Clinical trial results:
A trial comparing NNC0148-0287 C (insulin 287) versus insulin glargine U100, both in combination with metformin, with or without DPP4 inhibitors and with or without SGLT2 inhibitors, in basal insulin treated subjects with type 2 diabetes mellitus

Summary

EudraCT number	2018-003407-18
Trial protocol	CZ DE IT
Global end of trial date	27 January 2020

Results information

Result version number	v1 (current)
This version publication date	24 January 2021
First version publication date	24 January 2021

Trial information

Trial identification

Sponsor protocol code	NN1436-4466

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03922750
WHO universal trial number (UTN)	U1111-1219-5541

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), Clinical Reporting Anchor and Disclosure (1452), +1 866 8677178, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Anchor and Disclosure (1452), Novo Nordisk A/S, +1 866 8677178, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2019
Global end of trial reached?	Yes
Global end of trial date	27 January 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 on glycaemic control of treatment with once weekly insulin 287 using two different switch approaches versus once-daily insulin glargine U100 both in combination with metformin ± DPP4i ± SGLT2i in basal insulin analogue treated T2DM subjects.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (64th WMA general assembly; Oct 2013) and ICH Good Clinical Practice, including archiving of essential documents, (May 1996) and 21 CFR 312.120.

Background therapy:

Subjects were to receive background therapy with basal insulin analogue with metformin, with or without dipeptidyl peptidase-4 inhibitors (DPP4i) and with or without sodium-glucose cotransporter 2 inhibitors (SGLT2i) at the stable, pre-trial dose and at the same frequency during the entire treatment period unless due to safety concerns related to the background medication.

Evidence for comparator: -

Actual start date of recruitment	09 May 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 36
Country: Number of subjects enrolled	Czechia: 30
Country: Number of subjects enrolled	Germany: 32
Country: Number of subjects enrolled	Italy: 31
Country: Number of subjects enrolled	United States: 25
Worldwide total number of subjects	154
EEA total number of subjects	93

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	89
From 65 to 84 years	65
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 34 sites in 5 countries as follows: Canada (10), Italy (5), Czech Republic (4), Germany (5) and the United States (10). In addition, 3 sites in the United states and 1 site in Germany screened, but didn't randomise any subjects.

Pre-assignment

Screening details:

Subjects were randomised to receive once weekly insulin 287 using any of 2 different switch approaches or once daily insulin glargine.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Insulin 287 (without loading dose)

Arm description:

Subjects were to receive once weekly subcutaneous (s.c.) injection of insulin 287 for 16 weeks, using PDS290 prefilled pen-injector in a unit to unit switch approach.

Arm type	Experimental
Investigational medicinal product name	NNC0148-0287 C 4200 nmol/mL
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 weekly subcutaneous (s.c.) injection of insulin 287 for 16 weeks, using PDS290 prefilled pen-injector at a starting dose of 7 times the pre-trial basal insulin dose of the respective subjects ('unit to unit switch' approach: current daily dose x 7). subjects were to perform once daily pre-breakfast self-monitoring plasma glucose (SMPG). The dose was adjusted based on 3 pre-breakfast SMPG values measured on the 2 previous days and the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 millimoles per litre (mmol/L): dose reduced by 28 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 28 U. If the subject received a twice-daily regimen with any basal insulin analogue or a once-daily regimen with insulin glargine U300 prior to randomisation, the total daily insulin dose prior to randomisation was reduced by 20%.

Arm title	Insulin 287 (with 100% loading dose)

Arm description:

Subjects were to receive once weekly s.c. injection of insulin 287 for 16 weeks, using PDS290 prefilled pen-injector in a unit to unit switch with an additional 100% loading dose approach.

Arm type	Experimental
Investigational medicinal product name	NNC0148-0287 C 4200 nmol/mL
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 weekly s.c. injection of insulin 287 for 16 weeks, using PDS290 prefilled pen-injector at a starting dose of 7 times the pre-trial basal insulin dose of the respective subjects with additional loading dose (‘unit to unit switch with an additional 100% loading dose’ approach: current daily dose x 7 x 2). subjects were to perform once daily pre-breakfast SMPG. The dose was adjusted

based on 3 pre-breakfast SMPG values measured on the 2 previous days and the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 millimoles per litre (mmol/L): dose reduced by 28 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 28 U. If the subject received a twice-daily regimen with any basal insulin analogue or a once-daily regimen with insulin glargine U300 prior to randomisation, the total daily insulin dose prior to randomisation was reduced by 20%

Arm title	Insulin Glargine U100

Arm description:

Subjects were to receive once daily s.c. injection of insulin glargine U100 for 16 weeks, using SoloSTAR prefilled pen-injector.

Arm type	Active comparator
Investigational medicinal product name	Insulin Glargine U100
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 insulin glargine U100 for 16 weeks, using SoloSTAR prefilled pen-injector at a starting dose same as the pre-trial basal insulin. subjects were to perform once daily pre-breakfast SMPG. The dose was adjusted based on 3 pre-breakfast SMPG values measured on the 2 previous days and the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 millimoles per litre (mmol/L): dose reduced by 4 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 4 U. If the subject received a twice-daily regimen with any basal insulin analogue or a once-daily regimen with insulin glargine U300 prior to randomisation, the total daily insulin dose prior to randomisation was reduced by 20%.

Number of subjects in period 1	Insulin 287 (without loading dose)	Insulin 287 (with 100% loading dose)	Insulin Glargine U100
Started	50	54	50
Completed	50	53	50
Not completed	0	1	0
Lost to follow-up	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Insulin 287 (without loading dose)
Reporting group description:	
Subjects were to receive once weekly subcutaneous (s.c.) injection of insulin 287 for 16 weeks, using PDS290 prefilled pen-injector in a unit to unit switch approach.	
Reporting group title	Insulin 287 (with 100% loading dose)
Reporting group description:	
Subjects were to receive once weekly s.c. injection of insulin 287 for 16 weeks, using PDS290 prefilled pen-injector in a unit to unit switch with an additional 100% loading dose approach.	
Reporting group title	Insulin Glargine U100
Reporting group description:	
Subjects were to receive once daily s.c. injection of insulin glargine U100 for 16 weeks, using SoloSTAR prefilled pen-injector.	

Reporting group values	Insulin 287 (without loading dose)	Insulin 287 (with 100% loading dose)	Insulin Glargine U100
Number of subjects	50	54	50
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 62.1 ± 8.2	 62.4 ± 7.2	 60.5 ± 7.9
Gender Categorical Units: Subjects			
Female	11	15	17
Male	39	39	33

Reporting group values	Total		
Number of subjects	154		
Age Categorical Units: Subjects			
Age Continuous Units: years arithmetic mean standard deviation	 -	 	
Gender Categorical Units: Subjects			
Female	43		
Male	111		

End points

End points reporting groups

Reporting group title	Insulin 287 (without loading dose)
Reporting group description:	
Subjects were to receive once weekly subcutaneous (s.c.) injection of insulin 287 for 16 weeks, using PDS290 prefilled pen-injector in a unit to unit switch approach.	
Reporting group title	Insulin 287 (with 100% loading dose)
Reporting group description:	
Subjects were to receive once weekly s.c. injection of insulin 287 for 16 weeks, using PDS290 prefilled pen-injector in a unit to unit switch with an additional 100% loading dose approach.	
Reporting group title	Insulin Glargine U100
Reporting group description:	
Subjects were to receive once daily s.c. injection of insulin glargine U100 for 16 weeks, using SoloSTAR prefilled pen-injector.	

Primary: Time in target range 3.9–10.0 mmol/L (70-180 mg/dL) measured using continuous glucose monitoring (CGM)

End point title	Time in target range 3.9–10.0 mmol/L (70-180 mg/dL) measured using continuous glucose monitoring (CGM)
End point description:	
The percentage of time spent in glycaemic target range was calculated as 100 times the number of recorded measurements in glycaemic target range 3.9–10.0 mmol/L (70-180 mg/dL), both inclusive divided by the total number of recorded measurements. The endpoint was evaluated based on the data from the on-treatment without rescue medication observation period, which was the time period when a subject was on treatment with trial product, excluding any period after initiation of a non-randomised insulin treatment (rescue medication). Number of subjects analyzed = Number of subjects who contributed to the analysis.	
End point type	Primary
End point timeframe:	
During the last 2 weeks of treatment (week 15 and 16)	

End point values	Insulin 287 (without loading dose)	Insulin 287 (with 100% loading dose)	Insulin Glargine U100	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	49	53	50	
Units: Percentage of time				
least squares mean (standard deviation)	65.99 (± 2.34)	72.86 (± 2.13)	64.98 (± 2.23)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The response and change from baseline in response during last two weeks of treatment (week 15 and 16) were analysed using an analysis of covariance (ANCOVA) model with treatment, pre-trial insulin treatment and SGLT2i use as fixed factors, and baseline response as covariate. Missing endpoint values were imputed using multiple imputation based on own treatment arm with baseline response as a	

covariate. Each imputed dataset was analysed separately and estimates were combined using Rubin's rules.

Comparison groups	Insulin 287 (without loading dose) v Insulin Glargine U100
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7542
Method	ANCOVA
Parameter estimate	Estimated mean treatment difference
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.33
upper limit	7.35

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The response and change from baseline in response during last two weeks of treatment (week 15 and 16) were analysed using an analysis of covariance (ANCOVA) model with treatment, pre-trial insulin treatment and SGLT2i use as fixed factors, and baseline response as covariate. Missing endpoint values were imputed using multiple imputation based on own treatment arm with baseline response as a covariate. Each imputed dataset was analysed separately and estimates were combined using Rubin's rules.

Comparison groups	Insulin 287 (with 100% loading dose) v Insulin Glargine U100
Number of subjects included in analysis	103
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0107
Method	ANCOVA
Parameter estimate	Estimated mean treatment difference
Point estimate	7.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.83
upper limit	13.93

Secondary: Change in HbA1c

End point title	Change in HbA1c

End point description:

Estimated mean change from baseline (week 0, Visit 2) in glycosylated haemoglobin (HbA1c) at week 16 (Visit 18) is presented. The endpoint was evaluated based on the data from the on-treatment without rescue medication observation period, which was the time period when a subject was on treatment with trial product, excluding any period after initiation of a non-randomised insulin treatment (rescue medication). FAS included all randomised subjects.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 16 (V18)

End point values	Insulin 287 (without loading dose)	Insulin 287 (with 100% loading dose)	Insulin Glargine U100	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	54	50	
Units: Percentage point of HbA1c				
least squares mean (standard error)	-0.47 (± 0.09)	-0.77 (± 0.09)	-0.54 (± 0.09)	

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:

Estimated mean change from baseline week 0 (visit 2) in FPG at week 16 (Visit 18) is presented. The endpoint was evaluated based on the data from the on-treatment without rescue medication observation period, which was the time period when a subject was on treatment with trial product, excluding any period after initiation of a non-randomised insulin treatment (rescue medication). FAS 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 week 0 (V2) to week 16 (V18)

End point values	Insulin 287 (without loading dose)	Insulin 287 (with 100% loading dose)	Insulin Glargine U100	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	52	49	
Units: Millimoles per liter (mmol/L)				
least squares mean (standard deviation)	-0.83 (± 0.23)	-0.69 (± 0.22)	-0.57 (± 0.23)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight

End point title	Change in body weight

End point description:

Estimated mean change from baseline (week 0) in body weight at week 16 is presented. The endpoint was evaluated based on the data from the on-treatment without rescue medication observation period, which was the time period when a subject was on treatment with trial product, excluding any period

after initiation of a non-randomised insulin treatment (rescue medication). FAS included all randomised subjects.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 16 (V18)

End point values	Insulin 287 (without loading dose)	Insulin 287 (with 100% loading dose)	Insulin Glargine U100	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	54	50	
Units: Kilogram (Kg)				
least squares mean (standard error)	1.32 (± 0.36)	0.61 (± 0.34)	0.10 (± 0.34)	

Statistical analyses

No statistical analyses for this end point

Secondary: Weekly insulin dose

End point title	Weekly insulin dose

End point description:

Estimated mean average weekly insulin dose during the last 2 weeks of treatment is presented. The endpoint was evaluated based on the data from the on-treatment without rescue medication observation period, which was the time period when a subject was on treatment with trial product, excluding any period after initiation of a non-randomised insulin treatment (rescue medication). FAS included all randomised subjects.

End point type	Secondary

End point timeframe:

During the last 2 weeks of treatment (week 15 and 16)

End point values	Insulin 287 (without loading dose)	Insulin 287 (with 100% loading dose)	Insulin Glargine U100	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	54	50	
Units: Units of insulin (U)				
least squares mean (confidence interval 95%)	242.31 (205.49 to 285.74)	191.03 (163.06 to 223.81)	195.91 (166.19 to 230.94)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment emergent adverse events (TEAEs)

End point title	Number of treatment emergent adverse events (TEAEs)

End point description:

An adverse event(AE) is any untoward medical occurrence in a clinical trial subject administered or using a medicinal product, whether or not considered related to the medicinal product or usage. A TEAE was defined as an event that had onset date (or increase in severity) during the on-treatment observation period. The on-treatment observation period was the time period from first dose of trial product until the follow-up visit or the last date on trial product + 5 weeks for once daily insulin and +6 weeks for once weekly insulin. Safety analysis set (SAS) included all subjects exposed to at least one dose of trial product.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 21 (V20)

End point values	Insulin 287 (without loading dose)	Insulin 287 (with 100% loading dose)	Insulin Glargine U100	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	54	50	
Units: Count of events	77	85	76	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of severe hypoglycaemic episodes (level 3)

End point title	Number of severe hypoglycaemic episodes (level 3)

End point description:

Severe hypoglycaemic episodes (level 3) were defined as episodes that were associated with severe cognitive impairment requiring external assistance for recovery. Number of severe hypoglycaemic episodes that occurred during weeks 0-16 are presented. Safety analysis set (SAS) included all subjects exposed to at least one dose of trial product.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 16 (V18)

End point values	Insulin 287 (without loading dose)	Insulin 287 (with 100% loading dose)	Insulin Glargine U100	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	54	50	
Units: Count of events	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of clinically significant hypoglycaemic episodes (level 2) (below 3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)

End point title	Number of clinically significant hypoglycaemic episodes (level 2) (below 3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3)

End point description:

Clinically significant hypoglycaemic episodes (level 2) were defined as episodes that were sufficiently low to indicate serious, clinically important hypoglycaemia with plasma glucose value of <3.0 mmol/L (54 mg/dL). Severe hypoglycaemic episodes (level 3) were defined as episodes that were associated with severe cognitive impairment requiring external assistance for recovery. Number of clinically significant hypoglycaemic episodes (level 2), confirmed by blood glucose (BG)meter or severe hypoglycaemic episodes (level 3) that occured during weeks 0-16 are presented. SAS included all subjects exposed to at least one dose of trial product.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 16 (V18)

End point values	Insulin 287 (without loading dose)	Insulin 287 (with 100% loading dose)	Insulin Glargine U100	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	54	50	
Units: Count of events	3	17	16	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hypoglycaemic alert episodes (level 1) (equal to or above 3.0 and below 3.9 mmol/L (equal to or above 54 and below 70 mg/dL), confirmed by BG meter)

End point title	Number of hypoglycaemic alert episodes (level 1) (equal to or above 3.0 and below 3.9 mmol/L (equal to or above 54 and below 70 mg/dL), confirmed by BG meter)

End point description:

Hypoglycaemia alert value (level 1) was defined as episodes that were sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy. Number of hypoglycaemic alert episodes (level 1) (equal to or above 3.0 and below 3.9 mmol/L (equal to or above 54 and below 70 mg/dL), confirmed by BG meter) that occured during weeks 0-16 are presented. SAS included all subjects exposed to at least one dose of trial product.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 16 (V18)

End point values	Insulin 287 (without loading dose)	Insulin 287 (with 100% loading dose)	Insulin Glargine U100	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	50	54	50	
Units: Count of events	79	78	71	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Weeks 0-21

Adverse event reporting additional description:

Results are based on the safety analysis set which included all participants exposed to at least one dose of trial product. All presented adverse events are TEAEs. TEAE was defined as an event that had onset date (or increase in severity) during the on-treatment observation period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Insulin 287 (without loading dose)

Reporting group description:

Subjects were to receive once weekly subcutaneous (s.c.) injection of insulin 287 for 16 weeks, using PDS290 prefilled pen-injector at a starting dose of 7 times the pre-trial basal insulin dose of the respective subjects ('unit to unit switch' approach: current daily dose x 7). subjects were to perform once daily pre-breakfast self-monitoring plasma glucose (SMPG). The dose was adjusted based on 3 pre-breakfast SMPG values measured on the 2 previous days and the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 millimoles per litre (mmol/L): dose reduced by 28 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 28 U. If the subject received a twice-daily regimen with any basal insulin analogue or a once-daily regimen with insulin glargine U300 prior to randomisation, the total daily insulin dose prior to randomisation was reduced by 20%.

Reporting group title	Insulin Glargine U100

Reporting group description:

Subjects were to receive once daily s.c. injection of insulin glargine U100 for 16 weeks, using SoloSTAR prefilled pen-injector at a starting dose same as the pre-trial basal insulin. subjects were to perform once daily pre-breakfast SMPG. The dose was adjusted based on 3 pre-breakfast SMPG values measured on the 2 previous days and the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 millimoles per litre (mmol/L): dose reduced by 4 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 4 U. If the subject received a twice-daily regimen with any basal insulin analogue or a once-daily regimen with insulin glargine U300 prior to randomisation, the total daily insulin dose prior to randomisation was reduced by 20%.

Reporting group title	Insulin 287 (with 100% loading dose)

Reporting group description:

Subjects were to receive once weekly s.c. injection of insulin 287 for 16 weeks, using PDS290 prefilled pen-injector at a starting dose of 7 times the pre-trial basal insulin dose of the respective subjects with additional loading dose (‘unit to unit switch with an additional 100% loading dose’ approach: current daily dose x 7 x 2). subjects were to perform once daily pre-breakfast SMPG. The dose was adjusted based on 3 pre-breakfast SMPG values measured on the 2 previous days and the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 millimoles per litre (mmol/L): dose reduced by 28 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 28 U. If the subject received a twice-daily regimen with any basal insulin analogue or a once-daily regimen with insulin glargine U300 prior to randomisation, the total daily insulin dose prior to randomisation was reduced by 20%

Serious adverse events	Insulin 287 (without loading dose)	Insulin Glargine U100	Insulin 287 (with 100% loading dose)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	2 / 54 (3.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Injury, poisoning and procedural complications			
Facial bones fracture			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
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			
Acute myocardial infarction			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	0 / 54 (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			
Muscle abscess			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	Insulin 287 (without loading dose)	Insulin Glargine U100	Insulin 287 (with 100% loading dose)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 50 (36.00%)	18 / 50 (36.00%)	20 / 54 (37.04%)
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 50 (6.00%)	1 / 50 (2.00%)	1 / 54 (1.85%)
occurrences (all)	3	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 50 (2.00%)	3 / 50 (6.00%)	3 / 54 (5.56%)
occurrences (all)	1	3	3
General disorders and administration site conditions			
Instillation site haemorrhage			
subjects affected / exposed	0 / 50 (0.00%)	4 / 50 (8.00%)	0 / 54 (0.00%)
occurrences (all)	0	7	0
Medical device site haemorrhage			
subjects affected / exposed	2 / 50 (4.00%)	1 / 50 (2.00%)	5 / 54 (9.26%)
occurrences (all)	2	3	7
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	2 / 50 (4.00%)	3 / 50 (6.00%)	2 / 54 (3.70%)
occurrences (all)	2	3	2
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 50 (0.00%)	4 / 50 (8.00%)	1 / 54 (1.85%)
occurrences (all)	0	4	1
Diarrhoea			
subjects affected / exposed	1 / 50 (2.00%)	3 / 50 (6.00%)	2 / 54 (3.70%)
occurrences (all)	1	4	2
Nausea			
subjects affected / exposed	1 / 50 (2.00%)	3 / 50 (6.00%)	0 / 54 (0.00%)
occurrences (all)	1	4	0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	3 / 50 (6.00%)	1 / 50 (2.00%)	1 / 54 (1.85%)
occurrences (all)	4	2	1
Infections and infestations			

Influenza			
subjects affected / exposed	3 / 50 (6.00%)	0 / 50 (0.00%)	1 / 54 (1.85%)
occurrences (all)	3	0	1
Nasopharyngitis			
subjects affected / exposed	7 / 50 (14.00%)	2 / 50 (4.00%)	8 / 54 (14.81%)
occurrences (all)	8	3	9
Upper respiratory tract infection			
subjects affected / exposed	1 / 50 (2.00%)	4 / 50 (8.00%)	2 / 54 (3.70%)
occurrences (all)	1	4	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 May 2019	The following changes were made as per this amendment: Revised inclusion criteria #6 including subjects on SGLT2i.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported