Clinical trial results:
An investigational trial comparing the efficacy and safety of once weekly NNC0148-0287 C (insulin 287) versus once daily insulin glargine, both in combination with metformin, with or without DPP-4 inhibitors, in insulin naïve subjects with type 2 diabetes mellitus

Summary

EudraCT number	2018-000322-63
Trial protocol	SI CZ SK GR
Global end of trial date	17 January 2020

Results information

Result version number	v1 (current)
This version publication date	29 January 2021
First version publication date	29 January 2021

Trial information

Trial identification

Sponsor protocol code	NN1436-4383

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03751657
WHO universal trial number (UTN)	U1111-1208-4124

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, +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	04 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 December 2019
Global end of trial reached?	Yes
Global end of trial date	17 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect on glycaemic control after 26 weeks treatment of once weekly insulin 287 versus once daily insulin glargine both in combination with metformin with or without dipeptidyl peptidase-4 inhibitors in insulin-naïve type 2 diabetes mellitus subjects inadequately treated with metformin with or without dipeptidyl peptidase-4 inhibitors.

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 (Nov 2016, current Step 4 version) and FDA 21 CFR 312.120.

Background therapy:

Subjects were to continue their pre-trial metformin alone or in combination with Dipeptidyl peptidase 4 inhibitors (DPP4i) throughout the trial.

Evidence for comparator:

Not applicable

Actual start date of recruitment	29 November 2018
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: 34
Country: Number of subjects enrolled	Czechia: 43
Country: Number of subjects enrolled	Greece: 36
Country: Number of subjects enrolled	Poland: 42
Country: Number of subjects enrolled	Slovakia: 38
Country: Number of subjects enrolled	Slovenia: 17
Country: Number of subjects enrolled	United States: 37
Worldwide total number of subjects	247
EEA total number of subjects	176

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	167
From 65 to 84 years	80
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 49 sites in Canada (7), Czech Republic (9), Greece (5), Poland (6), Slovakia (6),Slovenia (2) and United States (14). One site in the United States screened, but didn't randomise any subject.

Pre-assignment

Screening details:

Insulin-naïve subjects with T2D inadequately controlled on metformin with or without DPP4i were randomized in a 1:1 manner to receive once weekly insulin 287 and once daily placebo or once weekly placebo and once daily insulin glargine subcutaneously (s.c).

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:

Insulin 287 and Insulin glargine were visually identical in order to maintain the blinding. The trial products were packed blinded and each box was labelled with a unique dispensing unit number.

Arms

Are arms mutually exclusive?	Yes
Arm title	Insulin 287

Arm description:

Subjects were to receive once weekly s.c. injection of insulin 287 using PDS290 prefilled pen-injector and once daily placebo for 26 weeks.

Arm type	Experimental
Investigational medicinal product name	NNC0148-0287 C
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 using PDS290 prefilled pen-injector at a starting dose of 70 units (U) and once daily placebo for 26 weeks. The insulin dose was then adjusted once weekly to reach the glycaemic target of 3.9-6.0 millimoles per liter (mmol/L) based on 3 pre-breakfast self-measured plasma glucose (SMPG) values measured on 2 previous days and on the day of the titration. If at least one pre-breakfast SMPG value was: < 3.0 mmol/L- dose reduced by 28 U, and 3.0-3.8- dose reduced by 14 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was: 3.9-6.0 mmol/L- no adjustment; 6.1-7.0 mmol/L- dose increased by 14U, and >7.0 mmol/L- dose increased by 28U.

Arm title	Insulin glargine

Arm description:

Subjects were to receive once daily s.c injection of Insulin glargine using 10 ml vial and syringe and once weekly placebo for 26 weeks.

Arm type	Active comparator
Investigational medicinal product name	Insulin glargine
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 using 10 ml vial and syringe at a starting dose of 10 U and once weekly placebo for 26 weeks. The insulin dose was then adjusted to reach the glycaemic target of 3.9-6.0 mmol/L based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the titration. If at least one pre-breakfast SMPG value was: < 3.0 mmol/L- dose reduced by 4 U, and 3.0-3.8 dose reduced by 2 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was: 3.9-6.0 mmol/L- no adjustment; 6.1-7.0 mmol/L- dose increased by 2 U, and >7.0 mmol/L- dose increased by 4 U.

Number of subjects in period 1	Insulin 287	Insulin glargine
Started	125	122
Completed	122	119
Not completed	3	3
Consent withdrawn by subject	1	1
Physician decision	-	1
Lost to follow-up	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Insulin 287
Reporting group description:	
Subjects were to receive once weekly s.c. injection of insulin 287 using PDS290 prefilled pen-injector and once daily placebo for 26 weeks.	
Reporting group title	Insulin glargine
Reporting group description:	
Subjects were to receive once daily s.c injection of Insulin glargine using 10 ml vial and syringe and once weekly placebo for 26 weeks.	

Reporting group values	Insulin 287	Insulin glargine	Total
Number of subjects	125	122	247
Age Categorical Units: Subjects			
Adults (18-64 years)	85	82	167
From 65-84 years	40	40	80
Age Continuous Units: years			
arithmetic mean	59.7	59.4	
standard deviation	± 8.2	± 9.5	-
Gender Categorical Units: Subjects			
Female	55	53	108
Male	70	69	139

End points

End points reporting groups

Reporting group title	Insulin 287
Reporting group description:	
Subjects were to receive once weekly s.c. injection of insulin 287 using PDS290 prefilled pen-injector and once daily placebo for 26 weeks.	
Reporting group title	Insulin glargine
Reporting group description:	
Subjects were to receive once daily s.c injection of Insulin glargine using 10 ml vial and syringe and once weekly placebo for 26 weeks.	

Primary: Change in glycated haemoglobin (HbA1c) (%-point)

End point title	Change in glycated haemoglobin (HbA1c) (%-point)
End point description:	
Change in HbA1c from baseline (week 0) to week 26 is presented. The endpoint was evaluated based on the data from on-treatment without ancillary treatment period, starting at the date of 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, or initiation of any diabetes treatment other than trial products and metformin +/- DPP4i, or increase of the dose of metformin or DPP4i. The Full analysis set (FAS) included all randomised participants. The number of subject analyzed is the number of subjects contributing to the analysis.	
End point type	Primary
End point timeframe:	
From baseline (week 0) to week 26	

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	120		
Units: Percentage point (%-point) of HbA1c				
least squares mean (standard error)				
%-point	-1.33 (± 0.07)	-1.15 (± 0.07)		

Statistical analyses

Statistical analysis title	Insulin 287 vs Insulin glargine
Statistical analysis description:	
The change from baseline in response after 26 weeks is analysed using a linear mixed model for repeated measures (MMRM) with an unstructured covariance matrix and treatment, region, use of DPP-4 inhibitor and visit as fixed factors, and baseline response as covariate. Furthermore, the model includes the interaction between visit and all explanatory variables.	
Comparison groups	Insulin 287 v Insulin glargine

Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0818
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.02

Primary: Change in glycated haemoglobin (HbA1c) (mmol/mol)

End point title	Change in glycated haemoglobin (HbA1c) (mmol/mol)

End point description:

Change in HbA1c from baseline (week 0) to 26 weeks of treatment is presented. The endpoint was evaluated based on the data from on-treatment without ancillary treatment period, started at the date of first dose of trial product until the last dose of trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin, or initiation of any diabetes treatment other than trial products and metformin +/-DPP4i, or increased the dose of metformin or DPP4i, or the end of the treatment if no ancillary treatment was initiated. The FAS included all randomised participants. The number of subject analyzed is the number of subjects contributing to the analysis.

End point type	Primary

End point timeframe:

From baseline (week 0) to week 26

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	120		
Units: millimoles per mole (mmol/mol)				
least squares mean (standard error)	-14.51 (± 0.79)	-12.54 (± 0.80)		

Statistical analyses

Statistical analysis title	Insulin 287 vs Insulin glargine

Statistical analysis description:

The change from baseline in response after 26 weeks is analysed using a linear mixed model for repeated measures (MMRM) with an unstructured covariance matrix and treatment, region, use of DPP-4 inhibitor and visit as fixed factors, and baseline response as covariate. Furthermore, the model includes the interaction between visit and all explanatory variables.

Comparison groups	Insulin 287 v Insulin glargine

Number of subjects included in analysis	242
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0818
Method	Mixed models analysis
Parameter estimate	Treatment difference
Point estimate	-1.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.19
upper limit	0.25

Secondary: Change in fasting plasma glucose (mmol/l)

End point title	Change in fasting plasma glucose (mmol/l)

End point description:

Change in fasting plasma glucose (PG) from baseline (week 0) to week 26 is presented. The endpoint was evaluated based on the data from on-treatment without ancillary treatment period, starting at the date of 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, or initiation of any diabetes treatment other than trial products and metformin +/- DPP4i, or increase of the dose of metformin or DPP4i. The FAS included all randomised participants. The number of subject analyzed is the number of subjects contributing to the analysis.

End point type	Secondary

End point timeframe:

From baseline (week 0) to week 26

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	121	116		
Units: Millimoles per liter (mmol/l)				
least squares mean (standard error)	-3.20 (± 0.16)	-2.99 (± 0.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Nine (9)-point profile (individual self-measured plasma glucose (SMPG) values) (mmol/l)

End point title	Nine (9)-point profile (individual self-measured plasma glucose (SMPG) values) (mmol/l)

End point description:

Subjects measured their plasma glucose (PG) using blood glucose meters (as plasma equivalent values of capillary whole blood glucose) at 9 time points represented in the table. 9-point SMPG profile after 26 weeks is presented. Results are based on the data from on-treatment without ancillary treatment period, starting at the date of 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, or initiation of any

diabetes treatment other than trial products and metformin +/- DPP4i, increase of the dose of metformin or DPP4i.The FAS included all randomised participants. The 'n' refers to the number of subjects contributing to the analysis for specific time point of the 9-point profile.

End point type	Secondary

End point timeframe:

At week 26

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	122		
Units: mmol/l				
least squares mean (standard error)				
Before breakfast (n = 109,108)	5.70 (± 0.19)	6.19 (± 0.19)		
90 minutes after start of breakfast (n = 103, 107)	7.90 (± 0.19)	8.51 (± 0.19)		
Before lunch (n = 109, 106)	6.09 (± 0.19)	6.19 (± 0.19)		
90 minutes after start of lunch (n = 107, 106)	7.83 (± 0.19)	8.50 (± 0.19)		
Before main evening meal (n = 108, 107)	6.55 (± 0.19)	6.96 (± 0.19)		
90min after start of main evening meal(n=106,104)	8.01 (± 0.19)	8.47 (± 0.19)		
Before bedtime (n = 104, 105)	7.35 (± 0.19)	7.87 (± 0.19)		
At 4:00 a.m. (n = 101, 102)	5.72 (± 0.19)	5.98 (± 0.19)		
Before breakfast the following day (n = 109, 108)	5.74 (± 0.19)	6.05 (± 0.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in mean of the 9-point profile, defined as the area under the profile divided by measurement time (mmol/l)

End point title	Change in mean of the 9-point profile, defined as the area under the profile divided by measurement time (mmol/l)

End point description:

Subjects measured their PG levels using blood glucose meters at 9 time points. Change from baseline (week 0) to week 26 is presented. Mean of the 9-point profile was defined as the area under the profile divided by measurement time. The endpoint was evaluated based on the data from on-treatment without ancillary treatment period, starting at the date of 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, or initiation of any diabetes treatment other than trial products and metformin +/- DPP4i, or increase of the dose of metformin or DPP4i.The FAS included all randomised participants. The number of subject analyzed is the number of subjects contributing to the analysis.

End point type	Secondary

End point timeframe:

From baseline (week 0) to week 26

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	111		
Units: mmol/l				
least squares mean (standard error)	-2.70 (± 0.12)	-2.26 (± 0.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Fluctuations of the 9-point profile (defined as the integrated absolute distance from the mean profile value divided by measurement time) (mmol/l)

End point title	Fluctuations of the 9-point profile (defined as the integrated absolute distance from the mean profile value divided by measurement time) (mmol/l)

End point description:

Subjects measured their PG levels using blood glucose meters at 9 time points. Presented fluctuation in 9-point SMPG profile is the integrated absolute distance from the mean profile value divided by measurement time. Results are based on the data from on-treatment without ancillary treatment period, starting at the date of 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, or initiation of any diabetes treatment other than trial products and metformin +/-DPP4i, or increase of the dose of metformin or DPP4i.The FAS included all randomised participants. The number of subject analyzed is the number of subjects contributing to the analysis.

End point type	Secondary

End point timeframe:

At week 26

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	111		
Units: mmol/l				
least squares mean (confidence interval 95%)	0.92 (0.84 to 1.01)	0.94 (0.86 to 1.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting C-peptide

End point title	Change in fasting C-peptide

End point description:

Fasting C-peptide at week 26 is presented (absolute value). The endpoint was evaluated based on the data from on-treatment without ancillary treatment period, starting at the date of 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, or initiation of any diabetes treatment other than trial products and metformin +/- DPP4i, or increase of the dose of metformin or DPP4i. The FAS included all randomised

participants. The number of subject analyzed is the number of subjects contributing to the analysis.

End point type	Secondary

End point timeframe:

From baseline (week 0) to week 26

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	115	112		
Units: Nanomoles per liter (nmol/l)				
least squares mean (confidence interval 95%)	0.44 (0.40 to 0.48)	0.47 (0.43 to 0.51)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight (kilogram)

End point title	Change in body weight (kilogram)

End point description:

Change in body weight from baseline (week 0) to week 26 is presented. The endpoint was evaluated based on the data from on-treatment without ancillary treatment period, starting at the date of 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, or initiation of any diabetes treatment other than trial products and metformin +/- DPP4i, or increase of the dose of metformin or DPP4i. The FAS included all randomised participants. The number of subject analyzed is the number of subjects contributing to the analysis.

End point type	Secondary

End point timeframe:

From baseline (week 0) to week 26

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	119		
Units: Kilogram				
least squares mean (standard error)	1.49 (± 0.36)	1.56 (± 0.37)		

Statistical analyses

No statistical analyses for this end point

Secondary: Weekly dose of insulin 287 and weekly dose of IGlar (U)

End point title	Weekly dose of insulin 287 and weekly dose of IGlar (U)

End point description:

Weekly dose of insulin 287 and weekly dose of glargine from week 24 visit to week 26 visit (at week 25 and week 26) are presented. The endpoint was evaluated based on the data from on-treatment without ancillary treatment period, starting at the date of 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, or initiation of any diabetes treatment other than trial products and metformin +/- DPP4i, or increase of the dose of metformin or DPP4i. The FAS included all randomised participants. The number of subject analyzed is the number of subjects contributing to the analysis.

End point type	Secondary

End point timeframe:

Week 24-26

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	117		
Units: Units of Insulin (U)				
least squares mean (confidence interval 95%)	229.06 (205.08 to 255.83)	284.05 (253.97 to 317.71)		

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 endpoint was evaluated based on the data from on-treatment period, starting at the date of first dose of trial product, and ending at follow-up visit, or the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin. The safety analysis set (SAS) included all subjects who received at least one dose of the investigational product or comparator.

End point type	Secondary

End point timeframe:

Baseline (week 0)-week 31

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	122		
Units: Number of events	229	158		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of hypoglycaemic alert episodes (level 1) (greater than or equal to 3.0 and less than 3.9 mmol/L (greater than or equal to 54 and less than70 mg/dL), confirmed by blood glucose (BG) meter)

End point title	Number of hypoglycaemic alert episodes (level 1) (greater than or equal to 3.0 and less than 3.9 mmol/L (greater than or equal to 54 and less than70 mg/dL), confirmed by blood glucose (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 with plasma glucose value of equal to or above (>=) 3.0 and less than (<) 3.9 mmol/L (>= 54 and < 70 mg/dL) confirmed by BG meter. Number of hypoglycaemic alert episodes (level 1) that occurred from week 0 to week 26 are presented. The SAS included all subjects who received at least one dose of the investigational product or comparator.

End point type	Secondary

End point timeframe:

Baseline (week 0)-week 26

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	122		
Units: Number of events	358	145		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of clinically significant hypoglycaemic episodes (level 2) (less than 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) (less than 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 less than (<) 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 BG meter or severe hypoglycaemic episodes (level 3) that occurred from week 0 to week 26 are presented. The SAS included all subjects who received at least one dose of the investigational product or comparator.

End point type	Secondary

End point timeframe:

Baseline (week 0)-week 26

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	122		
Units: Number of events	38	31		

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 from week 0 to week 26 are presented. The SAS included all subjects who received at least one dose of the investigational product or comparator.

End point type	Secondary

End point timeframe:

Baseline (week 0)-week 26

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	122		
Units: Number of events	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in anti-insulin 287 antibodies level

End point title	Change in anti-insulin 287 antibodies level

End point description:

Change in anti-insulin 287 antibodies level is not assessed because change in anti-insulin 287 antibody titres is a more meaningful way of describing the change in antibody levels. The results for change in anti-insulin 287 antibody titres are reported as a separate endpoint.

End point type	Secondary

End point timeframe:

Baseline (week 0)-week 31

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[1]	0[2]		
Units: % bound over total insulin 287 (%B/T)				
number (not applicable)				

Notes:

[1] - Change in anti-insulin 287 antibody titres was measured to assess the change in antibody levels.

[2] - Change in anti-insulin 287 antibody titres was measured to assess the change in antibody levels.

Statistical analyses

No statistical analyses for this end point

Secondary: Change in anti-insulin 287 antibody titres

End point title	Change in anti-insulin 287 antibody titres[3]

End point description:

Samples from the insulin 287 arm of the study were analysed for anti-insulin 287 antibodies. Confirmed anti-insulin 287 antibody positive samples had an antibody titre value determined. The endpoint was evaluated based on the data from in-trial period, starting at randomisation, and ending at the last direct participant-site contact, or when participant withdrew their informed consent, or the last participant-investigator contact for participants lost to follow-up, or death. The SAS included all subjects who received at least one dose of the investigational product or comparator.

End point type	Secondary

End point timeframe:

Baseline (week 0)-week 31

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is applicable only for Insulin 287 reporting group

End point values	Insulin 287			
Subject group type	Reporting group			
Number of subjects analysed	119			
Units: No Unit				
arithmetic mean (standard deviation)	979.9 (± 3177.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in cross-reactive anti-human insulin antibody status (positive/negative)

End point title	Change in cross-reactive anti-human insulin antibody status (positive/negative)

End point description:

Anti-insulin 287 or glargine antibodies were classified as negative if % B/T was below a certain cut point. Samples positive for anti-insulin 287 or glargine antibodies were further tested for cross-reactivity to endogenous insulin. Samples not further tested are categorised as not applicable (NA). Unknown refers to samples with insufficient volume to perform analysis. The endpoint was evaluated based on the data from in-trial period, starting at randomisation, and ending at the last direct subject-site contact, or when subject withdrew their informed consent, or the last subject-investigator contact for subjects lost

to follow-up, or death. The SAS included all subjects who received at least one dose of the investigational product or comparator. The 'n' refers to number of subjects with sample available.

End point type	Secondary

End point timeframe:

Baseline (week 0)-week 31

End point values	Insulin 287	Insulin glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	122		
Units: Number of subjects				
number (not applicable)				
Week 0 - Negative (n=125,122)	0	1		
Week 0 - Positive (n=125,122)	0	0		
Week 0 - Unknown (n=125,122)	1	9		
Week 0 - Not applicable (n=125,122)	124	112		
Week 31- Negative (n=120,115)	9	0		
Week 31- Positive (n=120,115)	86	26		
Week 31- Unknown (n=120,115)	0	0		
Week 31- Not Applicable (n=120,115)	25	89		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 to Week 31

Results are based on the SAS which included all subjects who received at least one dose of Insulin 287 or Insulin glargine.

The SAS included all subjects who received at least one dose of the investigational product or comparator.

Adverse event reporting additional description:

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 1st dose of trial product (week 0) until follow-up visit (week 31) or last date on trial product +5 weeks for once daily insulin and +6 weeks for once weekly insulin.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22

Reporting groups

Reporting group title	Insulin 287

Reporting group description:

Subjects were to receive once weekly s.c. injection of insulin 287 using PDS290 prefilled pen-injector and once daily placebo for 26 weeks.

Reporting group title	Insulin glargine

Reporting group description:

Subjects were to receive once daily s.c injection of Insulin glargine using 10 ml vial and syringe and once weekly placebo for 26 weeks.

Serious adverse events	Insulin 287	Insulin glargine	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 125 (1.60%)	3 / 122 (2.46%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Coronary artery disease			

subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral disorder			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Melaena			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatosplenomegaly			

subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Azotaemia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Emphysematous pyelonephritis			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypomagnesaemia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Insulin 287	Insulin glargine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 125 (20.80%)	16 / 122 (13.11%)	
Nervous system disorders			
Headache			

subjects affected / exposed	14 / 125 (11.20%)	3 / 122 (2.46%)	
occurrences (all)	31	3	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 125 (8.00%)	8 / 122 (6.56%)	
occurrences (all)	12	9	
Upper respiratory tract infection			
subjects affected / exposed	7 / 125 (5.60%)	6 / 122 (4.92%)	
occurrences (all)	7	8	

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32960514