Clinical trial results:
A 26-week trial comparing the effect and safety of once weekly insulin icodec and once daily insulin degludec, both with or without non-insulin anti-diabetic drugs, in subjects with type 2 diabetes treated with basal insulin

Summary

EudraCT number	2020-000454-10
Trial protocol	DE PT BG
Global end of trial date	01 March 2022

Results information

Result version number	v1 (current)
This version publication date	17 March 2023
First version publication date	17 March 2023

Trial information

Trial identification

Sponsor protocol code	NN1436-4478

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04770532
WHO universal trial number (UTN)	U1111-1247-4945

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Allé, Bagsvaerd, Denmark, 2880
Public contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com
Scientific contact	Clinical Reporting Office (2834), Novo Nordisk A/S, clinicaltrials@novonordisk.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 April 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 March 2022
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 demonstrate the effect on glycaemic control of once weekly insulin icodec, with or without non-insulin anti-diabetic drugs, in subjects with type 2 diabetes (T2D) treated with basal insulin.

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.

Evidence for comparator: -

Actual start date of recruitment	05 March 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	Poland: 30
Country: Number of subjects enrolled	Japan: 100
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 70
Country: Number of subjects enrolled	South Africa: 50
Country: Number of subjects enrolled	United States: 139
Country: Number of subjects enrolled	Germany: 45
Country: Number of subjects enrolled	Bulgaria: 33
Country: Number of subjects enrolled	Portugal: 29
Country: Number of subjects enrolled	Ukraine: 30
Worldwide total number of subjects	526
EEA total number of subjects	137

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)	294
From 65 to 84 years	232
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 71 sites in 9 countries as follows: United States of America (USA) (26), Ukraine (4), Portugal (6), Poland (3), Republic of Korea (7), Japan (9), Germany (6), Bulgaria (4), South Africa (6).

Pre-assignment

Screening details:

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.

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 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 3 units (U); 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 3 U.

Arm type	Experimental
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 degludec

Arm description:

Subjects were to receive once daily s.c. injection of Insulin degludec for 26 weeks, using PDS290 prefilled pen-injector at a dose in accordance with local label. Subjects were to perform once 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 20 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 20 U.

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

Dosage and administration details:

Insulin degludec was administered once daily subcutaneously at a dose strength of 100 units/mL.

Number of subjects in period 1	Insulin Icodec	Insulin degludec
Started	263	263
Full analysis set (FAS)	263	263
Safety analysis set (SAS)	262	263
Completed	260	258
Not completed	3	5
Physician decision	1	-
Consent withdrawn by subject	-	3
Death	2	2

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 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 3 units (U); 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 3 U.	
Reporting group title	Insulin degludec
Reporting group description:	
Subjects were to receive once daily s.c. injection of Insulin degludec for 26 weeks, using PDS290 prefilled pen-injector at a dose in accordance with local label. Subjects were to perform once 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 20 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 20 U.	

Reporting group values	Insulin Icodec	Insulin degludec	Total
Number of subjects	263	263	526
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)	145	149	294
From 65-84 years	118	114	232
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	62.35	62.60	
standard deviation	± 9.79	± 8.42	-
Gender Categorical Units: Subjects			
Female	101	123	224
Male	162	140	302

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 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 3 units (U); 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 3 U.

Reporting group title	Insulin degludec

Reporting group description:

Subjects were to receive once daily s.c. injection of Insulin degludec for 26 weeks, using PDS290 prefilled pen-injector at a dose in accordance with local label. Subjects were to perform once 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 20 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 20 U.

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) was 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 degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	263		
Units: Percentage (%) of HbA1c				
least squares mean (standard error)	-0.93 (± 0.05)	-0.71 (± 0.06)		

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 degludec
Number of subjects included in analysis	526
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	-0.08

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 degludec) 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 degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	260	257		
Units: millimoles per liter (mmol/L)				
least squares mean (standard error)	-1.58 (± 0.12)	-1.62 (± 0.12)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time in target-range 3.9–10.0 mmol/L (70-180 milligrams per deciliter [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 milligrams per deciliter [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, Dexcom G6 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 degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	239		
Units: Percentage (%) of time				
arithmetic mean (standard deviation)	63.13 (± 17.40)	59.50 (± 18.92)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction

End point title	Change in DTSQs (Diabetes Treatment Satisfaction Questionnaire) in total treatment satisfaction

End point description:

Change in DTSQs in total treatment satisfaction is presented. The DTSQ domain score was calculated by adding six item scores of items 1 and 4-8. Higher scores indicate higher levels of treatment satisfaction for items 1, 4 -8. For items 2 and 3, a higher score indicates a subject perceived experience of hyperglycaemia and hypoglycaemia. Lower scores indicate that blood glucose levels were unacceptably high (item 2) or low (item 3). The score has a minimum of 0 and a maximum of 36. The endpoint data was evaluated based on in-trial observation period. The period started at randomisation and ended at the date of: Last direct subject-site contact, withdrawal for subjects who withdrew their informed consent, Last subject-investigator contact as defined by investigator for subjects who were lost to follow-up and death for subjects who died before any of the above. FAS included all randomised subjects. Number of subjects analysed=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 degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	252	244		
Units: Score on a scale				
least squares mean (standard error)	4.22 (± 0.30)	2.96 (± 0.31)		

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:

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 degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	263		
Units: Episodes				
number (not applicable)	0	1		

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 degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	263		
Units: Episodes				
number (not applicable)	113	41		

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 degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	262	263		
Units: Episodes				
number (not applicable)	113	42		

Statistical analyses

No statistical analyses for this end point

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

End point title	Time spent < 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, Dexcom G6 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 degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	239		
Units: Percentage of time				
arithmetic mean (standard deviation)	0.34 (± 0.88)	0.22 (± 0.45)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time spent > 10 mmol/L (180 mg/dL) using CGM system, Dexcom G6

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

End point description:

Percentage of time spent > 10 mmol/L (180 mg/dL) using CGM system, Dexcom G6 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 degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	239		
Units: Percentage of time				
arithmetic mean (standard deviation)	35.52 (± 17.95)	39.71 (± 19.34)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean weekly insulin dose

End point title	Mean weekly insulin dose

End point description:

Mean weekly insulin dose 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.

End point type	Secondary

End point timeframe:

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

End point values	Insulin Icodec	Insulin degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	263		
Units: Units of Insulin				
least squares mean (confidence interval 95%)	267.96 (252.19 to 284.70)	244.22 (229.99 to 259.33)		

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 degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	263		
Units: Kilograms (kg)				
least squares mean (standard error)	1.40 (± 0.32)	-0.30 (± 0.36)		

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:

Safety analysis set included all randomised subjects who were randomly assigned to trial treatment and who took at least 1 dose of trial product. A treatment-emergent AE (TEAE) was defined as an AE that initiated or worsened on or after the date of first dose of study drug up to the end of trial (week 31). All presented AEs are treatment emergent.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24

Reporting groups

Reporting group title	Insulin Degludec

Reporting group description:

Subjects were to receive once daily s.c. injection of Insulin degludec for 26 weeks, using PDS290 prefilled pen-injector at a dose in accordance with local label. Subjects were to perform once 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 20 U; 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 20 U.

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 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 3 units (U); 4.4-7.2 mmol/L: no adjustment; > 7.2 mmol/L: dose increased by 3 U.

Serious adverse events	Insulin Degludec	Insulin Icodec	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 263 (6.08%)	22 / 262 (8.40%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon cancer stage II			
subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			

subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Surgical and medical procedures			
Toe amputation			
subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 263 (0.38%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hand fracture			

subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 263 (0.38%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic stroke			
subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thalamic infarction			

subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric dysplasia			
subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic pseudocyst			
subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (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			
Urethral stenosis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenocortical insufficiency acute			
subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone secretion			
subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	2 / 263 (0.76%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			

subjects affected / exposed	0 / 263 (0.00%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Campylobacter gastroenteritis			
subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 263 (0.00%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraspinal abscess			
subjects affected / exposed	0 / 263 (0.00%)	1 / 262 (0.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 263 (0.00%)	2 / 262 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			

subjects affected / exposed	1 / 263 (0.38%)	0 / 262 (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 / 263 (0.00%)	1 / 262 (0.38%)	
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	1 / 263 (0.38%)	0 / 262 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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 Degludec	Insulin Icodec	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 263 (14.83%)	50 / 262 (19.08%)	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 263 (3.42%)	14 / 262 (5.34%)	
occurrences (all)	10	20	
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	16 / 263 (6.08%)	10 / 262 (3.82%)	
occurrences (all)	17	11	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 263 (3.42%)	14 / 262 (5.34%)	
occurrences (all)	9	17	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 263 (3.80%)	22 / 262 (8.40%)	
occurrences (all)	14	28	

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