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 insulin-naïve subjects with type 2 diabetes mellitus

Summary

EudraCT number	2018-003406-11
Trial protocol	DE SK PL HU ES HR
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	NN1436-4465

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03951805
WHO universal trial number (UTN)	U1111-1219-5474

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	10 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 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:

The main objective of the trial was to compare the effect on glycaemic control of once weekly insulin 287 using 3 different titration algorithms, versus once daily insulin glargine U100, both in combination with metformin ± dipeptidyl peptidase 4 inhibitor (DPP4i) ± sodium-glucose cotransporter 2 inhibitor (SGLT2i) in insulin-naïve type 2 diabetes mellitus (T2DM) subjects.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (64th World Medical Association (WMA) general assembly; October 2013), International Council for Harmonisation (ICH) Good Clinical Practice, including archiving of essential documents, (09 November 2016) and 21 United States Code of Federal Regulations (CFR) 312.120 (Foreign Clinical Studies not Conducted Under an investigational new drug (IND), 2015).

Background therapy:

Subjects were to receive metformin with or without dipeptidyl peptidase-4 inhibitors (DPP4i) and with or without sodium-glucose cotransporter 2 inhibitors (SGLT2i) in accordance with standard of care or local label in the individual country. Doses were to be maintained 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	Croatia: 29
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Poland: 33
Country: Number of subjects enrolled	Slovakia: 27
Country: Number of subjects enrolled	Spain: 29
Country: Number of subjects enrolled	United States: 31
Worldwide total number of subjects	205
EEA total number of subjects	174

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)	129
From 65 to 84 years	76
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 38 sites in 7 countries as follows: Croatia (4), Germany (9), Hungary (3), Poland (4), Slovakia (5), Spain (4), United States (9). In addition, 1 site in Slovakia and 3 sites in the United States screened, but didn’t randomise any subjects.

Pre-assignment

Screening details:

Subjects were randomised to receive once weekly insulin 287 using one of 3 different titration algorithms (A, B, C), or once daily insulin glargine (titration algorithm D).

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 (Titration algorithm A)

Arm 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 70 units (U). The dose was adjusted weekly during the treatment period using titration algorithm A with American Diabetes Association (ADA) glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast self-measured plasma glucose (SMPG) values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 21 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 21 U. All subjects used metformin with or without DPP4i and with or without 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.

Arm type	Experimental
Investigational medicinal product name	NNC0148-0287 formulation 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 for 16 weeks, using PDS290 prefilled pen-injector at a starting dose of 70 U. The dose was adjusted weekly during the treatment period using titration algorithm A with ADA glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 21 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 21 U.

Arm title	Insulin 287 (Titration algorithm B)

Arm 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 70 U. The dose was adjusted weekly during the treatment period using titration algorithm B with ADA glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 28 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 28 U. All subjects used metformin with or without DPP4i and with or without 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.

Arm type	Experimental

Investigational medicinal product name	NNC0148-0287 formulation 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 for 16 weeks, using PDS290 prefilled pen-injector at a starting dose of 70 U. The dose was adjusted weekly during the treatment period using titration algorithm B with ADA glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 28 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 28 U.

Arm title	Insulin 287 (Titration algorithm C)

Arm 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 70 U. The dose was adjusted weekly during the treatment period using titration algorithm C with glycaemic target of 3.9-6.0 mmol/L (70-108 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 3.9 mmol/L: insulin dose reduced by 28 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 3.9-6.0 mmol/L: no adjustment; > 6.0 mmol/L: insulin dose increased by 28 U. All subjects used metformin with or without DPP4i and with or without 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.

Arm type	Experimental
Investigational medicinal product name	NNC0148-0287 formulation 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 for 16 weeks, using PDS290 prefilled pen-injector at a starting dose of 70 U. The dose was adjusted weekly during the treatment period using titration algorithm C with glycaemic target of 3.9-6.0 mmol/L (70-108 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 3.9 mmol/L: insulin dose reduced by 28 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 3.9-6.0 mmol/L: no adjustment; > 6.0 mmol/L: insulin dose increased by 28 U.

Arm title	Insulin glargine (Titration algorithm D)

Arm description:

Subjects were to receive once daily s.c. injection of Insulin glargine for 16 weeks, using SoloSTAR pre-filled pen-injector at a starting dose of 10 U. The dose was adjusted weekly during the treatment period using titration algorithm D with ADA glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 4 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 4 U. All subjects used metformin with or without DPP4i and with or without 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.

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 for 16 weeks, using SoloSTAR pre-filled pen-injector at a starting dose of 10 U. The dose was adjusted weekly during the treatment period using titration algorithm D with ADA glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one

pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 4 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 4 U.

Number of subjects in period 1	Insulin 287 (Titration algorithm A)	Insulin 287 (Titration algorithm B)	Insulin 287 (Titration algorithm C)
Started	51	51	52
Completed	50	51	52
Not completed	1	0	0
Adverse event, non-fatal	1	-	-

Number of subjects in period 1	Insulin glargine (Titration algorithm D)
Started	51
Completed	51
Not completed	0
Adverse event, non-fatal	-

Baseline characteristics

Reporting groups

Reporting group title	Insulin 287 (Titration algorithm A)

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 70 units (U). The dose was adjusted weekly during the treatment period using titration algorithm A with American Diabetes Association (ADA) glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast self-measured plasma glucose (SMPG) values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 21 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 21 U. All subjects used metformin with or without DPP4i and with or without 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.

Reporting group title	Insulin 287 (Titration algorithm B)

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 70 U. The dose was adjusted weekly during the treatment period using titration algorithm B with ADA glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 28 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 28 U. All subjects used metformin with or without DPP4i and with or without 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.

Reporting group title	Insulin 287 (Titration algorithm C)

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 70 U. The dose was adjusted weekly during the treatment period using titration algorithm C with glycaemic target of 3.9-6.0 mmol/L (70-108 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 3.9 mmol/L: insulin dose reduced by 28 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 3.9-6.0 mmol/L: no adjustment; > 6.0 mmol/L: insulin dose increased by 28 U. All subjects used metformin with or without DPP4i and with or without 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.

Reporting group title	Insulin glargine (Titration algorithm D)

Reporting group description:

Subjects were to receive once daily s.c. injection of Insulin glargine for 16 weeks, using SoloSTAR pre-filled pen-injector at a starting dose of 10 U. The dose was adjusted weekly during the treatment period using titration algorithm D with ADA glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 4 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 4 U. All subjects used metformin with or without DPP4i and with or without 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.

Reporting group values	Insulin 287 (Titration algorithm A)	Insulin 287 (Titration algorithm B)	Insulin 287 (Titration algorithm C)
Number of subjects	51	51	52
Age Categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	59.8	61.2	61.4
standard deviation	± 9.1	± 8.0	± 8.0
Gender Categorical Units: Subjects			
Female	24	23	24
Male	27	28	28

Reporting group values	Insulin glargine (Titration algorithm D)	Total	
Number of subjects	51	205	
Age Categorical Units: Subjects			

Age Continuous Units: years			
arithmetic mean	60.2		
standard deviation	± 8.1	-	
Gender Categorical Units: Subjects			
Female	24	95	
Male	27	110	

End points

End points reporting groups

Reporting group title	Insulin 287 (Titration algorithm A)

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 70 units (U). The dose was adjusted weekly during the treatment period using titration algorithm A with American Diabetes Association (ADA) glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast self-measured plasma glucose (SMPG) values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 21 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 21 U. All subjects used metformin with or without DPP4i and with or without 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.

Reporting group title	Insulin 287 (Titration algorithm B)

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 70 U. The dose was adjusted weekly during the treatment period using titration algorithm B with ADA glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 28 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 28 U. All subjects used metformin with or without DPP4i and with or without 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.

Reporting group title	Insulin 287 (Titration algorithm C)

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 70 U. The dose was adjusted weekly during the treatment period using titration algorithm C with glycaemic target of 3.9-6.0 mmol/L (70-108 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 3.9 mmol/L: insulin dose reduced by 28 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 3.9-6.0 mmol/L: no adjustment; > 6.0 mmol/L: insulin dose increased by 28 U. All subjects used metformin with or without DPP4i and with or without 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.

Reporting group title	Insulin glargine (Titration algorithm D)

Reporting group description:

Subjects were to receive once daily s.c. injection of Insulin glargine for 16 weeks, using SoloSTAR pre-filled pen-injector at a starting dose of 10 U. The dose was adjusted weekly during the treatment period using titration algorithm D with ADA glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 4 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 4 U. All subjects used metformin with or without DPP4i and with or without 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.

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:

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 considered exposed to trial product, excluding any period after initiation of a non-randomised

insulin treatment (rescue medication). The endpoint is based on data recorded by CGM system. It was required that at least 70% of the planned CGM measurements during weeks 15-16 were available for endpoint data to be included in the analysis. FAS included all randomised subjects. 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 (Titration algorithm A)	Insulin 287 (Titration algorithm B)	Insulin 287 (Titration algorithm C)	Insulin glargine (Titration algorithm D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	51	50
Units: Percentage of time				
least squares mean (standard error)	76.65 (± 1.81)	82.97 (± 1.80)	80.89 (± 1.81)	75.89 (± 1.82)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

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

Comparison groups	Insulin 287 (Titration algorithm A) v Insulin glargine (Titration algorithm D)
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7675
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.28
upper limit	5.8

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

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

Comparison groups	Insulin 287 (Titration algorithm B) v Insulin glargine (Titration

	algorithm D)
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0051
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	7.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.12
upper limit	12.04

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

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

Comparison groups	Insulin 287 (Titration algorithm C) v Insulin glargine (Titration algorithm D)
Number of subjects included in analysis	101
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0519
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	5.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	10.05

Secondary: Change in HbA1c

End point title	Change in HbA1c

End point description:

Estimated mean change in HbA1c (glycated haemoglobin) from baseline (week 0, visit 2) to end of treatment (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 considered exposed to 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 (Titration algorithm A)	Insulin 287 (Titration algorithm B)	Insulin 287 (Titration algorithm C)	Insulin glargine (Titration algorithm D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	52	51
Units: Percentage point of HbA1c				
least squares mean (standard error)	-1.00 (± 0.08)	-1.22 (± 0.08)	-1.38 (± 0.08)	-1.02 (± 0.08)

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 in FPG from baseline (week 0, visit 2) to end of treatment (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 considered exposed to 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 (Titration algorithm A)	Insulin 287 (Titration algorithm B)	Insulin 287 (Titration algorithm C)	Insulin glargine (Titration algorithm D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	50	51	49
Units: Millimoles per liter (mmol/L)				
least squares mean (standard error)	-2.23 (± 0.17)	-2.42 (± 0.17)	-3.01 (± 0.17)	-2.34 (± 0.17)

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 in body weight from baseline (week 0, visit 2) to end of treatment (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 considered

exposed to 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 (Titration algorithm A)	Insulin 287 (Titration algorithm B)	Insulin 287 (Titration algorithm C)	Insulin glargine (Titration algorithm D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	52	51
Units: Kilogram (Kg)				
least squares mean (standard error)	0.87 (± 0.35)	1.11 (± 0.35)	1.25 (± 0.35)	0.63 (± 0.35)

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 considered exposed to 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 (Titration algorithm A)	Insulin 287 (Titration algorithm B)	Insulin 287 (Titration algorithm C)	Insulin glargine (Titration algorithm D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	52	51
Units: Units of insulin				
least squares mean (confidence interval 95%)	142.47 (119.78 to 169.45)	176.38 (148.30 to 209.78)	208.90 (175.94 to 248.04)	145.56 (122.38 to 173.12)

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:

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 (Titration algorithm A)	Insulin 287 (Titration algorithm B)	Insulin 287 (Titration algorithm C)	Insulin glargine (Titration algorithm D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	52	51
Units: Count of events	44	67	58	45

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 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 (Titration algorithm A)	Insulin 287 (Titration algorithm B)	Insulin 287 (Titration algorithm C)	Insulin glargine (Titration algorithm D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	52	51
Units: Count of events	0	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 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 blood glucose (BG) meter or severe hypoglycaemic episodes (level 3) that occured from week 0 to week 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 (Titration algorithm A)	Insulin 287 (Titration algorithm B)	Insulin 287 (Titration algorithm C)	Insulin glargine (Titration algorithm D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	52	51
Units: Count of events	1	2	8	0

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 with plasma glucose value of equal to or above (>=) 3.0 and < 3.9 mmol/L (>= 54 and < 70 mg/dL) confirmed by BG meter. Number of hypoglycaemic alert episodes (level 1) that occured from week 0 to week 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 (Titration algorithm A)	Insulin 287 (Titration algorithm B)	Insulin 287 (Titration algorithm C)	Insulin glargine (Titration algorithm D)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	51	51	52	51
Units: Count of events	14	20	110	10

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Weeks 0-21
Results are based on the safety analysis set which included all subjects exposed to at least one dose of trial product. All presented adverse events are treatment emergent adverse events (TEAEs).

Adverse event reporting additional description:

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.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Insulin 287 (Titration algorithm A)

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 70 U. The dose was adjusted weekly during the treatment period using titration algorithm A with ADA glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 21 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 21 U. All subjects used metformin with or without DPP4i and with or without 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.

Reporting group title	Insulin 287 (Titration algorithm B)

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 70 U. The dose was adjusted weekly during the treatment period using titration algorithm B with ADA glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 28 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 28 U. All subjects used metformin with or without DPP4i and with or without 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.

Reporting group title	Insulin 287 (Titration algorithm C)

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 70 U. The dose was adjusted weekly during the treatment period using titration algorithm C with glycaemic target of 3.9-6.0 mmol/L (70-108 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 3.9 mmol/L: insulin dose reduced by 28 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 3.9-6.0 mmol/L: no adjustment; > 6.0 mmol/L: insulin dose increased by 28 U. All subjects used metformin with or without DPP4i and with or without 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.

Reporting group title	Insulin glargine (Titration algorithm D)

Reporting group description:

Subjects were to receive once daily s.c. injection of Insulin glargine for 16 weeks, using SoloSTAR pre-filled pen-injector at a starting dose of 10 U. The dose was adjusted weekly during the treatment period using titration algorithm D with ADA glycaemic target of 4.4-7.2 mmol/L (80-130 mg/dL), based on 3 pre-breakfast SMPG values measured on 2 previous days and on the day of the contact. If at least one pre-breakfast SMPG value was: < 4.4 mmol/L: insulin dose reduced by 4 U. Otherwise, the dose adjustment was based on the mean of SMPG values. If the mean was between 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: insulin dose increased by 4 U. All subjects used metformin with or without DPP4i and with or without SGLT2i at the stable, pre-trial dose and at the same frequency during the

Serious adverse events	Insulin 287 (Titration algorithm A)	Insulin 287 (Titration algorithm B)	Insulin 287 (Titration algorithm C)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 51 (5.88%)	1 / 51 (1.96%)	0 / 52 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Choroid neoplasm			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	0 / 52 (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
Metastasis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	0 / 52 (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
Transitional cell carcinoma			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	0 / 52 (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
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (0.00%)	0 / 52 (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			
Knee arthroplasty			
subjects affected / exposed	0 / 51 (0.00%)	0 / 51 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Erysipelas			

subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	0 / 52 (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
Pneumonia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 51 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Insulin glargine (Titration algorithm D)		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 51 (3.92%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Choroid neoplasm			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metastasis			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Transitional cell carcinoma			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Knee arthroplasty			

subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 51 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 51 (1.96%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Insulin 287 (Titration algorithm A)	Insulin 287 (Titration algorithm B)	Insulin 287 (Titration algorithm C)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 51 (17.65%)	10 / 51 (19.61%)	7 / 52 (13.46%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 51 (0.00%)	3 / 51 (5.88%)	5 / 52 (9.62%)
occurrences (all)	0	3	7
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	5 / 51 (9.80%)	2 / 51 (3.92%)	1 / 52 (1.92%)
occurrences (all)	5	3	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 51 (9.80%)	7 / 51 (13.73%)	2 / 52 (3.85%)
occurrences (all)	7	7	2

Non-serious adverse events	Insulin glargine (Titration algorithm D)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 51 (17.65%)		

Nervous system disorders Headache subjects affected / exposed occurrences (all)	 2 / 51 (3.92%) 3		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	 1 / 51 (1.96%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	 6 / 51 (11.76%) 6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2019	The following changes were made as per this amendment: • Addition of the wording 'with or without SGLT2i inhibitors' in title page • Inclusion criteria updated to allow subjects on SGLT2 inhibitors in addition to metformin ± DPP4i inhibitors, to be included in the trial • In connection to mentioning of background medication (metformin and DPP4i) SGLT2i was added in synopsis and statistical considerations • Addition of stratification of subjects based on whether or not they are entering the trial on SGLT2i or not in trial design and statistical consideration

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported