Clinical trial results:
Effectiveness and safety of once weekly insulin icodec used with DoseGuide versus once daily basal insulin analogues in an insulin naive type 2 diabetes population in a clinical practice setting (ONWARDS 5)

Summary

EudraCT number	2020-000476-38
Trial protocol	DE HU GR PL
Global end of trial date	29 August 2022

Results information

Result version number	v1 (current)
This version publication date	13 September 2023
First version publication date	13 September 2023

Trial information

Trial identification

Sponsor protocol code	NN1436-4481

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04760626
WHO universal trial number (UTN)	U1111-1247-5279

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	19 September 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the effectiveness on glycaemic control of once weekly insulin icodec used with DoseGuide in combination with non-insulin anti-diabetic drugs in insulin naive subjects with type 2 diabetes (T2D) in a clinical practice setting. This includes comparing the difference in change from baseline in HbA1c between insulin icodec used with DoseGuide and once daily basal insulin analogues after 52 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), International Council for Harmonisation (ICH) Good Clinical Practice, including archiving of essential documents (Current Step 4 version, Nov 2016), European standard (EN) International Organisation for Standardisation (ISO) 14155, Food and Drug Administration (FDA) 21 Code of Federal Regulations (CFR) 812 and 21 CFR 312.120.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 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	Canada: 181
Country: Number of subjects enrolled	Germany: 101
Country: Number of subjects enrolled	Greece: 136
Country: Number of subjects enrolled	Hungary: 142
Country: Number of subjects enrolled	Poland: 95
Country: Number of subjects enrolled	Turkey: 83
Country: Number of subjects enrolled	United States: 347
Worldwide total number of subjects	1085
EEA total number of subjects	474

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)	722
From 65 to 84 years	362
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 182 sites in 7 countries as follows (number of sites that screened subjects/ number of sites that randomised subjects): Canada (36/34), Germany (14/14), Greece (12/12), Hungary (12/12), Poland (11/10), Turkey (15/14), United States (82/80).

Pre-assignment

Screening details:

The trial duration was approximately 59 weeks, consisting of a 2-week screening period, followed by a 52-week randomisation period and a 5-week follow-up period. A total of 1250 subjects were screened of which 1085 subjects were randomised.

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 guided by the DoseGuide app, for 52 weeks using PDS290 prefilled pen-injector. 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.

Arm type	Experimental
Investigational medicinal product name	insulin icodec 700U/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 guided by the DoseGuide app.

Arm title	Once daily basal insulin analogue

Arm description:

Subjects were to receive once daily basal insulin analogue of (Insulin degludec using PDS290 prefilled pen-injector) or (Insulin glargine U100 or Insulin glargine U300 using SoloSTAR® pre-filled pen-injector) for 52 weeks, at a dose in accordance with local label. Titration of once daily basal insulin analogue comparators is at the discretion of the investigator according to local clinical practice. The recommended doses for all once daily basal insulin analogues will be based on the locally approved label.

Arm type	Experimental
Investigational medicinal product name	insulin glargine 100U/mL
Investigational medicinal product code	
Other name	Lantus 100U/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 in accordance with local label.

Investigational medicinal product name	insulin degludec 100U/mL
Investigational medicinal product code	
Other name	Tresiba 100U/mL
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Insulin degludec was administered once-daily subcutaneously at a dose in accordance with local label.

Investigational medicinal product name	insulin glargine 300U/mL
Investigational medicinal product code	
Other name	Lantus 300U/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 in accordance with local label.

Number of subjects in period 1	Insulin icodec	Once daily basal insulin analogue
Started	542	543
Full analysis set (FAS)	542	543
Satety analysis set (SAS)	542	538
Completed	497	493
Not completed	45	50
Adverse event, serious fatal	3	6
Physician decision	3	5
Consent withdrawn by subject	24	20
Lost to follow-up	14	19
Site closure	1	-

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 guided by the DoseGuide app, for 52 weeks using PDS290 prefilled pen-injector. 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.

Reporting group title	Once daily basal insulin analogue

Reporting group description:

Subjects were to receive once daily basal insulin analogue of (Insulin degludec using PDS290 prefilled pen-injector) or (Insulin glargine U100 or Insulin glargine U300 using SoloSTAR® pre-filled pen-injector) for 52 weeks, at a dose in accordance with local label. Titration of once daily basal insulin analogue comparators is at the discretion of the investigator according to local clinical practice. The recommended doses for all once daily basal insulin analogues will be based on the locally approved label.

Reporting group values	Insulin icodec	Once daily basal insulin analogue	Total
Number of subjects	542	543	1085
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)	359	363	722
From 65-84 years	182	180	362
85 years and over	1	0	1
Age Continuous Units: years			
arithmetic mean	59.15	59.39	
standard deviation	± 10.79	± 10.15	-
Gender Categorical Units: Subjects			
Female	233	230	463
Male	309	313	622

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 guided by the DoseGuide app, for 52 weeks using PDS290 prefilled pen-injector. 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.

Reporting group title	Once daily basal insulin analogue

Reporting group description:

Subjects were to receive once daily basal insulin analogue of (Insulin degludec using PDS290 prefilled pen-injector) or (Insulin glargine U100 or Insulin glargine U300 using SoloSTAR® pre-filled pen-injector) for 52 weeks, at a dose in accordance with local label. Titration of once daily basal insulin analogue comparators is at the discretion of the investigator according to local clinical practice. The recommended doses for all once daily basal insulin analogues will be based on the locally approved label.

Primary: Change in glycated haemoglobin (HbA1c)

End point title	Change in glycated haemoglobin (HbA1c)

End point description:

Change in HbA1c from baseline (week 0) to week 52 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	Primary

End point timeframe:

From baseline week 0 (V2) to week 52 (V6)

End point values	Insulin icodec	Once daily basal insulin analogue		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	542	542		
Units: Percentage of HbA1c				
least squares mean (standard error)	-1.68 (± 0.09)	-1.31 (± 0.12)		

Statistical analyses

Statistical analysis title	Statistical Analysis Set 1

Statistical analysis description:

The response and change from baseline in response after 52 weeks were analysed using an analysis of covariance (ANCOVA) model with region and randomised treatment as fixed factors, and baseline HbA1c as a covariate.

Comparison groups	Insulin icodec v Once daily basal insulin analogue
Number of subjects included in analysis	1084
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.66
upper limit	-0.09

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 with doseguide minus once daily basal insulin analogue) was strictly below 0.3 percent 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 DTSQs questionnaire was used to assess subjects treatment satisfaction which contained 8 components and evaluates the diabetes treatment in terms of convenience, flexibility and general feelings towards the treatment. The result presented is the treatment satisfaction summary score, which is the sum of 6 of the 8 items of the DTSQs questionnaire. Total scores for treatment satisfaction range from 0-36 with 0 being the lowest and 36 being the highest score in total treatment satisfaction. 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 52 (V6)

End point values	Insulin icodec	Once daily basal insulin analogue		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	513	500		
Units: Score on a scale				
least squares mean (standard error)	4.68 (± 0.25)	3.90 (± 0.25)		

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 (V8), 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. Safety analysis set included all subjects who were randomly assigned to trial treatment and who took at least 1 dose of trial product. 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 57 (V8)

End point values	Insulin icodec	Once daily basal insulin analogue		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	542	538		
Units: Episodes				
number (not applicable)	0	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Trim-D (Treatment Related Impact Measure for Diabetes) compliance domain

End point title	Trim-D (Treatment Related Impact Measure for Diabetes) compliance domain

End point description:

Treatment Related Impact Measure for Diabetes (TRIM-D) Compliance domain at week 52 is presented. The TRIM-D questionnaire was developed to capture the impact of diabetes treatment on patients' functioning and well-being. The compliance domain from the questionnaire was used to measure the compliance between the treatment groups. The total TRIM-D compliance score is computed by summing across the items and then transforming to a 0-100 scale. The total TRIM-D compliance score can range from 0 to 100 with higher score indicating better compliance. FAS included all randomised subjects.

End point type	Secondary

End point timeframe:

At end of treatment week 52 (V6)

End point values	Insulin icodec	Once daily basal insulin analogue		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	542	543		
Units: Score on a scale				
least squares mean (standard error)	90.42 (± 0.64)	87.37 (± 0.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time from baseline to treatment discontinuation or intensification

End point title	Time from baseline to treatment discontinuation or intensification

End point description:

Time from baseline to treatment discontinuation or intensification from baseline (week 0) to week 52 is presented. 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 analyzed=subjects with available data for this endpoint.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 52 (V6)

End point values	Insulin icodec	Once daily basal insulin analogue		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	50		
Units: Days				
median (full range (min-max))	20.1 (0.0 to 51.0)	13.9 (0.0 to 55.1)		

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 blood glucose (BG) meter)

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

End point description:

Number of clinically significant hypoglycaemic episodes (level 2) (below 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 (V8), 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. Safety analysis set included all subjects who were randomly assigned to trial treatment and who took at least 1 dose of trial product. 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 57 (V8)

End point values	Insulin icodec	Once daily basal insulin analogue		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	542	538		
Units: Episodes				
number (not applicable)	104	76		

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:

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) is presented. 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 (V8), 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. 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 57 (V8)

End point values	Insulin icodec	Once daily basal insulin analogue		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	542	538		
Units: Episodes				
number (not applicable)	104	81		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline week 0 (V2) to week 57 (V8)

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	Once daily basal insulin analogue

Reporting group description:

Subjects were to receive once daily basal insulin analogue of (Insulin degludec using PDS290 prefilled pen-injector) or (Insulin glargine U100 or Insulin glargine U300 using SoloSTAR® pre-filled pen-injector) for 52 weeks, at a dose in accordance with local label. Titration of once daily basal insulin analogue comparators is at the discretion of the investigator according to local clinical practice. The recommended doses for all once daily basal insulin analogues will be based on the locally approved label.

Reporting group title	Insulin icodec

Reporting group description:

Subjects were to receive once weekly subcutaneous (s.c.) injection of Insulin icodec guided by the DoseGuide app, for 52 weeks using PDS290 prefilled pen-injector. 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.

Serious adverse events	Once daily basal insulin analogue	Insulin icodec	
Total subjects affected by serious adverse events			
subjects affected / exposed	57 / 538 (10.59%)	45 / 542 (8.30%)	
number of deaths (all causes)	7	3	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Basal cell carcinoma			

subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer metastatic			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bowen's disease			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign renal neoplasm			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal cancer			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive breast carcinoma			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			

subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung cancer metastatic			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	1 / 538 (0.19%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 538 (0.19%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypertensive urgency			

subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous stenosis			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cardiac pacemaker replacement			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin neoplasm excision			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Drug intolerance			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 538 (0.37%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Localised oedema			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary mass			

subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
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			
Ankle fracture			
subjects affected / exposed	2 / 538 (0.37%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periprocedural myocardial infarction			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Post procedural inflammation			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematuria			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hypertrophic cardiomyopathy			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (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 coronary syndrome			
subjects affected / exposed	0 / 538 (0.00%)	2 / 542 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arrhythmia			
subjects affected / exposed	0 / 538 (0.00%)	2 / 542 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 538 (0.19%)	4 / 542 (0.74%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 538 (0.00%)	3 / 542 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			

subjects affected / exposed	2 / 538 (0.37%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	5 / 538 (0.93%)	2 / 542 (0.37%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (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 / 538 (0.37%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Palpitations			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amnesia			

subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral artery embolism			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral atrophy			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
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	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			

subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
White matter lesion			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (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 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Ocular ischaemic syndrome			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Eosinophilic oesophagitis			

subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 538 (0.00%)	2 / 542 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 538 (0.56%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress urinary incontinence			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ureterolithiasis			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (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			
Arthralgia			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (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 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigger finger			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (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			
Appendicitis			

subjects affected / exposed	1 / 538 (0.19%)	1 / 542 (0.18%)	
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	3 / 538 (0.56%)	2 / 542 (0.37%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
COVID-19			
subjects affected / exposed	0 / 538 (0.00%)	3 / 542 (0.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
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 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster infection neurological			

subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
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	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 538 (0.00%)	2 / 542 (0.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sweat gland infection			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			

subjects affected / exposed	2 / 538 (0.37%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 538 (0.19%)	0 / 542 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 538 (0.00%)	1 / 542 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Once daily basal insulin analogue	Insulin icodec	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 538 (10.22%)	40 / 542 (7.38%)	
Infections and infestations			
COVID-19			
subjects affected / exposed	55 / 538 (10.22%)	40 / 542 (7.38%)	
occurrences (all)	57	43	

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