Clinical trial results:
Efficacy and safety of semaglutide once-weekly versus placebo as add on to SGLT-2i in subjects with type 2 diabetes mellitus. A 30-week randomised, double-blind, placebo-controlled trial

Summary

EudraCT number	2016-000904-27
Trial protocol	NO AT
Global end of trial date	06 August 2018

Results information

Result version number	v1 (current)
This version publication date	22 August 2019
First version publication date	22 August 2019

Trial information

Trial identification

Sponsor protocol code	NN9535-4269

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03086330
WHO universal trial number (UTN)	U1111-1180-1213
Other trial identifiers	JapicCTI: 173542

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	18 February 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 July 2018
Global end of trial reached?	Yes
Global end of trial date	06 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of semaglutide s.c. 1.0 mg once-weekly versus placebo as add-on to SGLT-2 inhibitor monotherapy or in combination with either metformin or SU on glycaemic control after 30 weeks of treatment in subjects with T2D.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (2013) and ICH Good Clinical Practice, including archiving of essential documents, (1996) and 21 CFR 312.120.

Background therapy:

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors, metformin and sulphonylurea (SU) were considered as background medications. All participants were to be on a SGLT-2 inhibitor treatment. Subjects were to continue their anti-diabetic background medication throughout the trial at the same dose level with the same frequency as at the trial entry unless rescue criteria were met, or a safety concern related to acute renal impairment or hospitalization for major surgical procedures or acute serious medical illnesses occurred. All background medications were to be used in accordance with standard of care in the individual country and were not to exceed the maximum approved dose in the individual country.

Evidence for comparator:

Not applicable.

Actual start date of recruitment	15 March 2017
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	Austria: 39
Country: Number of subjects enrolled	Canada: 47
Country: Number of subjects enrolled	Japan: 50
Country: Number of subjects enrolled	Norway: 27
Country: Number of subjects enrolled	Russian Federation: 40
Country: Number of subjects enrolled	United States: 99
Worldwide total number of subjects	302
EEA total number of subjects	66

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)	244
From 65 to 84 years	58
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 61 sites in 6 countries as follows: Austria (4 sites), Canada (8 sites), Japan (4 sites), Norway (4 sites), Russian Federation (5 sites), United States of America (USA) (36 sites). In addition, 1 site in Norway and 3 sites in the USA screened, but didn't randomise any participant.

Pre-assignment

Screening details:

Not applicable.

Period 1

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

Blinding implementation details:

According to standard pharmacovigilance procedures, specific members of the Novo Nordisk A/S Global Safety department were not blinded to suspected unexpected serious adverse reaction (SUSARs; for reporting purpose), whereas the clinical study group and the investigator remained blinded throughout the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Semaglutide 1.0 mg

Arm description:

Participants received semaglutide in a dose escalation manner for 30 weeks: 0.25 mg (weeks 1 to 4), 0.50 mg (weeks 5 to 8) and
1.0 mg (weeks 9 to 30).

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

Dosage and administration details:

Semaglutide was taken once weekly as subcutaneous (s.c.) injections.

Arm title	Placebo

Arm description:

Participants received matching placebo (for semaglutide) in a dose escalation manner for 30 weeks. Dose escalation for placebo matched that for semaglutide with regards to volume.

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

Dosage and administration details:

Placebo was taken once weekly as s.c. injections.

Number of subjects in period 1	Semaglutide 1.0 mg	Placebo
Started	151	151
Completed	147	147
Not completed	4	4
Consent withdrawn by subject	3	2
Lost to follow-up	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Semaglutide 1.0 mg
Reporting group description:	
Participants received semaglutide in a dose escalation manner for 30 weeks: 0.25 mg (weeks 1 to 4), 0.50 mg (weeks 5 to 8) and 1.0 mg (weeks 9 to 30).	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo (for semaglutide) in a dose escalation manner for 30 weeks. Dose escalation for placebo matched that for semaglutide with regards to volume.	

Reporting group values	Semaglutide 1.0 mg	Placebo	Total
Number of subjects	151	151	302
Age Categorical			
Units: Subjects			
Adults (18-64 years)	123	121	244
From 65-84 years	28	30	58
Age Continuous			
Units: years			
arithmetic mean	57.5	56.6	
standard deviation	± 8.9	± 10.1	-
Gender Categorical			
Units: Subjects			
Female	62	64	126
Male	89	87	176
Glycosylated haemoglobin (HbA1c)			
Units: Percentage HbA1c			
arithmetic mean	8.0	8.1	
standard deviation	± 0.8	± 0.8	-

End points

End points reporting groups

Reporting group title	Semaglutide 1.0 mg
Reporting group description:	
Participants received semaglutide in a dose escalation manner for 30 weeks: 0.25 mg (weeks 1 to 4), 0.50 mg (weeks 5 to 8) and 1.0 mg (weeks 9 to 30).	
Reporting group title	Placebo
Reporting group description:	
Participants received matching placebo (for semaglutide) in a dose escalation manner for 30 weeks. Dose escalation for placebo matched that for semaglutide with regards to volume.	

Primary: Change in HbA1c

End point title	Change in HbA1c
End point description:	
Change from baseline (week 0) in HbA1c was evaluated at week 30. Results are based on the 'on-treatment without rescue medication' observation period, which started at the date of first dose of trial product and ended at the first date of any of the following: 1) the last dose of trial product + 7 days or 2) initiation of rescue medication. Population description: 'Full analysis set (FAS)' included all randomised participants. Number of subjects analysed = number of participants with available data.	
End point type	Primary
End point timeframe:	
From baseline to week 30	

End point values	Semaglutide 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	127		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)	-1.6 (± 0.8)	-0.2 (± 0.9)		

Statistical analyses

Statistical analysis title	Semaglutide 1.0 mg versus Placebo
Statistical analysis description:	
The responses were analysed using an analysis of covariance (ANCOVA) with treatment, stratification factor and region as fixed factors and baseline value as covariate. Before analysis, missing data were multiple imputed using observed data from participants within the same group defined by randomised treatment, using a regression model including stratification factor and region as categorical effects and data from baseline and all previous visits as covariates.	
Comparison groups	Semaglutide 1.0 mg v Placebo

Number of subjects included in analysis	247
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.61
upper limit	-1.24

Secondary: Change in body weight (kg)

End point title	Change in body weight (kg)

End point description:

Change from baseline (week 0) in body weight was evaluated at week 30. Results are based on the 'on-treatment without rescue medication' observation period. Population description: 'FAS' included all randomised participants. Number of subjects analysed = number of participants with available data.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	128		
Units: Kg				
arithmetic mean (standard deviation)	-4.7 (± 4.3)	-1.0 (± 3.1)		

Statistical analyses

Statistical analysis title	Semaglutide 1.0 mg versus placebo

Statistical analysis description:

The responses were analysed using an ANCOVA with treatment, stratification factor and region as fixed factors and baseline value as covariate. Before analysis, missing data were multiple imputed using observed data from participants within the same group defined by randomised treatment, using a regression model including stratification factor and region as categorical effects and data from baseline and all previous visits as covariates.

Comparison groups	Semaglutide 1.0 mg v Placebo

Number of subjects included in analysis	249
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-3.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	-2.93

Secondary: Change in fasting plasma glucose

End point title	Change in fasting plasma glucose

End point description:

Change from baseline (week 0) in fasting plasma glucose (FPG) was evaluated at week 30. Results are based on the 'on-treatment without rescue medication' observation period. Population description: 'FAS' included all randomised participants. Number of subjects analysed = number of participants with available data.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	128		
Units: mmol/L				
arithmetic mean (standard deviation)	-2.26 (± 2.05)	0.07 (± 2.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in systolic and diastolic blood pressure

End point title	Change in systolic and diastolic blood pressure

End point description:

Change from baseline (week 0) in systolic and diastolic blood pressure was evaluated at week 30. Results are based on the 'on-treatment without rescue medication' observation period. Population description: 'FAS' included all randomised participants. Number of subjects analysed = number of participants with available data.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	128		
Units: mmHg				
arithmetic mean (standard deviation)				
Systolic blood pressure	-4.3 (± 14.5)	1.1 (± 12.3)		
Diastolic blood pressure	-0.1 (± 8.1)	-0.1 (± 6.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in scores for selected patient reported outcomes (PRO): Diabetes Treatment Satisfaction Questionnaire (DTSQ)

End point title	Change in scores for selected patient reported outcomes (PRO): Diabetes Treatment Satisfaction Questionnaire (DTSQ)

End point description:

Change from baseline (week 0) in PRO questionnaire, DTSQ was evaluated at week 30. Results are based on the 'on-treatment without rescue medication' observation period. The DTSQ measures satisfaction with diabetes treatment. The DTSQ consists of 8 items evaluating 6 aspects of treatment satisfaction and 2 perceived recent event rates of hyperglycemia/hypoglycemia. Each item is scored on a 7- point Likert scale ranging from 0 (very dissatisfied) to 6 (very satisfied). Items evaluating 6 aspects (items 3-8) of treatment satisfaction are summed to produce a total treatment satisfaction score; DTSQ status total scores range from 0-36, with higher scores indicating greater satisfaction; the perceived frequency of hyperglycemia/hypoglycemia items are scored separately, with lower scores indicating better perceived blood glucose control. Population description: 'FAS' included all randomised participants. Number of subjects analysed = number of participants with available data.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	125		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
1) Feeling of unacceptably high blood sugars	-2.2 (± 1.9)	-0.8 (± 2.2)		
2) Feeling of unacceptably low blood sugars	0.3 (± 1.5)	-0.4 (± 1.5)		
Total treatment satisfaction score (Sum of 3-8)	4.2 (± 6.6)	1.9 (± 7.0)		
3) Satisfaction with current treatment	0.8 (± 1.6)	0.2 (± 1.4)		
4) Convenience of current treatment	0.7 (± 1.3)	0.5 (± 1.3)		
5) Flexibility of current treatment	0.7 (± 1.5)	0.4 (± 1.7)		

6) Satisfaction with understanding of diabetes	0.5 (± 1.2)	0.5 (± 1.5)		
7) Recommending treatment to others	0.8 (± 1.3)	0.2 (± 1.8)		
8) Satisfaction to continue with present treatment	0.8 (± 1.7)	0.2 (± 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects who achieve HbA1c ≤6.5% (48 mmol/mol), American Association of Clinical Endocrinologists target (yes/no)

End point title	Subjects who achieve HbA1c ≤6.5% (48 mmol/mol), American Association of Clinical Endocrinologists target (yes/no)

End point description:

Percentage of participants with HbA1c equal to or below 6.5% (48 mmol/mol) was evaluated at week 30. Results are based on the 'on-treatment without rescue medication' observation period. Population description: 'FAS' included all randomised participants. Number of subjects analysed = number of participants with available data.

End point type	Secondary

End point timeframe:

After 30 weeks' treatment

End point values	Semaglutide 1.0 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	127		
Units: Percentage of participants				
number (not applicable)	60.0	3.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 to week 30 (treatment period) + 42 days (follow-up period).

Adverse event reporting additional description:

Results are based on the safety analysis set (SAS), which included all participants exposed to at least one dose of trial product (semaglutide or placebo). 'Number of deaths causally related to treatment' is the data considered to present under 'total number of deaths resulting from adverse events'.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Semaglutide 1.0 mg

Reporting group description:

Participants received semaglutide in a dose escalation manner for 30 weeks: 0.25 mg (weeks 1 to 4), 0.50 mg (weeks 5 to 8) and 1.0 mg (weeks 9 to 30).

Reporting group title	Placebo

Reporting group description:

Participants received matching placebo (for semaglutide) in a dose escalation manner for 30 weeks. Dose escalation for placebo matched that for semaglutide with regards to volume.

Serious adverse events	Semaglutide 1.0 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 150 (4.67%)	6 / 151 (3.97%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Laryngeal squamous cell carcinoma			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
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			
Accidental overdose			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			

subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Thyroidectomy			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal artery occlusion			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ischaemic			

subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis bacterial			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurocysticercosis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Semaglutide 1.0 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 150 (32.67%)	28 / 151 (18.54%)	
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	2 / 150 (1.33%)	8 / 151 (5.30%)	
occurrences (all)	2	9	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	10 / 150 (6.67%)	0 / 151 (0.00%)	
occurrences (all)	10	0	
Diarrhoea			
subjects affected / exposed	17 / 150 (11.33%)	9 / 151 (5.96%)	
occurrences (all)	21	11	
Nausea			
subjects affected / exposed	29 / 150 (19.33%)	5 / 151 (3.31%)	
occurrences (all)	37	7	
Vomiting			
subjects affected / exposed	14 / 150 (9.33%)	3 / 151 (1.99%)	
occurrences (all)	21	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 150 (5.33%)	8 / 151 (5.30%)	
occurrences (all)	9	11	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported