Clinical trial results:
A 26-week trial comparing the effect and safety of once weekly Insulin Icodec and once daily Insulin Glargine 100 units/mL, both in combination with bolus Insulin with or without non-insulin anti-diabetic drugs, in subjects with Type 2 Diabetes on a basal-bolus regimen (ONWARDS 4)

Summary

EudraCT number	2020-000474-16
Trial protocol	NL BE IT
Global end of trial date	16 June 2022

Results information

Result version number	v1 (current)
This version publication date	02 July 2023
First version publication date	02 July 2023

Trial information

Trial identification

Sponsor protocol code	NN1436-4480

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04880850
WHO universal trial number (UTN)	U1111-1247-5269
Other trial identifiers	Japanese registration number: jRCT2031210076

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Novo Nordisk A/S, Clinical Reporting Office (2834), clinicaltrials@novonordisk.com
Scientific contact	Novo Nordisk A/S, Clinical Reporting Office (2834), 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	22 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 June 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the effect on glycaemic control of once weekly insulin icodec in combination with insulin aspart, with or without non-insulin anti-diabetic drugs, in subjects with type 2 diabetes (T2D) on a basalbolus regimen. This includes comparing the difference in change from baseline in glycosylated haemoglobin (HbA1c) between insulin icodec and insulin glargine after 26 weeks of treatment to a non-inferiority limit of 0.3%.

Protection of trial subjects:

The trial was conducted in accordance with the Declaration of Helsinki (64th World Medical Association (WMA) general Assembly; Oct 2013) and International Council for Harmonisation (ICH) Good Clinical Practice, including archiving of essential documents (Current Step 4 version, Nov 2016), and 21 Code of Federal Regulations (CFR) 312.120.

Background therapy:

After randomisation subjects continued their pre-trial non-insulin anti-diabetic background medication throughout the entire trial except from sulfonylureas and glinides, which had to be discontinued at randomisation. Insulin aspart should be administered with meals 2-4 times daily subcutaneously at a dose strength of 100 units/ milliliter (mL).

Evidence for comparator: -

Actual start date of recruitment	14 May 2021
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	Belgium: 18
Country: Number of subjects enrolled	India: 93
Country: Number of subjects enrolled	Italy: 40
Country: Number of subjects enrolled	Japan: 85
Country: Number of subjects enrolled	Mexico: 66
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Romania: 39
Country: Number of subjects enrolled	Russian Federation: 95
Country: Number of subjects enrolled	United States: 133
Worldwide total number of subjects	582
EEA total number of subjects	110

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)	373
From 65 to 84 years	209
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 83 sites in 9 countries as follows: Belgium (5), India (9), Italy (6), Japan (9), Mexico (3), Netherlands (5), Romania (6), Russia (10), United States (30).

Pre-assignment

Screening details:

The trial duration is approximately 33 weeks, consisting of a 2-week screening period, followed by a 26-week randomised treatment period and a 5-week follow-up period.

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 Icodec

Arm description:

Subjects were to receive once weekly subcutaneous (s.c.) injection of Insulin icodec for 26 weeks, using PDS290 prefilled pen-injector in combination with insulin aspart at a starting dose of 7 times the pre-trial total daily basal insulin dose + 50% of their 7 times total daily basal insulin dose. The following weekly dose was 7 times the total daily 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: lesser than (<) 4.4 millimoles per liter (mmol/L): dose reduced by 20 units (U); 4.4-7.2 mmol/L: no adjustment; greater than (>) 7.2 mmol/L: dose increased by 20 U. Dose titration of insulin aspart was based on the respective premeal(s) and bedtime SMPG measured.

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

Dosage and administration details:

Insulin aspart was administered with meals 2-4 times daily subcutaneously at a dose strength of 100 units/ milliliter (mL).

Investigational medicinal product name	insulin icodec 700 U/mL PDS290
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin icodec was administered once-weekly subcutaneously at a dose strength of 700 units/ milliliter (mL).

Arm title	Insulin Glargine

Arm description:

Subjects were to receive once daily s.c. injection of Insulin glargine for 26 weeks, using SoloSTAR pre-filled pen-injector in combination with insulin aspart. Subjects were to perform daily 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 mmol/L: dose reduced by 3 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 3 U. Dose titration of insulin aspart was based on the respective premeal(s) and bedtime SMPG measured.

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

Dosage and administration details:

Insulin aspart was administered with meals 2-4 times daily subcutaneously at a dose strength of 100 units/ milliliter (mL).

Investigational medicinal product name	Lantus
Investigational medicinal product code	
Other name	Lantus 100 units/mL
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin Glargine was administered once-daily subcutaneously at a dose strength of 100 units/ milliliter (mL).

Number of subjects in period 1	Insulin Icodec	Insulin Glargine
Started	291	291
Full analysis set (FAS)	291	291
Safety analysis set (SAS)	291	291
Completed	275	273
Not completed	16	18
Adverse event, serious fatal	2	1
Consent withdrawn by subject	9	10
Physician decision	2	1
Lost to follow-up	3	6

Baseline characteristics

Reporting groups

Reporting group title	Insulin Icodec

Reporting group description:

Subjects were to receive once weekly subcutaneous (s.c.) injection of Insulin icodec for 26 weeks, using PDS290 prefilled pen-injector in combination with insulin aspart at a starting dose of 7 times the pre-trial total daily basal insulin dose + 50% of their 7 times total daily basal insulin dose. The following weekly dose was 7 times the total daily 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: lesser than (<) 4.4 millimoles per liter (mmol/L): dose reduced by 20 units (U); 4.4-7.2 mmol/L: no adjustment; greater than (>) 7.2 mmol/L: dose increased by 20 U. Dose titration of insulin aspart was based on the respective premeal(s) and bedtime SMPG measured.

Reporting group title	Insulin Glargine

Reporting group description:

Subjects were to receive once daily s.c. injection of Insulin glargine for 26 weeks, using SoloSTAR pre-filled pen-injector in combination with insulin aspart. Subjects were to perform daily 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 mmol/L: dose reduced by 3 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 3 U. Dose titration of insulin aspart was based on the respective premeal(s) and bedtime SMPG measured.

Reporting group values	Insulin Icodec	Insulin Glargine	Total
Number of subjects	291	291	582
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	189	184	373
From 65-84 years	102	107	209
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	59.67	59.91	
standard deviation	± 10.13	± 9.92	-
Gender Categorical Units: Subjects			
Female	137	141	278
Male	154	150	304

End points

End points reporting groups

Reporting group title	Insulin Icodec

Reporting group description:

Subjects were to receive once weekly subcutaneous (s.c.) injection of Insulin icodec for 26 weeks, using PDS290 prefilled pen-injector in combination with insulin aspart at a starting dose of 7 times the pre-trial total daily basal insulin dose + 50% of their 7 times total daily basal insulin dose. The following weekly dose was 7 times the total daily 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: lesser than (<) 4.4 millimoles per liter (mmol/L): dose reduced by 20 units (U); 4.4-7.2 mmol/L: no adjustment; greater than (>) 7.2 mmol/L: dose increased by 20 U. Dose titration of insulin aspart was based on the respective premeal(s) and bedtime SMPG measured.

Reporting group title	Insulin Glargine

Reporting group description:

Subjects were to receive once daily s.c. injection of Insulin glargine for 26 weeks, using SoloSTAR pre-filled pen-injector in combination with insulin aspart. Subjects were to perform daily 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 mmol/L: dose reduced by 3 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 3 U. Dose titration of insulin aspart was based on the respective premeal(s) and bedtime SMPG measured.

Primary: Change in Glycated haemoglobin (HbA1c)

End point title	Change in Glycated haemoglobin (HbA1c)

End point description:

Change in HbA1c from baseline week 0 (V2) to week 26 (V28) is presented. The endpoint data was evaluated based on the in-trial observation period. In-trial observation period started at randomisation and ended at the date of: The last direct subject-site contact, withdrawal for subjects who withdrew their informed consent, the last subject-investigator contact as defined by the investigator for subjects who were lost to follow-up (i.e., possibly an unscheduled phone visit) and death for subjects who died before any of the above. Full analysis set (FAS) included all randomised subjects.

End point type	Primary

End point timeframe:

From baseline week 0 (V2) to week 26 (V28)

End point values	Insulin Icodec	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	291		
Units: Percentage (%) of HbA1c				
least squares mean (standard error)	-1.16 (± 0.05)	-1.18 (± 0.05)		

Statistical analyses

Statistical analysis title	Statistical Analysis Set 1

Statistical analysis description:

The response and change from baseline in response after 26 weeks were analysed using an analysis of

covariance (ANCOVA) model with treatment, region and personal continuous glucose monitoring (CGM) device use as fixed factors, and baseline response as covariate.

Comparison groups	Insulin Icodec v Insulin Glargine
Number of subjects included in analysis	582
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	0.15

Notes:

[1] - Non-inferiority of insulin icodec was considered confirmed if the upper limit of the two-sided 95% confidence interval (CI) for mean treatment difference (insulin icodec minus insulin glargine) was strictly below 0.3%.

Secondary: Change in fasting plasma glucose (FPG)

End point title	Change in fasting plasma glucose (FPG)

End point description:

Change in FPG from baseline week 0 (V2) to week 26 (V28) is presented. The endpoint data was evaluated based on the in-trial observation period. In-trial observation period started at randomisation and ended at the date of: The last direct subject-site contact, withdrawal for subjects who withdrew their informed consent, the last subject-investigator contact as defined by the investigator for subjects who were lost to follow-up (i.e., possibly an unscheduled phone visit) and death for subjects who died before any of the above. FAS included all randomised subjects. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 26 (V28)

End point values	Insulin Icodec	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	283	284		
Units: millimoles per liter (mmol/L)				
least squares mean (standard error)	-1.75 (± 0.16)	-1.61 (± 0.16)		

Statistical analyses

No statistical analyses for this end point

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

	severe hypoglycaemic episodes (level 3)

End point description:

Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) is presented. Clinically significant hypoglycaemia (level 2) is defined as plasma glucose value of < 3.0 mmol/L (54 mg/dL) confirmed by BG meter. Severe hypoglycaemia (level 3) is defined as hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. The endpoint data was evaluated based on on-treatment observation period. On-treatment period started at the date of first dose of trial product and ended at the first date of any of the following: The end of trial visit (V30), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin and the end-date for in-trial observation period. Safety analysis set included all subjects who were randomly assigned to trial treatment and who took at least 1 dose of trial product.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 31 (V30)

End point values	Insulin Icodec	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	291		
Units: Episodes				
number (not applicable)	944	938		

Statistical analyses

No statistical analyses for this end point

Secondary: Time spent below 3.0 mmol/L (54 mg/dL) using continuous glucose monitoring (CGM) system, Dexcom G6

End point title	Time spent below 3.0 mmol/L (54 mg/dL) using continuous glucose monitoring (CGM) system, Dexcom G6

End point description:

Percentage of time spent less than (<) 3.0 mmol/L (54 mg/dL) using CGM system from week 22 to week 26 is presented. The endpoint data was evaluated based on the in-trial observation period. In-trial observation period started at randomisation and ended at the date of: The last direct subject-site contact, withdrawal for subjects who withdrew their informed consent, the last subject-investigator contact as defined by the investigator for subjects who were lost to follow-up (i.e., possibly an unscheduled phone visit) and death for subjects who died before any of the above. Full analysis set included all randomised subjects. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From week 22 (V24) to week 26 (V28)

End point values	Insulin Icodec	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	237		
Units: Percentage (%) of time				
arithmetic mean (standard deviation)	0.73 (± 1.14)	0.61 (± 1.07)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by blood glucose (BG) meter)

End point title	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL) confirmed by blood glucose (BG) meter)

End point description:

Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 millimoles per liter [mmol/L] (54 mg/dL), confirmed by BG meter) is presented. Clinically significant hypoglycaemia (level 2) is defined as plasma glucose value of less than (<) 3.0 mmol/L (54 mg/dL) confirmed by BG meter. The endpoint data was evaluated based on on-treatment observation period. On-treatment period started at the date of first dose of trial product and ended at the first date of any of the following: End of trial visit (V30), Last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin (corresponding to 5 weeks after the end of dosing interval for both treatment arms) and the end-date for in-trial observation period. The on-treatment period represented the time period in which a subject was considered exposed to trial product. Safety analysis set included all subjects who were randomly assigned to trial treatment and who took at least 1 dose of trial product.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 31 (V30)

End point values	Insulin Icodec	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	291		
Units: Episodes				
number (not applicable)	937	935		

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:

Number of severe hypoglycaemic episodes (level 3) is presented. Severe hypoglycaemia (level 3) is defined as hypoglycaemia with severe cognitive impairment requiring external assistance for recovery. The endpoint data was evaluated based on the on-treatment observation period. The on-treatment

period started at the date of first dose of trial product as recorded on the electronic case report form (eCRF), and ended at the first date of any of the following: The end of trial visit (V30), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin (corresponding to 5 weeks after the end of the dosing interval for both treatment arms) and the end-date for the in-trial observation period. The on-treatment period represented the time period in which a subject was considered exposed to trial product. Safety analysis set included all subjects who were randomly assigned to trial treatment and who took at least 1 dose of trial product.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 31 (V30)

End point values	Insulin Icodec	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	291		
Units: Episodes				
number (not applicable)	7	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Time in target-range 3.9–10.0 mmol/L (70-180 mg/dL) using continuous glucose monitoring (CGM) system, Dexcom G6

End point title	Time in target-range 3.9–10.0 mmol/L (70-180 mg/dL) using continuous glucose monitoring (CGM) system, Dexcom G6

End point description:

Percentage of time in target-range 3.9–10.0 mmol/L (70-180 milligrams per deciliter [mg/dL]) using continuous glucose monitoring (CGM) system from week 22 to week 26 is presented. Time in target range is defined 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 data was evaluated based on the in-trial observation period. In-trial observation period started at randomisation and ended at the date of: The last direct subject-site contact, withdrawal for subjects who withdrew their informed consent, the last subject-investigator contact as defined by the investigator for subjects who were lost to follow-up (i.e., possibly an unscheduled phone visit) and death for subjects who died before any of the above. FAS included all randomised subjects. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From week 22 (V24) to week 26 (V28)

End point values	Insulin Icodec	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	237		
Units: Percentage (%) of time				
arithmetic mean (standard deviation)	66.88 (± 15.62)	66.44 (± 16.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean weekly insulin dose

End point title	Mean weekly insulin dose

End point description:

Estimated mean weekly insulin dose during the last 2 weeks of treatment (from week 24 to week 26) is presented. The endpoint data was evaluated based on the on-treatment observation period. The on-treatment period started at the date of first dose of trial product as recorded on the electronic case report form (eCRF), and ended at the first date of any of the following: The end of trial visit (V30), the last date on trial product + 5 weeks for once daily insulin and + 6 weeks for once weekly insulin (corresponding to 5 weeks after the end of the dosing interval for both treatment arms) and the end-date for the in-trial observation period. The on-treatment period represented the time period in which a subject was considered exposed to trial product. FAS included all randomised subjects. Number of subjects analyzed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From week 24 (V26) to week 26 (V28)

End point values	Insulin Icodec	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	273	266		
Units: Units of insulin				
least squares mean (confidence interval 95%)	513.54 (486.10 to 542.52)	559.05 (528.63 to 591.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in body weight

End point title	Change in body weight

End point description:

Change in body weight from baseline week 0 (V2) to week 26 (V28) is presented. The endpoint data was evaluated based on the in-trial observation period. In-trial observation period started at randomisation and ended at the date of: The last direct subject-site contact, withdrawal for subjects who withdrew their informed consent, the last subject-investigator contact as defined by the investigator for subjects who were lost to follow-up (i.e., possibly an unscheduled phone visit) and death for subjects who died before any of the above. Full analysis set included all randomised subjects.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 26 (V28)

End point values	Insulin Icodec	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	291	291		
Units: Kilograms (kg)				
least squares mean (standard error)	2.73 (± 0.29)	2.16 (± 0.40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time spent above 10 mmol/L (180 mg/dL) using continuous glucose monitoring (CGM) system, Dexcom G6

End point title	Time spent above 10 mmol/L (180 mg/dL) using continuous glucose monitoring (CGM) system, Dexcom G6

End point description:

Percentage of time spent > 10 mmol/L (180 mg/dL) using CGM system from week 22 to week 26 is presented. The endpoint data was evaluated based on the in-trial observation period. In-trial observation period started at randomisation and ended at the date of: The last direct subject-site contact, withdrawal for subjects who withdrew their informed consent, the last subject-investigator contact as defined by the investigator for subjects who were lost to follow-up (i.e., possibly an unscheduled phone visit) and death for subjects who died before any of the above. Full analysis set included all randomised subjects. Number of subjects analyzed = subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From week 22 (V24) to week 26 (V28)

End point values	Insulin Icodec	Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	244	237		
Units: Percentage (%) of time				
arithmetic mean (standard deviation)	30.47 (± 15.90)	31.30 (± 16.67)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline week 0 to week 31

Adverse event reporting additional description:

All presented AEs are treatment emergent. Treatment emergent adverse events (TEAEs): events that had onset date during on-treatment period, time period in which subjects was considered exposed to trial product. Safety analysis set included all randomised subjects randomly assigned to trial treatment who took at least 1 dose of trial product.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Insulin icodec

Reporting group description:

Subjects were to receive once weekly subcutaneous (s.c.) injection of Insulin icodec for 26 weeks, using PDS290 prefilled pen-injector in combination with insulin aspart at a starting dose of 7 times the pre-trial total daily basal insulin dose + 50% of their 7 times total daily basal insulin dose. The following weekly dose was 7 times the total daily 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 liter (mmol/L): dose reduced by 20 units (U); 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 20 U. Dose titration of insulin aspart was based on the respective premeal(s) and bedtime SMPG measured.

Reporting group title	Insulin Glargine

Reporting group description:

Subjects were to receive once daily s.c. injection of Insulin glargine for 26 weeks, using SoloSTAR pre-filled pen-injector in combination with insulin aspart. Subjects were to perform daily 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 mmol/L: dose reduced by 3 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 3 U. Dose titration of insulin aspart was based on the respective premeal(s) and bedtime SMPG measured.

Serious adverse events	Insulin icodec	Insulin Glargine	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 291 (7.56%)	25 / 291 (8.59%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic neoplasm			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			

subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine neuroendocrine tumour			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine cancer			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral artery stenosis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			

subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 291 (0.34%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 291 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coronary artery disease			
subjects affected / exposed	1 / 291 (0.34%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 291 (0.34%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 291 (0.69%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic coma			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			

Diabetic retinal oedema			
subjects affected / exposed	0 / 291 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic kidney disease			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal colic			

subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 291 (0.34%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	4 / 291 (1.37%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coronavirus infection			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 291 (0.69%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 291 (0.34%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 291 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	3 / 291 (1.03%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Insulin icodec	Insulin Glargine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 291 (16.49%)	44 / 291 (15.12%)	
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	12 / 291 (4.12%)	15 / 291 (5.15%)	
occurrences (all)	14	15	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	15 / 291 (5.15%)	9 / 291 (3.09%)	
occurrences (all)	18	9	
Infections and infestations			
COVID-19			
subjects affected / exposed	25 / 291 (8.59%)	22 / 291 (7.56%)	
occurrences (all)	25	24	

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/36106652

http://www.ncbi.nlm.nih.gov/pubmed/37156252