Clinical trial results:
Efficacy and safety of semaglutide once weekly versus insulin glargine once daily as add on to metformin with or without sulphonylurea in insulin-naïve subjects with type 2 diabetes

Summary

EudraCT number	2013-004392-12
Trial protocol	SI SK DE GB NL RO HR
Global end of trial date	03 September 2015

Results information

Result version number	v1 (current)
This version publication date	18 September 2016
First version publication date	18 September 2016

Trial information

Trial identification

Sponsor protocol code	NN9535-3625

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02128932
WHO universal trial number (UTN)	U1111-1146-0211

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Global Clinical Registry (GCR 1452), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Global Clinical Registry (GCR 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	11 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	03 September 2015
Global end of trial reached?	Yes
Global end of trial date	03 September 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of once-weekly dosing of two dose levels of semaglutide versus insulin glargine once-daily on glycaemic control after 30 weeks of treatment in insulin-naïve subjects with type 2 diabetes.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice.

Background therapy:

The following compounds were considered as background medication and were administered at the described doses:
Metformin: doses ≥1500 mg or maximum tolerated dose. Treatment with extended/slow release was allowed
Sulphonylurea (SU): doses ≥half of maximum dose allowed according to national label.

Evidence for comparator:

Not applicable

Actual start date of recruitment	04 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 41
Country: Number of subjects enrolled	Croatia: 25
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 81
Country: Number of subjects enrolled	India: 83
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 30
Country: Number of subjects enrolled	Mexico: 44
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Romania: 44
Country: Number of subjects enrolled	Slovakia: 45
Country: Number of subjects enrolled	Slovenia: 38
Country: Number of subjects enrolled	South Africa: 40
Country: Number of subjects enrolled	United Kingdom: 89
Country: Number of subjects enrolled	United States: 495
Worldwide total number of subjects	1082
EEA total number of subjects	349

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)	840
From 65 to 84 years	242
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 196 sites in 14 countries Argentina: 3 sites; Croatia: 3 sites; France: 5 sites; Germany: 11 sites; India: 12 sites; Macedonia: 3 sites; Mexico: 3 sites; Netherlands: 3 sites; Romania: 5 sites; Slovakia: 5 sites; Slovenia: 3 sites; South Africa: 4 sites; United Kingdom: 13 sites; United States :123 sites.

Pre-assignment

Screening details:

Insulin-naïve subjects diagnosed with type 2 diabetes and on stable diabetes treatment with metformin or metformin and SU (metformin ≥1500 mg or maximum tolerated dose and SU ≥ half of maximum allowed dose according to national label) for at least 90 days before screening. Stable is defined as unchanged medication and unchanged dose.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Open label, active-controlled, parallel design, multinational, three-armed trial

Arms

Are arms mutually exclusive?	Yes
Arm title	Semaglutide 0.5 mg/week

Arm description:

Subjects on semaglutide followed a fixed dose-escalation. The maintenance dose of 0.5 mg was to be reached after 4 doses (4 weeks) of 0.25 mg semaglutide. Doses could not be changed during the trial after the maintenance dose had been reached. There were 49 premature dis continuations in this arm.

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

Dosage and administration details:

One test pen was to be supplied per subject at the screening visit in order to ensure the subject`s willingness and ability to self-inject. The test pen contained semaglutide placebo, solution for injection, 1.5 mL pre-filled PDS290 pen-injector and was to be administered once. The PDS290 pen-injector for semaglutide is a prefilled pen integrated with a 1.5 mL cartridge containing semaglutide 1.34 mg/mL and is designed to be used with NovoFine®, NovoFine® Plus and NovoTwist® disposable needles Once weekly (same day of the week) administered by s.c. injection in thigh, abdomen or upper arm, at any time of the day

Arm title	Semaglutide 1.0 mg/week

Arm description:

Subjects randomised to semaglutide followed a fixed dose-escalation regimen, The maintenance dose of 1.0 mg was to be reached after 4 doses (4 weeks) of 0.25 mg, followed by 4 doses (4 weeks) of 0.5 mg semaglutide. Doses could not be changed during the trial after the maintenance dose had been reached. There were 55 premature dis continuations in this arm.

Arm type	Experimental

Investigational medicinal product name	Semaglutide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

One test pen was to be supplied per subject at the screening visit in order to ensure the subject`s willingness and ability to self-inject. The test pen contained semaglutide placebo, solution for injection, 1.5 mL pre-filled PDS290 pen-injector and was to be administered once. The PDS290 pen-injector for semaglutide is a prefilled pen integrated with a 1.5 mL cartridge containing semaglutide 1.34 mg/mL and is designed to be used with NovoFine®, NovoFine® Plus and NovoTwist® disposable needles Once weekly (same day of the week) administered by s.c. injection in thigh, abdomen or upper arm, at any time of the day.

Arm title	Insulin glargine

Arm description:

Subjects on insulin glargine were to start on 10 IU subcutaneous(s.c.) injected once daily (OD). The insulin dose adjustment had to aim to reach a pre-breakfast FPG of 4.0 to <5.5 mmol/L (71- <100 mg/dL). There were 26 premature dis continuations in this arm.

Arm type	Active comparator
Investigational medicinal product name	Lantus
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Once daily solution for injection in a 3 mL pre-filled SoloStar® pen to be administered in the thigh, abdomen or upper arm , at any time of the day

Number of subjects in period 1	Semaglutide 0.5 mg/week	Semaglutide 1.0 mg/week	Insulin glargine
Started	362	360	360
Completed	335	341	342
Not completed	27	19	18
Not completed	27	19	18

Baseline characteristics

Reporting groups	
Reporting group title	Semaglutide 0.5 mg/week
Reporting group description:	
Subjects on semaglutide followed a fixed dose-escalation. The maintenance dose of 0.5 mg was to be reached after 4 doses (4 weeks) of 0.25 mg semaglutide. Doses could not be changed during the trial after the maintenance dose had been reached. There were 49 premature dis continuations in this arm.	
Reporting group title	Semaglutide 1.0 mg/week
Reporting group description:	
Subjects randomised to semaglutide followed a fixed dose-escalation regimen, The maintenance dose of 1.0 mg was to be reached after 4 doses (4 weeks) of 0.25 mg, followed by 4 doses (4 weeks) of 0.5 mg semaglutide. Doses could not be changed during the trial after the maintenance dose had been reached. There were 55 premature dis continuations in this arm.	
Reporting group title	Insulin glargine
Reporting group description:	
Subjects on insulin glargine were to start on 10 IU subcutaneous(s.c.) injected once daily (OD). The insulin dose adjustment had to aim to reach a pre-breakfast FPG of 4.0 to <5.5 mmol/L (71- <100 mg/dL). There were 26 premature dis continuations in this arm.	

Reporting group values	Semaglutide 0.5 mg/week	Semaglutide 1.0 mg/week	Insulin glargine
Number of subjects	362	360	360
Age Categorical			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
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)	278	281	281
From 65-84 years	84	79	79
85 years and over	0	0	0
Age Continuous			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: years			
arithmetic mean	56.5	56.7	56.2
standard deviation	± 10.3	± 10.4	± 10.6
Gender Categorical			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: Subjects			
Female	165	178	165
Male	197	182	195

HbA1c			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: percentage			
arithmetic mean	8.13	8.25	8.13
standard deviation	± 0.85	± 0.94	± 0.88
Fasting Plasma Glucose			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: mg/dL			
arithmetic mean	172.4	179.2	174.2
standard deviation	± 50.52	± 53.74	± 49.06
Body weight			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: kg			
arithmetic mean	93.73	94	92.61
standard deviation	± 21.39	± 22.48	± 21.52
Diastolic blood pressure			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: mmHg			
arithmetic mean	79.67	80.32	79.78
standard deviation	± 8.04	± 8.32	± 9.2
Systolic Blood Pressure			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: mmHg			
arithmetic mean	131.57	132.21	132.38
standard deviation	± 14.06	± 16.05	± 15.77

Reporting group values	Total		
Number of subjects	1082		
Age Categorical			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	840		
From 65-84 years	242		
85 years and over	0		

Age Continuous			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: years			
arithmetic mean			
standard deviation	-		
Gender Categorical			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: Subjects			
Female	508		
Male	574		
HbA1c			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: percentage			
arithmetic mean			
standard deviation	-		
Fasting Plasma Glucose			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: mg/dL			
arithmetic mean			
standard deviation	-		
Body weight			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: kg			
arithmetic mean			
standard deviation	-		
Diastolic blood pressure			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: mmHg			
arithmetic mean			
standard deviation	-		
Systolic Blood Pressure			
Full analysis set (FAS): included all randomised subjects who had received at least one dose of randomised semaglutide (s.c.) or insulin glargine. Subjects in the FAS contributed to the evaluation based on the treatment assigned at randomisation.			
Units: mmHg			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Semaglutide 0.5 mg/week

Reporting group description:

Subjects on semaglutide followed a fixed dose-escalation. The maintenance dose of 0.5 mg was to be reached after 4 doses (4 weeks) of 0.25 mg semaglutide. Doses could not be changed during the trial after the maintenance dose had been reached. There were 49 premature dis continuations in this arm.

Reporting group title	Semaglutide 1.0 mg/week

Reporting group description:

Subjects randomised to semaglutide followed a fixed dose-escalation regimen, The maintenance dose of 1.0 mg was to be reached after 4 doses (4 weeks) of 0.25 mg, followed by 4 doses (4 weeks) of 0.5 mg semaglutide. Doses could not be changed during the trial after the maintenance dose had been reached. There were 55 premature dis continuations in this arm.

Reporting group title	Insulin glargine

Reporting group description:

Subjects on insulin glargine were to start on 10 IU subcutaneous(s.c.) injected once daily (OD). The insulin dose adjustment had to aim to reach a pre-breakfast FPG of 4.0 to <5.5 mmol/L (71- <100 mg/dL). There were 26 premature dis continuations in this arm.

Primary: Change in HbA1c

End point title	Change in HbA1c

End point description:

Change in HbA1c from baseline to week 30. These analyses were done using the FAS. The full analysis set (FAS) included all randomised subjects who had received at least one dose ofrandomised semaglutide 0.5 mg, semaglutide 1.0 mg or insulin glargine.

End point type	Primary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg/week	Semaglutide 1.0 mg/week	Insulin glargine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	362	360	360	
Units: percentage				
least squares mean (standard error)	-1.21 (± 0.05)	-1.64 (± 0.05)	-0.83 (± 0.05)	

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

The post baseline responses were analysed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

Comparison groups	Semaglutide 0.5 mg/week v Insulin glargine

Number of subjects included in analysis	722
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.52
upper limit	-0.24

Notes:

[1] - Non-inferiority was concluded if the upper limit of the two-sided 95% confidence interval for the estimated treatment difference between semaglutide 1.0 mg or semaglutide 0.5 mg and insulin glargine was below the pre-specified non-inferiority margin (0.3 %).

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

The post baseline responses were analysed using a mixed model for repeated measurements with treatment and country as fixed factors and baseline value as covariate, all nested within visit.

Comparison groups	Semaglutide 1.0 mg/week v Insulin glargine
Number of subjects included in analysis	720
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.96
upper limit	-0.67

Notes:

[2] - Non-inferiority was concluded if the upper limit of the two-sided 95% confidence interval for the estimated treatment difference between semaglutide 1.0 mg or semaglutide 0.5 mg and insulin glargine was below the pre-specified non-inferiority margin (0.3 %).

Secondary: Change in body weight

End point title	Change in body weight

End point description:

Change in body weight from baseline to week 30. These analyses were done using the FAS. The full analysis set (FAS) included all randomised subjects who had received at least one dose of randomised semaglutide 0.5 mg, semaglutide 1.0 mg or insulin glargine.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg/week	Semaglutide 1.0 mg/week	Insulin glargine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	362	360	360	
Units: kg				
least squares mean (standard error)	-3.47 (± 0.24)	-5.17 (± 0.24)	1.15 (± 0.23)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Fasting plasma glucose

End point title	Change in Fasting plasma glucose

End point description:

Change in Fasting plasma glucose from baseline to week 30. These analyses were done using the FAS. The full analysis set (FAS) included all randomised subjects who had received at least one dose of randomised semaglutide 0.5 mg, semaglutide 1.0 mg or insulin glargine

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg/week	Semaglutide 1.0 mg/week	Insulin glargine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	362	360	360	
Units: mg/dL				
least squares mean (standard error)	-36.74 (± 2.14)	-49.21 (± 2.15)	-38.18 (± 2.03)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in diastolic blood pressure

End point title	Change in diastolic blood pressure

End point description:

Change in diastolic blood pressure from baseline to week 30. These analyses were done using the FAS. The full analysis set (FAS) included all randomised subjects who had received at least one dose of randomised semaglutide 0.5mg, semaglutide 1.0 mg or insulin glargine.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg/week	Semaglutide 1.0 mg/week	Insulin glargine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	362	360	360	
Units: mmHg				
least squares mean (standard error)	-1.38 (± 0.43)	-0.98 (± 0.44)	-1.44 (± 0.41)	

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 basleine to week 30. These analyses were done using the FAS. The full analysis set (FAS) included all randomised subjects who had received at least one dose of randomised semaglutide 0.5 mg, semaglutide 1.0 mg or insulin glargine.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg/week	Semaglutide 1.0 mg/week	Insulin glargine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	362	360	360	
Units: mmHg				
least squares mean (standard error)	-4.65 (± 0.72)	-5.17 (± 0.73)	-1.68 (± 0.68)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in patient reported outcome questionnaires (PROs), SF-36v2™

End point title	Change in patient reported outcome questionnaires (PROs), SF-36v2™

End point description:

The Short Form (SF)-36v2™ health survey (SF-36v2™)questionnaire was to be used to assess the subject’s overall HRQoL and could also be used to estimate quality adjusted life years, which is used in cost effectiveness calculations. This questionnaire contains 36 items and measures the individual overall health related quality of life on 8 domains; physical functioning, role functioning, bodily pain, general health, vitality, social functioning, role emotional and mental health. These analyses were done using the FAS. The full analysis set (FAS) included all randomised subjects who had received at least one dose of randomised semaglutide 0.5 mg, semaglutide 1.0 mg or insulin glargine.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg/week	Semaglutide 1.0 mg/week	Insulin glargine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	362	360	360	
Units: Score on a scale				
least squares mean (standard error)				
Bodily pain	0.95 (± 0.51)	1.76 (± 0.51)	0.9 (± 0.48)	
General Health	1.95 (± 0.38)	2.78 (± 0.38)	1.63 (± 0.36)	
Mental Component summary, MCS	1.23 (± 0.47)	1.33 (± 0.47)	0.25 (± 0.44)	
Mental Health	1.69 (± 0.46)	1.17 (± 0.47)	0.54 (± 0.44)	
Physical Component summary, PCS	1.18 (± 0.36)	2.09 (± 0.36)	1.18 (± 0.34)	
Physical Functioning	1.64 (± 0.43)	1.49 (± 0.43)	0.69 (± 0.41)	
Role -emotional	0.88 (± 0.54)	1.73 (± 0.54)	0.06 (± 0.51)	
Role -physical	0.9 (± 0.46)	1.97 (± 0.46)	0.78 (± 0.43)	
Social functinoning	1.13 (± 0.48)	1.04 (± 0.48)	0.36 (± 0.45)	
Vitality	1.71 (± 0.46)	2.09 (± 0.46)	0.95 (± 0.44)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in patient reported outcome questionnaires. (PROs), DTSQs

End point title	Change in patient reported outcome questionnaires. (PROs), DTSQs

End point description:

The Diabetes Treatment Satisfaction Questionnaire (DTSQs) questionnaire was to be used to assess a subject's treatment satisfaction. This questionnaire contains 8 items and measures the treatment for diabetes (including insulin, tablets and/or diet) in terms of convenience, flexibility and general feelings regarding treatment. These analyses were done using the FAS. The full analysis set (FAS) included all randomised subjects who had received at least one dose of randomised semaglutide 0.5 mg, semaglutide 1.0 mg or insulin glargine. The result presented is the 'Treatment Satisfaction' summary score, which is the sum of 6 of the 8 items of the DTSQs questionnaire.

End point type	Secondary

End point timeframe:

From baseline to week 30

End point values	Semaglutide 0.5 mg/week	Semaglutide 1.0 mg/week	Insulin glargine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	362	360	360	
Units: Scores on a scale				
least squares mean (standard error)				
Treatment satisfaction	4.86 (± 0.28)	5.37 (± 0.29)	3.99 (± 0.27)	

Statistical analyses

No statistical analyses for this end point

Secondary: Subjects who achieve HbA1c ≤6.5% (48 mmol/mol), American Association of Clinical Endocrinologists (AACE)

End point title	Subjects who achieve HbA1c ≤6.5% (48 mmol/mol), American Association of Clinical Endocrinologists (AACE)

End point description:

Subjects who achieve HbA1c ≤6.5% (48 mmol/mol), American Association of Clinical Endocrinologists (AACE) after 30 weeks of treatment

End point type	Secondary

End point timeframe:

After 30 weeks' treatment

End point values	Semaglutide 0.5 mg/week	Semaglutide 1.0 mg/week	Insulin glargine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	362	360	360	
Units: Number of subjects				
number (not applicable)				
Yes	135	195	63	
No	227	165	297	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from the first trial-related activity after the subject had signed the informed consent until the end of the post-treatment follow-up period. (Week 0-week 30 and 5 week follow-up period)

Adverse event reporting additional description:

A treatment-emergent adverse event (TEAE) was defined as an AE that had onset date (or increased in severity) during the 'on-treatment' observation period. The 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	18

Reporting groups

Reporting group title	Semaglutide 0.5 mg/week

Reporting group description:

Subjects on semaglutide followed a fixed dose-escalation. The maintenance dose of 0.5 mg was to be reached after 4 doses (4 weeks) of 0.25 mg semaglutide. Doses could not be changed during the trial after the maintenance dose had been reached.

Reporting group title	Insulin glargine

Reporting group description:

Subjects on insulin glargine were to start on 10 IU subcutaneous (S.C.) injected once daily (OD) The insulin dose adjustment had to aim to reach a pre-breakfast FPG of 4.0 to <5.5 mmol/L (71- <100 mg/dL).

Reporting group title	Semaglutide 1.0 mg/week

Reporting group description:

Subjects randomised to semaglutide followed a fixed dose-escalation regimen, The maintenance dose of 1.0 mg was to be reached after 4 doses (4 weeks) of 0.25 mg, followed by 4 doses (4 weeks) of 0.5 mg semaglutide. Doses could not be changed during the trial after the maintenance dose had been reached.

Serious adverse events	Semaglutide 0.5 mg/week	Insulin glargine	Semaglutide 1.0 mg/week
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 362 (6.08%)	18 / 360 (5.00%)	17 / 360 (4.72%)
number of deaths (all causes)	4	2	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Nasopharyngeal cancer			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Pancreatic carcinoma metastatic			

subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Thyroid neoplasm			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Surgical and medical procedures			
Carotid endarterectomy			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Coronary arterial stent insertion			
subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eyelid operation			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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

Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Immune system disorders			
Corneal graft rejection			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
Reproductive system and breast disorders			
Endometrial hyperplasia			
subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Bronchial hyperreactivity			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
Investigations			
Weight decreased			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
Jaw fracture			
subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumocephalus			
subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	1 / 360 (0.28%)
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			
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
Atrial fibrillation			
subjects affected / exposed	1 / 362 (0.28%)	1 / 360 (0.28%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
Ischaemic cardiomyopathy			

subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
Myocarditis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Cerebrovascular accident			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
Ischaemic stroke			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Migraine with aura			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
Sciatica			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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 ischaemic attack			

subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	2 / 360 (0.56%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VIIth nerve paralysis			
subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Anal fissure			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
Intestinal obstruction			

subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Nausea			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
Pancreatitis acute			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Vomiting			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	1 / 360 (0.28%)
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 and connective tissue disorders			
Chondropathy			
subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intervertebral disc protrusion			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
Osteoarthritis			
subjects affected / exposed	1 / 362 (0.28%)	1 / 360 (0.28%)	2 / 360 (0.56%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Bronchitis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	0 / 362 (0.00%)	1 / 360 (0.28%)	0 / 360 (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
Gangrene			
subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin abscess			
subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis B			

subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 362 (0.00%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 362 (0.55%)	1 / 360 (0.28%)	0 / 360 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Sepsis			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	0 / 360 (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
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 362 (0.28%)	0 / 360 (0.00%)	1 / 360 (0.28%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 362 (0.55%)	0 / 360 (0.00%)	0 / 360 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Semaglutide 0.5 mg/week	Insulin glargine	Semaglutide 1.0 mg/week
Total subjects affected by non-serious adverse events			
subjects affected / exposed	172 / 362 (47.51%)	107 / 360 (29.72%)	192 / 360 (53.33%)
Investigations			
Lipase increased			
subjects affected / exposed	36 / 362 (9.94%)	15 / 360 (4.17%)	30 / 360 (8.33%)
occurrences (all)	39	17	32
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 362 (5.25%)	20 / 360 (5.56%)	23 / 360 (6.39%)
occurrences (all)	40	26	33
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	59 / 362 (16.30%)	16 / 360 (4.44%)	69 / 360 (19.17%)
occurrences (all)	67	18	118
Dyspepsia			
subjects affected / exposed	12 / 362 (3.31%)	2 / 360 (0.56%)	24 / 360 (6.67%)
occurrences (all)	24	2	39
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 362 (1.10%)	3 / 360 (0.83%)	19 / 360 (5.28%)
occurrences (all)	4	4	20
Nausea			
subjects affected / exposed	77 / 362 (21.27%)	12 / 360 (3.33%)	80 / 360 (22.22%)
occurrences (all)	101	15	117
Vomiting			
subjects affected / exposed	24 / 362 (6.63%)	10 / 360 (2.78%)	37 / 360 (10.28%)
occurrences (all)	28	12	119
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	11 / 362 (3.04%)	7 / 360 (1.94%)	18 / 360 (5.00%)
occurrences (all)	11	10	20
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	45 / 362 (12.43%)	44 / 360 (12.22%)	29 / 360 (8.06%)
occurrences (all)	58	51	37
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	10 / 362 (2.76%) 10	24 / 360 (6.67%) 25	14 / 360 (3.89%) 16
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	25 / 362 (6.91%) 34	1 / 360 (0.28%) 1	23 / 360 (6.39%) 23

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