Clinical trial results:
A 52-week study comparing the efficacy and safety of once weekly IcoSema and once weekly insulin icodec, both treatment arms with or without oral anti-diabetic drugs, in participants with type 2 diabetes inadequately controlled with daily basal insulin. COMBINE 1

Summary

EudraCT number	2020-005281-34
Trial protocol	FI NO BE BG PT HR IT
Global end of trial date	23 April 2024

Results information

Result version number	v1 (current)
This version publication date	09 May 2025
First version publication date	09 May 2025

Trial information

Trial identification

Sponsor protocol code	NN1535-4591

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05352815
WHO universal trial number (UTN)	U1111-1260-8259
Other trial identifiers	China Drug Trials (China): CTR20220768, Japan Registry for Clinical Trials (jRCT): jRCT2031220146

Notes:

Sponsors

Sponsor organisation name	Novo Nordisk A/S
Sponsor organisation address	Novo Alle, 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 June 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To confirm superiority of once weekly IcoSema compared with once weekly insulin icodec, both treatment arms with or without oral anti-diabetic drugs (OADs), in terms of glycaemic control measured by change in Haemoglobin A1c (HbA1c) from baseline after 52 weeks in subjects with type 2 diabetes (T2D) inadequately controlled with daily basal insulin.

Protection of trial subjects:

The study was conducted in accordance with the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil. Oct 2013) and ICH Good Clinical Practice, including archiving of essential documents (Current step 4 version. 09 Nov 2016).

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	01 June 2022
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	Australia: 40
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Bulgaria: 59
Country: Number of subjects enrolled	China: 100
Country: Number of subjects enrolled	Finland: 27
Country: Number of subjects enrolled	Croatia: 46
Country: Number of subjects enrolled	India: 30
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Japan: 124
Country: Number of subjects enrolled	Korea, Republic of: 83
Country: Number of subjects enrolled	Mexico: 115
Country: Number of subjects enrolled	Norway: 15
Country: Number of subjects enrolled	Poland: 57
Country: Number of subjects enrolled	Portugal: 28
Country: Number of subjects enrolled	Romania: 47
Country: Number of subjects enrolled	Serbia: 31
Country: Number of subjects enrolled	Türkiye: 46

Country: Number of subjects enrolled	Taiwan: 30
Country: Number of subjects enrolled	United States: 295
Country: Number of subjects enrolled	South Africa: 81
Worldwide total number of subjects	1291
EEA total number of subjects	316

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)	784
From 65 to 84 years	507
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 192 sites in 20 countries.

Pre-assignment

Screening details:

Subjects with type 2 diabetes (T2D) inadequately controlled with daily basal insulin were randomised in 1:1 ratio to receive subcutaneous (s.c.) injection of IcoSema or insulin icodec once weekly with or without oral anti-diabetic drugs (OADs).

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	IcoSema

Arm description:

Subjects received once weekly subcutaneous injections of 700 units per milliliter (U/mL) of insulin icodec and 2 milligrams per milliliter(mg/mL) of semaglutide for 52 weeks.

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

Dosage and administration details:

Once-weekly subcutaneous injections of insulin icodec and semaglutide were administered for 52 weeks.

Arm title	Insulin Icodec

Arm description:

Subjects received once weekly subcutaneous injections of 700 units per milliliter (U/mL) of insulin icodec for 52 weeks.

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

Dosage and administration details:

Once-weekly subcutaneous injections of insulin icodec was administered for 52 weeks.

Number of subjects in period 1	IcoSema	Insulin Icodec
Started	646	645
Full analysis set (FAS)	646	645
Safety analysis set (SAS)	644	644
Exposed	644	644
Completed	611	611
Not completed	35	34
Adverse event, serious fatal	2	3
Consent withdrawn by subject	28	24
Lost to follow-up	4	7
Site closure	1	-

Baseline characteristics

Reporting groups	
Reporting group title	IcoSema
Reporting group description:	
Subjects received once weekly subcutaneous injections of 700 units per milliliter (U/mL) of insulin icodec and 2 milligrams per milliliter(mg/mL) of semaglutide for 52 weeks.	
Reporting group title	Insulin Icodec
Reporting group description:	
Subjects received once weekly subcutaneous injections of 700 units per milliliter (U/mL) of insulin icodec for 52 weeks.	

Reporting group values	IcoSema	Insulin Icodec	Total
Number of subjects	646	645	1291
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)	381	403	784
From 65-84 years	265	242	507
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	60.5	60.7	
standard deviation	± 10.5	± 10.2	-
Gender Categorical Units: Participants			
Female	246	246	492
Male	400	399	799
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	101	110	211
Not Hispanic or Latino	545	535	1080
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	5	1	6
Asian	216	204	420
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	19	25	44
White	404	410	814
More than one race	2	4	6
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	IcoSema
Reporting group description:	
Subjects received once weekly subcutaneous injections of 700 units per milliliter (U/mL) of insulin icodec and 2 milligrams per milliliter(mg/mL) of semaglutide for 52 weeks.	
Reporting group title	Insulin Icodec
Reporting group description:	
Subjects received once weekly subcutaneous injections of 700 units per milliliter (U/mL) of insulin icodec for 52 weeks.	

Primary: Change in glycated haemoglobin (HbA1c)

End point title	Change in glycated haemoglobin (HbA1c)
End point description:	
Change from baseline (week 0) to week 52 in HbA1c is presented. The outcome measure was evaluated based on the data from in study period, where all data from randomisation until last date of any of the following: 1) last direct subject-site contact; 2)subjects who withdrew their informed consent; 3) last subject-investigator contact as defined by the investigator for subjects who lost to follow-up (i.e. possibly an unscheduled phone visit); 4) death of subjects who died before any of the above. Full Analysis Set (FAS) included all randomised subjects. Overall number of subjects analyzed = subjects with available data.	
End point type	Primary
End point timeframe:	
From baseline week 0 (V2) to week 52 (V54)	

End point values	IcoSema	Insulin Icodec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	598	605		
Units: Percentage point of HbA1c				
arithmetic mean (standard deviation)	-1.60 (± 0.99)	-0.90 (± 1.01)		

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description:	
Change in HbA1c from baseline to week 52 is analysed using an analysis of covariance (ANCOVA) model with region and randomised treatment as fixed factors and baseline HbA1c as covariate. Missing HbA1c values at week 52 are imputed by using multiple imputation. Each imputed dataset is analysed separately and estimates are combined using Rubin's rules.	
Comparison groups	IcoSema v Insulin Icodec

Number of subjects included in analysis	1203
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.76
upper limit	-0.57

Notes:

[1] - Total number of subjects included in statistical analysis is 1291. The number given here is auto-calculated by the system.

Secondary: Number of clinically significant hypoglycaemic episodes (level 2) (less than 3.0 millimoles per litre [mmol/L] (54 milligram per decilitre [mg/dL]), confirmed by blood glucose [BG] meter) or severe hypoglycaemic episodes (level 3)

End point title	Number of clinically significant hypoglycaemic episodes (level 2) (less than 3.0 millimoles per litre [mmol/L] (54 milligram per decilitre [mg/dL]), confirmed by blood glucose [BG] meter) or severe hypoglycaemic episodes (level 3)

End point description:

Hypoglycaemic episodes were classified according to the American Diabetes Association/ International Hypoglycaemia Study Group, where glycemic criteria for level 2 was less than (<) 3.0 mmol/L (54 mg/dL) and level 3 had no specific glucose threshold. The outcome measure was evaluated based on data from on treatment period, where all data from date of first dose of randomised treatment as recorded on the electronic case report form (eCRF) until the first date of any of the following: 1) last follow-up visit ; 2) last date on randomised treatment +6 weeks (corresponding to 5 weeks after the end of the dosing interval for both treatment arms); 3) end date for the in-study data points sets. Safety analysis set (SAS) included all randomised subjects who are exposed to randomised treatment.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 57 (V56)

End point values	IcoSema	Insulin Icodec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	644		
Units: Episodes				
number (not applicable)	91	424		

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 from baseline (week 0) to week 52 in body weight is presented. The outcome measure was evaluated based on the data from in study period, where all data from randomisation until last date of any of the following: 1) last direct subject-site contact; 2) subjects who withdrew their informed consent; 3) last subject-investigator contact as defined by the investigator for subjects who lost to follow-up (i.e. possibly an unscheduled phone visit); 4) death of subjects who died before any of the above. FAS included all randomised subjects. Overall number of subjects analyzed = subjects with available data.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 52 (V54)

End point values	IcoSema	Insulin Icodec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	606	610		
Units: Kilogram (Kg)				
arithmetic mean (standard deviation)	-3.71 (± 4.87)	1.96 (± 4.76)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time spent more than 10.0 mmol/L (180 mg/dL) using continuous glucose monitoring (CGM) system, Dexcom G6

End point title	Time spent more than 10.0 mmol/L (180 mg/dL) using continuous glucose monitoring (CGM) system, Dexcom G6

End point description:

Time spent above threshold is defined as 100 times the number of recorded measurements above the threshold, divided by the total number of recorded measurements. The outcome measure was evaluated based on the data from in study period: Data from randomisation until last date of any of the following: 1) the last direct subject-site contact; 2) withdrawal for subjects who withdraw their informed consent; 3) the last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up (i.e. possibly an unscheduled phone visit); 4) death for subjects who die before any of the above. FAS included all randomised subjects. Overall number of subjects analyzed = subjects with available data.

End point type	Secondary

End point timeframe:

From week 48 (V50) to week 52 (V54)

End point values	IcoSema	Insulin Icodec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	481	488		
Units: Percentage of time				
arithmetic mean (standard deviation)	23.2 (± 16.3)	36.7 (± 18.7)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Time spent below threshold was defined as 100 times the number of recorded measurements below the threshold, divided by the total number of recorded measurements. The outcome measure was evaluated based on the data from in study period: Data from randomisation until last date of any of the following: 1) the last direct subject-site contact; 2) withdrawal for subjects who withdraw their informed consent; 3) the last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up (i.e. possibly an unscheduled phone visit); 4) death for subjects who die before any of the above. FAS included all randomised subjects. Overall number of subjects analyzed = subjects with available data.

End point type	Secondary

End point timeframe:

From week 48 (V50) to week 52 (V54)

End point values	IcoSema	Insulin Icodec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	481	488		
Units: Percentage of time				
arithmetic mean (standard deviation)	0.27 (± 0.55)	0.33 (± 0.82)		

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Time in range was defined as 100 times the number of recorded measurements in glycemic range 3.9-10.0 mmol/L (70-180 mg/dL), both inclusive, divided by the total number of recorded measurements. The outcome measure was evaluated based on the data from in study period: Data from randomisation until last date of any of the following: 1) the last direct subject-site contact; 2) withdrawal for subjects who withdraw their informed consent; 3) the last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up (i.e. possibly an unscheduled phone visit); 4) death for subjects who die before any of the above. FAS included all randomised subjects. Overall number of subjects analyzed = subjects with available data.

End point type	Secondary

End point timeframe:

From week 48 (V50) to week 52 (V54)

End point values	IcoSema	Insulin Icodec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	481	488		
Units: Percentage of time				
arithmetic mean (standard deviation)	75.9 (± 16.1)	61.9 (± 18.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in fasting plasma glucose (FPG)

End point title	Change in fasting plasma glucose (FPG)

End point description:

Change in FPG from baseline (week 0) to week 52 is presented. The outcome measure was evaluated based on the data from in study period: Data from randomisation until last date of any of the following: 1) the last direct subject-site contact; 2) withdrawal for subjects who withdraw their informed consent; 3) the last subject-investigator contact as defined by the investigator for subjects who are lost to follow-up (i.e. possibly an unscheduled phone visit); 4) death for subjects who die before any of the above. FAS included all randomised subjects. Overall number of subjects analyzed = subjects with available data.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 52 (V54)

End point values	IcoSema	Insulin Icodec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	552	572		
Units: Millimoles per litre (mmol/L)				
arithmetic mean (standard deviation)	-1.90 (± 3.01)	-1.65 (± 2.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Weekly basal insulin dose

End point title	Weekly basal insulin dose

End point description:

Estimated mean average weekly basal insulin dose from week 50 to week 52 of treatment is presented.

The outcome measure was evaluated based on data from on treatment period, where all data from date of first dose of randomised treatment as recorded on the electronic case report form (eCRF) until the first date of any of the following: 1) last follow-up visit (V56); 2) last date on randomised treatment +6 weeks (corresponding to 5 weeks after the end of the dosing interval for both treatment arms); 3) end-date for the in-study data points sets. SAS included all randomised subjects who are exposed to randomised treatment. Overall number of subjects analyzed = subjects with available data.

End point type	Secondary

End point timeframe:

From week 50 (V52) to week 52 (V54)

End point values	IcoSema	Insulin Icodec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	575	596		
Units: Units of insulin				
arithmetic mean (standard deviation)	170.6 (± 83.3)	366.5 (± 225.5)		

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:

Hypoglycaemic episodes were classified according to the American Diabetes Association/ International Hypoglycaemia Study Group, where glycemic criteria for level 3 had no specific glucose threshold. The outcome measure was evaluated based on data from on treatment period, where all data from date of first dose of randomised treatment as recorded on the electronic case report form (eCRF) until the first date of any of the following: 1) last follow-up visit; 2) last date on randomised treatment +6 weeks(corresponding to 5 weeks after the end of the dosing interval for both treatment arms); 3) end-date for the in-study data points sets. SAS included all randomised subjects who are exposed to randomised treatment. Overall number of subjects analyzed = subjects with available data.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 57 (V56)

End point values	IcoSema	Insulin Icodec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	644		
Units: Episodes				
number (not applicable)	1	5		

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)

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

End point description:

Hypoglycaemic episodes were classified according to the American Diabetes Association/ International Hypoglycaemia Study Group, where glycemic criteria for level 2 was less than (<) 3.0 mmol/L (54 mg/dL). The outcome measure was evaluated based on data from on treatment period, where all data from date of first dose of randomised treatment as recorded on the electronic case report form (eCRF) until the first date of any of the following: 1) last follow-up visit ; 2) last date on randomised treatment +6 weeks (corresponding to 5 weeks after the end of the dosing interval for both treatment arms); 3) end-date for the in-study data points sets. SAS included all randomised subjects who are exposed to randomised treatment. Overall number of subjects analyzed = subjects with available data.

End point type	Secondary

End point timeframe:

From baseline week 0 (V2) to week 57 (V56)

End point values	IcoSema	Insulin Icodec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	644	644		
Units: Episodes				
number (not applicable)	90	419		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Week 0 to week 57

Adverse event reporting additional description:

Presented AEs are TEAEs, defined as event with onset during on treatment period where all data from date of first dose of randomised treatment as recorded on electronic case report form until first date of any of the below: last follow up visit; last date on randomised treatment +6 weeks; end-date for in-study data points.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26

Reporting groups

Reporting group title	Insulin Icodec

Reporting group description:

Subjects received once weekly subcutaneous injections of 700 units per milliliter (U/mL) of insulin icodec for 52 weeks.

Reporting group title	IcoSema

Reporting group description:

Subjects received once weekly subcutaneous injections of 700 units per milliliter (U/mL) of insulin icodec and 2 milligrams per milliliter(mg/mL) of semaglutide for 52 weeks.

Serious adverse events	Insulin Icodec	IcoSema	
Total subjects affected by serious adverse events			
subjects affected / exposed	69 / 644 (10.71%)	59 / 644 (9.16%)	
number of deaths (all causes)	3	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			

subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal proliferative breast lesion			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (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	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	2 / 644 (0.31%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal adenocarcinoma			

subjects affected / exposed	1 / 644 (0.16%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery occlusion			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 644 (0.31%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (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 shock			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (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			
Breast haematoma			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cystocele			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatomegaly			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (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	2 / 644 (0.31%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	3 / 644 (0.47%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary fibrosis			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Adjustment disorder with depressed mood			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Insomnia			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose decreased			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cartilage injury			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
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 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip injury			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			

subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
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 / 644 (0.16%)	2 / 644 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress fracture			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 644 (0.16%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth fracture			

subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (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	5 / 644 (0.78%)	2 / 644 (0.31%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 644 (0.31%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 644 (0.31%)	2 / 644 (0.31%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Degenerative aortic valve disease			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	3 / 644 (0.47%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	4 / 644 (0.62%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 644 (0.31%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	2 / 644 (0.31%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic unconsciousness			
subjects affected / exposed	2 / 644 (0.31%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	1 / 644 (0.16%)	2 / 644 (0.31%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelopathy			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine with aura			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			

subjects affected / exposed	1 / 644 (0.16%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Macular oedema			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			

subjects affected / exposed	2 / 644 (0.31%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastroparesis			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 644 (0.00%)	2 / 644 (0.31%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	1 / 644 (0.16%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			

subjects affected / exposed	0 / 644 (0.00%)	2 / 644 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotid gland enlargement			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Terminal ileitis			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (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	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	2 / 644 (0.31%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 644 (0.31%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			

subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (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 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postrenal failure			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tubulointerstitial nephritis			

subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
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			
Arthralgia			
subjects affected / exposed	0 / 644 (0.00%)	2 / 644 (0.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
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 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthropathy			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (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 / 644 (0.16%)	0 / 644 (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			

Abscess limb			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 644 (0.16%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 644 (0.16%)	3 / 644 (0.47%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (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	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia influenzal			

subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 644 (0.62%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (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	1 / 644 (0.16%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound sepsis			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			

subjects affected / exposed	1 / 644 (0.16%)	0 / 644 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 644 (0.00%)	1 / 644 (0.16%)	
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 / 644 (0.47%)	0 / 644 (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	IcoSema	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	258 / 644 (40.06%)	354 / 644 (54.97%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	19 / 644 (2.95%)	37 / 644 (5.75%)	
occurrences (all)	27	41	
Headache			
subjects affected / exposed	20 / 644 (3.11%)	33 / 644 (5.12%)	
occurrences (all)	26	58	
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	35 / 644 (5.43%)	41 / 644 (6.37%)	
occurrences (all)	41	46	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	8 / 644 (1.24%)	39 / 644 (6.06%)	
occurrences (all)	8	55	
Diarrhoea			
subjects affected / exposed	46 / 644 (7.14%)	102 / 644 (15.84%)	
occurrences (all)	65	187	
Nausea			

subjects affected / exposed	24 / 644 (3.73%)	153 / 644 (23.76%)	
occurrences (all)	29	348	
Dyspepsia			
subjects affected / exposed	10 / 644 (1.55%)	44 / 644 (6.83%)	
occurrences (all)	11	64	
Vomiting			
subjects affected / exposed	17 / 644 (2.64%)	68 / 644 (10.56%)	
occurrences (all)	19	118	
Infections and infestations			
COVID-19			
subjects affected / exposed	61 / 644 (9.47%)	67 / 644 (10.40%)	
occurrences (all)	62	68	
Nasopharyngitis			
subjects affected / exposed	51 / 644 (7.92%)	38 / 644 (5.90%)	
occurrences (all)	62	50	
Upper respiratory tract infection			
subjects affected / exposed	69 / 644 (10.71%)	54 / 644 (8.39%)	
occurrences (all)	84	64	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 644 (0.16%)	38 / 644 (5.90%)	
occurrences (all)	1	48	

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