80 (5.00%) 4 5 / 80 (6.25%) 7		
Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) Influenza subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Sinusitis	2 / 80 (2.50%) 2 6 / 80 (7.50%) 6 12 / 80 (15.00%) 22		

<p>subjects affected / exposed occurrences (all)</p> <p>Upper respiratory tract infection subjects affected / exposed occurrences (all)</p> <p>Urinary tract infection subjects affected / exposed occurrences (all)</p>	<p>1 / 80 (1.25%) 1</p> <p>5 / 80 (6.25%) 6</p> <p>0 / 80 (0.00%) 0</p>		
<p>Metabolism and nutrition disorders</p> <p>Decreased appetite subjects affected / exposed occurrences (all)</p> <p>Diabetes mellitus subjects affected / exposed occurrences (all)</p> <p>Hyperglycaemia subjects affected / exposed occurrences (all)</p>	<p>4 / 80 (5.00%) 4</p> <p>4 / 80 (5.00%) 5</p> <p>7 / 80 (8.75%) 8</p>		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 September 2016	The following changes were made as per this amendment: -Clarification of process for handling increased levels of liver blood parameters -Clarification that exclusion criterion 20 (retinopathy) is only applicable to subjects with type 2 diabetes (T2D) -Additional section added: Fundoscopy/fundus photography -Exclusion criterion for severe renal impairment (estimated glomerular filtration rate (eGFR) < 30 milliliter per minute per meter square (mL/min/m ²)) added, and continuous eGFR measurements during the trial
29 December 2016	The following changes were made as per this amendment: -Subjects developing T2D during the trial can be treated with antidiabetic medication -Exclusion criterion 8 updated: vitamin E and pioglitazone treatment must be stable for 90 days prior to screening/baseline liver biopsy -Statistical section updated: supportive analysis of the primary endpoint without pooling the placebo arms added. A sensitivity analysis of the primary endpoint where vitamin E use is included as a factor in the model, and a subgroup analysis for subjects who use vitamin E versus subjects who do not use vitamin E, added -Collection of daily dose for treatment with vitamin E and pioglitazone included -Text regarding new identified risk (retinopathy) included in risk/benefit section
26 May 2017	The following changes were made as per this amendment: -Changes to eligibility criteria implemented: Inclusion criteria 1 and 5, exclusion criteria 5, 6, 10, and 15 amended; Exclusion criteria 12 and 16 deleted -As a consequence of amending exclusion criterion 10 a new section with guidance on treatment of subjects with poorly controlled glycaemia included -Optional pre-screening included (blood samples and imaging (not involving radiation)) -Footnote to primary endpoint updated to clarify definition of resolution of NASH -Screen failure rate updated to 65% -Restrictions on bolus insulin treatment removed and short-term systemic use (less than or equal to (≤) 14 days) of corticosteroids allowed -Visit 10 must be attended in a fasting state (for calcitonin measurement)
02 October 2017	The following changes were made as per this amendment: -Global sample size reduction: from 372 to 288 randomised subjects -Expected time for planned duration of recruitment period increased from 78 to 103 weeks -Inclusion of subjects with fibrosis stage 1 (inclusion criterion 7 has been updated) -Re-test of INR allowed (if screening albumin is within central laboratory reference range) -Rephrased exclusion criterion 9 regarding treatment with drugs with potential effect on steatosis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported