



## Clinical trial results:

**A 52 week study comparing the efficacy and safety of once weekly IcoSema and daily insulin glargine 100 units/mL combined with insulin aspart, both treatment arms with or without oral anti diabetic drugs, in participants with type 2 diabetes inadequately controlled with daily basal insulin.**

### Summary

EudraCT number	2020-005309-18
Trial protocol	DE IT HU CZ FR SI
Global end of trial date	14 November 2023

### Results information

Result version number	v1 (current)
This version publication date	28 November 2024
First version publication date	28 November 2024

### Trial information

#### Trial identification

Sponsor protocol code	NN1535-4593
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05013229
WHO universal trial number (UTN)	U1111-1260-8295

Notes:

#### Sponsors

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

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 December 2023
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 November 2023
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To confirm non-inferiority of once weekly IcoSema compared with daily insulin glargine combined with insulin aspart, both treatment arms with or without oral anti-diabetic drugs (OAD), in terms of glycaemic control measured by change in Glycosylated Haemoglobin (HbA1c) from baseline after 52 weeks in subjects with type 2 diabetes (T2D) inadequately controlled with daily basal insulin using a non-inferiority margin of 0.3%-point.

Protection of trial subjects:

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

Background therapy:

OADs were regarded as non-investigational medicinal products (non-IMPs) in this trial. Subjects were to continue OADs throughout the entire study except for treatment sulfonylureas, glinides and dipeptidyl peptidase (DPP) 4 inhibitors that were to be discontinued at randomisation.

Evidence for comparator:

Not applicable

Actual start date of recruitment	30 November 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	Czechia: 31
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Germany: 52
Country: Number of subjects enrolled	Hungary: 26
Country: Number of subjects enrolled	India: 90
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Japan: 83
Country: Number of subjects enrolled	Malaysia: 39
Country: Number of subjects enrolled	Poland: 57
Country: Number of subjects enrolled	Slovenia: 22
Country: Number of subjects enrolled	South Africa: 36
Country: Number of subjects enrolled	Thailand: 33
Country: Number of subjects enrolled	Türkiye: 24
Country: Number of subjects enrolled	United States: 143

Worldwide total number of subjects	679
EEA total number of subjects	231

Notes:

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**Subjects enrolled per age group**

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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)	440
From 65 to 84 years	239
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The trial was conducted at 123 sites in 14 countries (123 sites screened/109 randomised subjects) as follows: Czech Republic (8/8); France(5/5); Germany(6/6); Hungary(4/4); India(14/1); Italy(5/5); Japan(11/11); Malaysia(6/6); Poland(6/6); Slovenia(4/4); South Africa(5/5); Thailand(5/5); Turkey(5/5) and United States(39/38).

### 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 daily insulin glargine combined with 2-4 times daily injections of insulin aspart 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
<b>Arm title</b>	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:

IcoSema was administered subcutaneously at dose strength of 700 units/mL and 2 mg/mL once weekly.

<b>Arm title</b>	Insulin glargine and insulin aspart
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Arm description:

Subjects received subcutaneous injections of 100 U/mL of insulin glargine once daily combined with 100 U/mL of insulin aspart 2-4 times daily with meals for 52 weeks.

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

Dosage and administration details:

Insulin glargine at dose strength 100 units/mL was administered subcutaneously once daily and 100 units/mL of insulin aspart was administered subcutaneously with meals 2-4 times daily.

<b>Number of subjects in period 1</b>	IcoSema	Insulin glargine and insulin aspart
Started	340	339
Full Analysis Set (FAS)	340	339
Safety Analysis Set (SAS)	340	328
Completed	324	301
Not completed	16	38
Consent withdrawn by subject	13	28
Death	1	2
Lost to follow-up	1	6
Site closure	1	2

## 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 glargine and insulin aspart
Reporting group description:	Subjects received subcutaneous injections of 100 U/mL of insulin glargine once daily combined with 100 U/mL of insulin aspart 2-4 times daily with meals for 52 weeks.

Reporting group values	IcoSema	Insulin glargine and insulin aspart	Total
Number of subjects	340	339	679
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)	210	230	440
From 65-84 years	130	109	239
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	60.2	59.1	-
standard deviation	± 10.7	± 9.9	-
Sex: Female, Male Units: Participants			
Female	140	140	280
Male	200	199	399
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	130	133	263
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	19	16	35
White	179	184	363
More than one race	0	0	0
Unknown or Not Reported	12	6	18
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	12	23	35
Not Hispanic or Latino	316	310	626
Unknown or Not Reported	12	6	18



## 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 glargine and insulin aspart
Reporting group description: Subjects received subcutaneous injections of 100 U/mL of insulin glargine once daily combined with 100 U/mL of insulin aspart 2-4 times daily with meals for 52 weeks.	

### Primary: Change in HbA1c

End point title	Change in HbA1c
End point description: Change from baseline (week 0) to week 52 in HbA1c is presented. The end point 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. Full Analysis Set (FAS) comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.	
End point type	Primary
End point timeframe: From baseline week 0 (V2) to week 52 (V54)	

End point values	IcoSema	Insulin glargine and insulin aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	317	297		
Units: Percentage of HbA1c				
arithmetic mean (standard deviation)	-1.50 (± 1.05)	-1.51 (± 1.00)		

### Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: HbA1c and 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.	
Comparison groups	IcoSema v Insulin glargine and insulin aspart

Number of subjects included in analysis	614
Analysis specification	Pre-specified
Analysis type	non-inferiority <sup>[1]</sup>
P-value	< 0.0001
Method	ANCOVA
Parameter estimate	Treatment difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.09

Notes:

[1] - Total number of subjects included in statistical analysis is 679. The number given here is auto-calculated by the system.

### Secondary: Change in body weight

End point title	Change in body weight
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End point description:

Change from baseline (week 0) to week 52 in body weight is presented. The end point 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 comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary
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End point timeframe:

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

End point values	IcoSema	Insulin glargine and insulin aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	301		
Units: Kilogram (kg)				
arithmetic mean (standard deviation)	-3.60 (± 4.76)	3.21 (± 5.51)		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) (Number of episodes)

End point title	Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) (Number of episodes)
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End point description:

Hypoglycaemic episodes were classified as level 2 if plasma glucose levels were less than (<) 3.0

mmol/L (54 mg/dL); and level 3 had no specific glucose threshold but were associated with severe cognitive impairment requiring external assistance for recovery. End point was evaluated based on data from on-treatment period: data from date of first dose of randomised treatment as recorded on electronic case report form (eCRF) until first date of any of following: 1) last follow-up visit (V56); 2) last date on randomised treatment +6 weeks (corresponding to 5 weeks after end of dosing interval for both treatment arms); 3) end-date for in-study data points sets. Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL), confirmed by BG meter) or severe hypoglycaemic episodes (level 3) were presented. Safety Analysis Set (SAS): subjects exposed to randomised treatment. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary
End point timeframe:	
From baseline week 0 (V2) to week 57 (V56)	

End point values	IcoSema	Insulin glargine and insulin aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	340	328		
Units: Episodes				
number (not applicable)	75	745		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Weekly insulin dose (total)

End point title	Weekly insulin dose (total)
End point description:	
Weekly insulin dose (total) from week 50 to week 52 is presented. The end point was evaluated based on data from on-treatment period: 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 subjects exposed to randomised treatment. Overall number of subjects analyzed = subjects with available data for this end point.	
End point type	Secondary
End point timeframe:	
From week 50 (V52) to week 52 (V54)	

End point values	IcoSema	Insulin glargine and insulin aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	306	285		
Units: Units of insulin				
arithmetic mean (standard deviation)	190.5 (± 91.0)	507.4 (± 298.5)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time in range 3.9-10.0 mmol/L (70-180 mg/dL)

End point title	Time in range 3.9-10.0 mmol/L (70-180 mg/dL)
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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 end point 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. Percentage of time in range 3.9-10.0 mmol/L (70-180 mg/dL) using continuous glucose monitoring (CGM) system, Dexcom G6 were presented. FAS comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary
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End point timeframe:

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

End point values	IcoSema	Insulin glargine and insulin aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	268		
Units: Percentage of time				
arithmetic mean (standard deviation)	68.93 (± 20.87)	66.32 (± 17.99)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time spent < 3.0 mmol/L (54 mg/dL)

End point title	Time spent < 3.0 mmol/L (54 mg/dL)
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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 end point 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. Percentage of time spent less than 3.0 mmol/L (54 mg/dL) using CGM system, Dexcom G6 were presented. FAS comprised all randomised subjects. Overall number of subjects analyzed = subjects with

available data for this end point.

End point type	Secondary
End point timeframe:	
From week 48 (V50) to week 52 (V54)	

End point values	IcoSema	Insulin glargine and insulin aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	268		
Units: Percentage of time				
arithmetic mean (standard deviation)	0.20 ( $\pm$ 0.45)	0.48 ( $\pm$ 0.85)		

### Statistical analyses

No statistical analyses for this end point

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

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

DTSQs was used to assess a subject's treatment satisfaction. This questionnaire contained 8 components and measures the treatment for diabetes (including insulin, tablets and/or diet) in terms of convenience, flexibility and general feelings regarding treatment. The value presented is the 'Treatment Satisfaction' summary score, which is the sum of 6 of the 8 items of the DTSQs questionnaire. Response options range from 6 (best case) to 0 (worst case). Total scores for treatment satisfaction range from 0-36. Higher scores indicate higher satisfaction. FAS comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary
End point timeframe:	
From baseline week 0 (V2) to week 52 (V54)	

End point values	IcoSema	Insulin glargine and insulin aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	281	262		
Units: Units on a score				
arithmetic mean (standard deviation)	4.83 ( $\pm$ 8.04)	1.86 ( $\pm$ 7.05)		

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Time spent > 10.0 mmol/L (180 mg/dL)**

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End point title	Time spent > 10.0 mmol/L (180 mg/dL)
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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 end point 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. Percentage of time spent more than 10.0 mmol/L (180 mg/dL) using continuous CGM system, Dexcom G6 were presented. FAS comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

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End point type	Secondary
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End point timeframe:

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

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End point values	IcoSema	Insulin glargine and insulin aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	268		
Units: Percentage of time				
arithmetic mean (standard deviation)	30.3 (± 21.2)	31.9 (± 19.0)		

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**Statistical analyses**

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No statistical analyses for this end point

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**Secondary: Change in fasting plasma glucose (FPG)**

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End point title	Change in fasting plasma glucose (FPG)
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End point description:

Change in FPG from baseline (week 0) to week 52 is presented. The end point 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 comprised all randomised subjects. Overall number of subjects analyzed = subjects with available data for this end point.

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End point type	Secondary
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End point timeframe:

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

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<b>End point values</b>	IcoSema	Insulin glargine and insulin aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	273		
Units: mmol/L				
arithmetic mean (standard deviation)	-1.52 (± 2.80)	-2.17 (± 3.57)		

### 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)
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End point description:

Hypoglycaemic episodes were classified as level 2 if plasma glucose levels were < 3.0 mmol/L (54 mg/dL). The end point was evaluated based on data from on-treatment period: 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. Number of clinically significant hypoglycaemic episodes (level 2) (<3.0 mmol/L (54 mg/dL)) were presented. SAS included all subjects exposed to randomised treatment. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary
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End point timeframe:

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

<b>End point values</b>	IcoSema	Insulin glargine and insulin aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	340	328		
Units: Episodes				
number (not applicable)	71	740		

### 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)
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End point description:

Hypoglycaemic episodes were classified as level 3 if there was no specific glucose threshold but were associated with severe cognitive impairment requiring external assistance for recovery. The end point was evaluated based on data from on-treatment period: 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. Number of severe hypoglycaemic episodes (level 3) were presented. SAS included all subjects exposed to randomised treatment. Overall number of subjects analyzed = subjects with available data for this end point.

End point type	Secondary
End point timeframe:	
From baseline week 0 (V2) to week 57 (V56)	

<b>End point values</b>	IcoSema	Insulin glargine and insulin aspart		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	340	328		
Units: Episodes				
number (not applicable)	4	5		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From baseline (week 0) to week 57

Adverse event reporting additional description:

All the presented adverse events (AEs) are treatment emergent adverse events (TEAEs). TEAE: events that had onset date during on-treatment period, time period in which subjects was considered exposed to trial product. SAS included all subjects exposed to randomised treatment.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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### Reporting groups

Reporting group title	Insulin Glargine & Insulin Aspart
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Reporting group description:

Subjects received subcutaneous injections of 100 U/mL of insulin glargine once daily combined with 100 U/mL of insulin aspart 2-4 times daily with meals for 52 weeks.

Reporting group title	IcoSema
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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 Glargine & Insulin Aspart	IcoSema	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 328 (9.15%)	43 / 340 (12.65%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive lobular breast carcinoma			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung carcinoma cell type unspecified stage I			

subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Vascular disorders</b>			
Accelerated hypertension			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive urgency			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Surgical and medical procedures</b>			
Spinal nerve stimulator removal			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>General disorders and administration site conditions</b>			
Chest discomfort			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gait disturbance			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sudden death			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device loosening			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood lactic acid increased			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cortisol increased			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Anastomotic stenosis			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
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 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 328 (0.00%)	2 / 340 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post-traumatic neck syndrome			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (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	2 / 328 (0.61%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			

subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (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 / 328 (0.30%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fractured base			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular graft stenosis			

subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Congenital, familial and genetic disorders</b>			
Atrial septal defect			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Cardiac disorders</b>			
Aortic valve stenosis			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 328 (0.30%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coronary artery disease			
subjects affected / exposed	0 / 328 (0.00%)	2 / 340 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (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	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 328 (0.61%)	2 / 340 (0.59%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery occlusion			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial syndrome			

subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Focal dyscognitive seizures</b>			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Dizziness</b>			
subjects affected / exposed	1 / 328 (0.30%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Epilepsy</b>			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Facial paresis</b>			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Haemorrhage intracranial</b>			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Ischaemic stroke</b>			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Monoparesis</b>			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Subarachnoid haemorrhage</b>			

subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 328 (0.30%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diabetic retinopathy			
subjects affected / exposed	0 / 328 (0.00%)	2 / 340 (0.59%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiretinal membrane			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye haemorrhage			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular oedema			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic ischaemic neuropathy			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			

subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Retinal aneurysm</b>			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Vitreous haemorrhage</b>			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Gastrointestinal disorders</b>			
<b>Diarrhoea</b>			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Enteritis</b>			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Mesenteric artery thrombosis</b>			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Pancreatitis acute</b>			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Mechanical ileus</b>			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Vomiting</b>			

subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Hepatobiliary disorders</b>			
Cholecystitis			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic steatosis			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Renal and urinary disorders</b>			
Acute kidney injury			
subjects affected / exposed	0 / 328 (0.00%)	2 / 340 (0.59%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 328 (0.00%)	3 / 340 (0.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Musculoskeletal and connective tissue disorders</b>			
Foot deformity			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteoarthritis			
subjects affected / exposed	1 / 328 (0.30%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal pain			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	2 / 328 (0.61%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			

subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Infection</b>		
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Intervertebral discitis</b>		
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Osteomyelitis</b>		
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Pneumonia</b>		
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Post procedural sepsis</b>		
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Sepsis</b>		
subjects affected / exposed	2 / 328 (0.61%)	0 / 340 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
<b>Urosepsis</b>		
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
<b>Wound infection</b>		

subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Metabolism and nutrition disorders</b>			
Dehydration			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 328 (0.30%)	0 / 340 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 328 (0.00%)	2 / 340 (0.59%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	0 / 328 (0.00%)	1 / 340 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Insulin Glargine & Insulin Aspart	IcoSema	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 328 (29.27%)	169 / 340 (49.71%)	
<b>Eye disorders</b>			
Diabetic retinopathy			
subjects affected / exposed	18 / 328 (5.49%)	22 / 340 (6.47%)	
occurrences (all)	22	23	

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 328 (2.44%)	74 / 340 (21.76%)	
occurrences (all)	8	151	
Vomiting			
subjects affected / exposed	9 / 328 (2.74%)	34 / 340 (10.00%)	
occurrences (all)	12	90	
Diarrhoea			
subjects affected / exposed	18 / 328 (5.49%)	43 / 340 (12.65%)	
occurrences (all)	19	68	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	12 / 328 (3.66%)	23 / 340 (6.76%)	
occurrences (all)	16	24	
Infections and infestations			
COVID-19			
subjects affected / exposed	26 / 328 (7.93%)	36 / 340 (10.59%)	
occurrences (all)	26	37	
Upper respiratory tract infection			
subjects affected / exposed	9 / 328 (2.74%)	19 / 340 (5.59%)	
occurrences (all)	14	23	
Nasopharyngitis			
subjects affected / exposed	36 / 328 (10.98%)	33 / 340 (9.71%)	
occurrences (all)	45	49	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 328 (0.30%)	18 / 340 (5.29%)	
occurrences (all)	1	19	

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported