Clinical trial results:
A Phase 3, Parallel-Design, Open-Label, Randomized Control Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared to Insulin Degludec in Insulin Naïve Adults With Type 2 Diabetes

Summary

EudraCT number	2021-005891-21
Trial protocol	GR
Global end of trial date	10 April 2024

Results information

Result version number	v2 (current)
This version publication date	06 June 2025
First version publication date	23 April 2025
Version creation reason	• Correction of full data set Update the incorrect analysis population description for outcomes related to continuous glucose monitoring (CGM) and limitations sections.

Trial information

Trial identification

Sponsor protocol code	I8H-MC-BDCX

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05362058
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 18262

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-285-4559,

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	10 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine the effect and safety of insulin efsitora alfa (LY3209590) compared to degludec in adult participants with type 2 diabetes who are starting basal insulin for the first time.The study consists of a 1-week screening period, a 2-week lead-in period, a 52-week treatment period, and a 5-week safety follow-up period. The study will last up to 60 weeks.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 June 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Brazil: 83
Country: Number of subjects enrolled	Canada: 41
Country: Number of subjects enrolled	China: 134
Country: Number of subjects enrolled	Czechia: 98
Country: Number of subjects enrolled	Germany: 57
Country: Number of subjects enrolled	Greece: 32
Country: Number of subjects enrolled	Japan: 144
Country: Number of subjects enrolled	Mexico: 99
Country: Number of subjects enrolled	Korea, Republic of: 19
Country: Number of subjects enrolled	United States: 221
Worldwide total number of subjects	928
EEA total number of subjects	187

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)	672
From 65 to 84 years	256
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants continued their protocol-specified stable therapy with 1 to 3 non-insulin antihyperglycemic medications, including glucagon-like peptide-1 (GLP-1) receptor agonists (RA), as well as non-GLP-1 receptor agonists such as dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, (Continued..)

Pre-assignment

Screening details:

biguanides (e.g., metformin), alpha-glucosidase inhibitors, sulfonylureas (SUs), or thiazolidinediones throughout the study, at the discretion of the investigator.

Period 1

Period 1 title	Treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	500 U/mL - Insulin Efsitora Alfa

Arm description:

Participants received 500 units per milliliter (U/mL) of insulin efsitora alfa administered subcutaneously (SC) once weekly (QW) over a 52-week treatment period, followed by a 5-week safety follow-up period.

Arm type	Experimental
Investigational medicinal product name	Insulin Efsitora Alfa
Investigational medicinal product code	
Other name	LY3209590, Basal Insulin-FC
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 500 U/mL insulin efsitora alfa administered SC QW.

Arm title	100 U/mL - Insulin Degludec

Arm description:

Participants received 100 U/mL insulin degludec administered SC once daily (QD) over a 52-week treatment period, followed by a 5-week safety follow-up period.

Arm type	Active comparator
Investigational medicinal product name	Insulin Degludec
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 100 U/mL insulin degludec administered SC QD.

Number of subjects in period 1	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec
Started	466	462
Participants Using GLP-1 RA	232	232
Participants Not Using GLP-1 RA	234	230
Received at least 1 dose of study drug	466	462
Completed	441	439
Not completed	25	23
Assigned treatment by mistake	3	4
Physician decision	1	-
Consent withdrawn by subject	10	11
Adverse event, non-fatal	3	3
Death	1	1
Non-compliance with study drug	-	1
Lost to follow-up	6	3
Protocol deviation	1	-

Period 2

Period 2 title	Follow-Up Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	500 U/mL - Insulin Efsitora Alfa

Arm description:

Participants who received 500 U/mL insulin efsitora alfa administered SC QW in the treatment period were required to complete a safety follow-up period, and participants who discontinued the study treatment prematurely were encouraged to remain in the study for safety monitoring.

Arm type	Experimental
Investigational medicinal product name	Insulin Efsitora Alfa
Investigational medicinal product code	
Other name	LY3209590, Basal Insulin-FC
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 500 U/mL insulin efsitora alfa administered SC QW.

Arm title	100 U/mL - Insulin Degludec

Arm description:

Participants who received 100 U/mL insulin degludec administered SC QD in the treatment period were required to complete a safety follow-up period and participants who discontinued the study treatment prematurely were encouraged to remain in the study for safety monitoring.

Arm type	Active comparator

Investigational medicinal product name	Insulin Degludec
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

Participants received 100 U/mL insulin degludec administered SC QD.

Number of subjects in period 2	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec
Started	445	444
Completed	441	439
Not completed	4	5
Consent withdrawn by subject	-	3
Death	1	-
Lost to follow-up	2	1
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	500 U/mL - Insulin Efsitora Alfa
Reporting group description:	
Participants received 500 units per milliliter (U/mL) of insulin efsitora alfa administered subcutaneously (SC) once weekly (QW) over a 52-week treatment period, followed by a 5-week safety follow-up period.	
Reporting group title	100 U/mL - Insulin Degludec
Reporting group description:	
Participants received 100 U/mL insulin degludec administered SC once daily (QD) over a 52-week treatment period, followed by a 5-week safety follow-up period.	

Reporting group values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec	Total
Number of subjects	466	462	928
Age categorical			
Analysis Population Description (APD): All randomized participants.			
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)	331	341	672
From 65-84 years	135	121	256
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	185	197	382
Male	281	265	546
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	119	123	242
Not Hispanic or Latino	345	335	680
Unknown or Not Reported	2	4	6
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	34	36	70
Asian	163	164	327
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	31	27	58
White	235	233	468
More than one race	3	2	5
Unknown or Not Reported	0	0	0
Region of Enrollment			
Units: Subjects			
Brazil	40	43	83

Canada	18	23	41
China	67	67	134
Czechia	48	50	98
Germany	30	27	57
Greece	17	15	32
Japan	71	73	144
Mexico	50	49	99
South Korea	11	8	19
United States	114	107	221
HemoglobinA1c (HbA1c)			
HbA1c is the glycosylated fraction of hemoglobin A. It is measured to identify average plasma glucose concentration over prolonged periods of time.			
Units: Percentage of HbA1c			
arithmetic mean	8.21	8.23	
standard deviation	± 0.96	± 0.96	-

End points

End points reporting groups

Reporting group title	500 U/mL - Insulin Efsitora Alfa
Reporting group description:	
Participants received 500 units per milliliter (U/mL) of insulin efsitora alfa administered subcutaneously (SC) once weekly (QW) over a 52-week treatment period, followed by a 5-week safety follow-up period.	
Reporting group title	100 U/mL - Insulin Degludec
Reporting group description:	
Participants received 100 U/mL insulin degludec administered SC once daily (QD) over a 52-week treatment period, followed by a 5-week safety follow-up period.	
Reporting group title	500 U/mL - Insulin Efsitora Alfa
Reporting group description:	
Participants who received 500 U/mL insulin efsitora alfa administered SC QW in the treatment period were required to complete a safety follow-up period, and participants who discontinued the study treatment prematurely were encouraged to remain in the study for safety monitoring.	
Reporting group title	100 U/mL - Insulin Degludec
Reporting group description:	
Participants who received 100 U/mL insulin degludec administered SC QD in the treatment period were required to complete a safety follow-up period and participants who discontinued the study treatment prematurely were encouraged to remain in the study for safety monitoring.	

Primary: Change From Baseline in HbA1c at Week 52 [Noninferiority Analysis]

End point title	Change From Baseline in HbA1c at Week 52 [Noninferiority Analysis]
End point description:	
HbA1c is the glycosylated fraction of hemoglobin A. It is measured to identify average plasma glucose concentration over prolonged periods of time.Least Squares (LS) mean was determined using Analysis of Covariance (ANCOVA) model with Baseline + Country + GLP-1 RA Use at Randomization Flag + SU Use at Randomization Flag + Treatment (Type III sum of squares) as variables. Missing data at Week 52 were imputed by return-to-baseline multiple imputations approach. APD:All randomized participants who received at least one dose of the study drug and had HbA1c measurement at baseline or Week 52. Participants who discontinued the study drug due to inadvertent enrollment were excluded.	
End point type	Primary
End point timeframe:	
Baseline, Week 52	

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	463	458		
Units: millimoles per mole (mmol/mol)				
least squares mean (standard error)	-13.75 (± 0.514)	-12.79 (± 0.517)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	921
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.39
upper limit	0.47

Notes:

[1] - The noninferiority margin (NIM) of 0.4% is equivalent to a NIM of 4.372 mmol/mol.

Secondary: Change From Baseline in HbA1c at Week 52 in Participants Using GLP-1 Receptor Agonists [Noninferiority Analysis]

End point title	Change From Baseline in HbA1c at Week 52 in Participants Using GLP-1 Receptor Agonists [Noninferiority Analysis]

End point description:

HbA1c is the glycosylated fraction of hemoglobin A. It is measured to identify average plasma glucose concentration over prolonged periods of time.LS mean was determined using ANCOVA model with Baseline + Country + SU Use at Randomization Flag + Treatment (Type III sum of squares) as variables. Missing data at Week 52 were imputed by return-to-baseline multiple imputations approach. APD:All randomized participants who continued using GLP-1 receptor agonists and received at least one dose of the study drug, had HbA1c measurement at baseline or Week 52. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	230	231		
Units: millimoles per mole (mmol/mol)				
least squares mean (standard error)	-13.73 (± 0.764)	-13.04 (± 0.761)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec

Number of subjects included in analysis	461
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.81
upper limit	1.42

Notes:

[2] - The noninferiority margin (NIM) of 0.4% is equivalent to a NIM of 4.372 mmol/mol.

Secondary: Change From Baseline in HbA1c at Week 52 in Participants Not Using GLP-1 Receptor Agonists [Noninferiority Analysis]

End point title	Change From Baseline in HbA1c at Week 52 in Participants Not Using GLP-1 Receptor Agonists [Noninferiority Analysis]

End point description:

HbA1c is the glycosylated fraction of hemoglobin A. It is measured to identify average plasma glucose concentration over prolonged periods of time. LS mean was determined using ANCOVA model with Baseline + Country + SU Use at Randomization Flag + Treatment (Type III sum of squares) as variables. Missing data at Week 52 were imputed by return-to-baseline multiple imputations approach. APD: All randomized participants who were not using GLP-1 receptor agonists and received at least one dose of the study drug, had HbA1c measurement at baseline or Week 52. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	233	227		
Units: millimoles per mole (mmol/mol)				
least squares mean (standard error)	-13.74 (± 0.686)	-12.55 (± 0.698)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec

Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.11
upper limit	0.72

Notes:

[3] - The noninferiority margin (NIM) of 0.4% is equivalent to a NIM of 4.372 mmol/mol.

Secondary: Change From Baseline in HbA1c at Week 52 [Superiority Analysis]

End point title	Change From Baseline in HbA1c at Week 52 [Superiority Analysis]

End point description:

HbA1c is the glycosylated fraction of hemoglobin A. It is measured to identify average plasma glucose concentration over prolonged periods of time. LS mean was determined using ANCOVA model with Baseline + Country + GLP-1 RA Use at Randomization Flag + SU Use at Randomization Flag + Treatment (Type III sum of squares) as variables. Missing data at Week 52 were imputed by return-to-baseline multiple imputations approach. APD: All randomized participants who received at least one dose of the study drug and had HbA1c measurement at baseline or Week 52. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	463	458		
Units: millimoles per mole (mmol/mol)				
least squares mean (standard error)	-13.75 (± 0.514)	-12.79 (± 0.517)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	921
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.188
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.96

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.39
upper limit	0.47

Secondary: Percentage of Time in the Blood Glucose Range Between 70 and 180 mg/dL [3.9 and 10.0 mmol/L] - Week 48 to Week 52

End point title	Percentage of Time in the Blood Glucose Range Between 70 and 180 mg/dL [3.9 and 10.0 mmol/L] - Week 48 to Week 52

End point description:

Percentage of time spent within the blood glucose range of 70 to 180 milligrams per deciliter (mg/dL) [3.9 to 10.0 millimoles per liter (mmol/L)], as measured during the continuous glucose monitoring (CGM) session over a 24-hour period, from Week 48 to Week 52. APD: All randomized participants who took at least 1 dose of the study drug and had CGM data collected using the Dexcom G6 system at baseline or Week 48-52 were included. Participants who discontinued the study drug due to inadvertent enrollment were excluded. As pre-specified in the statistical analysis plan, outcome data were analyzed only from CGM data collected by the Dexcom G6 system.

End point type	Secondary

End point timeframe:

Week 48 to Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	387	381		
Units: Percentage of time				
least squares mean (standard error)	64.27 (± 1.076)	61.18 (± 1.085)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

LS mean was determined using ANCOVA model with Baseline + Country + HbA1c Stratum at Baseline + GLP-1 RA Use at Randomization + SU Use at Randomization + Treatment (Type III sum of squares) as variables. Missing data at baseline were imputed using multiple imputation under the assumption of missing at random, while missing data at Week 48-52 were imputed using a return-to-baseline multiple imputation approach.

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	768
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	3.09

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.09
upper limit	6.08

Secondary: Change From Baseline in HbA1c at Week 26 [Superiority Analysis]

End point title	Change From Baseline in HbA1c at Week 26 [Superiority Analysis]

End point description:

HbA1c is the glycosylated fraction of hemoglobin A. It is measured to identify average plasma glucose concentration over prolonged periods of time. LS mean was determined using ANCOVA model with Baseline + Country + GLP-1 RA Use at Randomization Flag + SU Use at Randomization Flag + Treatment (Type III sum of squares) as variables. Missing data at Week 26 were imputed by return-to-baseline multiple imputations approach. APD: All randomized participants who received at least one dose of the study drug and had HbA1c measurement at baseline or Week 26. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 26

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	463	458		
Units: millimoles per mole (mmol/mol)				
least squares mean (standard error)	-14.95 (± 0.431)	-14.26 (± 0.434)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	921
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.26
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.89
upper limit	0.51

Secondary: Percentage of Time in the Blood Glucose Range Between 70 and 180 mg/dL [3.9 and 10.0 mmol/L] - Week 22 to Week 26

End point title	Percentage of Time in the Blood Glucose Range Between 70 and 180 mg/dL [3.9 and 10.0 mmol/L] - Week 22 to Week 26

End point description:

Percentage of time spent within the blood glucose range of 70 to 180 mg/dL (3.9 to 10.0 mmol/L), as measured during the CGM session over a 24-hour period, from Week 22 to Week 26. APD: All randomized participants who took at least 1 dose of the study drug and had CGM data collected using the Dexcom G6 system at baseline or Week 22-26 were included. Participants who discontinued the study drug due to inadvertent enrollment were excluded. As pre-specified in the statistical analysis plan, outcome data were analyzed only from CGM data collected by the Dexcom G6 system.

End point type	Secondary

End point timeframe:

Week 22 to Week 26

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	385	382		
Units: Percentage of time				
least squares mean (standard error)	66.12 (± 0.991)	65.85 (± 0.990)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

LS mean was determined using ANCOVA model with Baseline + Country + HbA1c Stratum at Baseline + GLP-1 RA Use at Randomization + SU Use at Randomization + Treatment (Type III sum of squares) as variables. Missing data at baseline were imputed using multiple imputation under the assumption of missing at random, while missing data at Week 22-26 were imputed using a return-to-baseline multiple imputation approach.

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	767
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.848
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.48
upper limit	3.02

Secondary: Change From Baseline in Fasting Blood Glucose (FBG)

End point title	Change From Baseline in Fasting Blood Glucose (FBG)

End point description:

Change from baseline in fasting blood glucose measured by self-monitoring blood glucose (SMBG). APD: All randomized participants who received at least one dose of the study drug and had evaluable data for this outcome at Baseline, Week 26, or Week 52 were included in the analysis. For the Week 26 analysis, data from Baseline and Week 26 were considered, while for the Week 52 analysis, data from Baseline and Week 52 were included. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 26, Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	458[4]	451[5]		
Units: millimoles per liter (mmol/L)				
least squares mean (standard error)				
Week 26	-3.21 (± 0.083)	-3.50 (± 0.083)		
Week 52	-3.32 (± 0.078)	-3.33 (± 0.078)		

Notes:

[4] - Number of subjects analysed (n) at Week 26 = 458 and Week 52 = 458

[5] - Number of subjects analysed (n) at Week 26 = 451 and Week 52 = 448

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 26 (Statistical Analysis) - LS mean was determined using ANCOVA model with Baseline + Country + HbA1c Stratum at Baseline + GLP-1 RA Use at Randomization + SU Use at Randomization + Treatment (Type III sum of squares) as variables. Missing data at Baseline were imputed with multiple imputation with assumption of missing at random. Missing data at week 26 were imputed by return-to-baseline multiple imputations approach.

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	0.52

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Week 52 (Statistical Analysis) - Total number of subjects analysed (N) for this outcome = 906. LS mean was determined using ANCOVA model with Baseline + Country + HbA1c Stratum at Baseline + GLP-1 RA Use at Randomization + SU Use at Randomization + Treatment (Type III sum of squares) as variables. Missing data at Baseline were imputed with multiple imputation with assumption of missing at random. Missing data at week 52 were imputed by return-to-baseline multiple imputations approach.

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	909
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.918
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.23

Secondary: Glucose Variability

End point title	Glucose Variability

End point description:

Glucose variability measured as coefficient of variation (CV) for blood glucose during the CGM session over a 24-hour period, between Week 22 to Week 26 and Week 48 to Week 52 was reported.LS mean was determined using Mixed Model Repeated Measures (MMRM) model with Baseline + Country +HbA1c Stratum at Baseline + GLP-1 RA Use at Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. APD: All randomized participants who took at least 1 dose of the study drug and had Dexcom G6 system CGM data collected at baseline and at least 1 post-baseline value were included. Participants who discontinued the study drug due to inadvertent enrollment were excluded. As pre-specified in the statistical analysis plan, outcome data were analyzed only from CGM data collected by the Dexcom G6 system.

End point type	Secondary

End point timeframe:

Week 22 to Week 26 and Week 48 to Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	368	360		
Units: Percentage of CV				
least squares mean (standard error)				
Week 22 to Week 26	26.31 (± 0.250)	26.67 (± 0.251)		
Week 48 to Week 52	26.29 (± 0.243)	26.81 (± 0.246)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Week 22 to Week 26 (Statistical Analysis)	
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.06
upper limit	0.34

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Week 48 to Week 52 (Statistical Analysis)	
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.138
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.19
upper limit	0.17

Secondary: Basal Insulin Dose

End point title	Basal Insulin Dose

End point description:

The insulin dose was calculated based on the participant's entry of daily or weekly insulin doses in an electronic diary. The average weekly basal insulin dose at Week 26 and Week 52 was reported.
LS mean was determined using MMRM model with Country + HbA1c Stratum at Baseline + GLP-1 RA Use at Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. APD: All randomized participants who received at least one dose of the study drug and had a baseline and at least one post-baseline value for this outcome.Participants who discontinued the study drug due to inadvertent enrollment were excluded.

End point type	Secondary

End point timeframe:

Week 26 and Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	463	457		
Units: Units per week (U/week)				
least squares mean (standard error)				
Week 26	292.8 (± 6.30)	305.9 (± 6.17)		
Week 52	314.7 (± 6.25)	334.4 (± 6.22)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 26 (Statistical Analysis)

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	920
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.136
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-13.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.5
upper limit	4.1

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Week 52 (Statistical Analysis)	
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	920
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-19.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-37
upper limit	-2.4

Secondary: Hypoglycemia Event Rate

End point title	Hypoglycemia Event Rate
End point description: A hypoglycemic event with blood glucose (BG) levels of less than (<) 54 mg/dL (3.0 mmol/L) [Level 2] or Severe Hypoglycemia [Level 3] was reported. A severe hypoglycemic event was characterized by altered mental or physical status, requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions for the treatment of hypoglycemia. Group mean was reported and determined by Negative binomial model using Number of episodes = HbA1c at Baseline (%) + Treatment, with log (exposure in days/365.25) as an offset variable. APD:All randomized participants who received at least one dose of the study drug.	
End point type	Secondary
End point timeframe: Baseline up to Week 52	

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	466	462		
Units: Events per participant-year of exposure				
arithmetic mean (standard error)	0.58 (± 0.062)	0.45 (± 0.058)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec

Number of subjects included in analysis	928
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.111
Method	Negative binomial model
Parameter estimate	Relative Rate
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.78

Secondary: Nocturnal Hypoglycemia Event Rate

End point title	Nocturnal Hypoglycemia Event Rate

End point description:

The event rate of participant-reported clinically significant nocturnal hypoglycemia (defined as blood glucose level <54 mg/dL (3.0 mmol/L) or severe hypoglycemia and occurs at night and presumably during sleep between midnight and 6:00 AM), measured during treatment phase up to week 52. Group mean was reported and determined by Negative binomial model using Number of episodes = HbA1c at Baseline (%) + Treatment, with log (exposure in days/365.25) as an offset variable. APD: All randomized participants who received at least one dose of the study drug.

End point type	Secondary

End point timeframe:

Baseline up to Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	466	462		
Units: Events per participant-year of exposure				
arithmetic mean (standard error)	0.08 (± 0.018)	0.08 (± 0.018)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	928
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.983
Method	Negative binomial model
Parameter estimate	Relative Rate
Point estimate	1.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.89

Secondary: Change From Baseline in Body Weight

End point title	Change From Baseline in Body Weight

End point description:

Change from baseline in body weight was reported. LS mean was determined by MMRM model with Baseline + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. APD:All randomized participants who received at least one dose of the study drug, had a baseline and at least one post- baseline value for this outcome were included.

End point type	Secondary

End point timeframe:

Baseline, Week 26, Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	465	461		
Units: Kilogram (kg)				
least squares mean (standard error)				
Change from Baseline at Week 26	3.16 (± 0.158)	2.66 (± 0.158)		
Change from Baseline at Week 52	3.60 (± 0.158)	3.54 (± 0.159)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Change from Baseline at Week 26 (Statistical Analysis)

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	926
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.064
upper limit	0.94

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Change from Baseline at Week 52 (Statistical Analysis)	
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	926
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.801
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.056
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.38
upper limit	0.5

Secondary: Percentage of Time in Hypoglycemia Range With Blood Glucose <70 mg/dL (3.9 mmol/L)

End point title	Percentage of Time in Hypoglycemia Range With Blood Glucose <70 mg/dL (3.9 mmol/L)

End point description:

Percentage of time spent in the hypoglycemia range with blood glucose <70 mg/dL (3.9 mmol/L), as measured during the CGM session over a 24-hour period from Week 8 to Week 12, Week 22 to Week 26, and Week 48 to Week 52 was reported.LS mean was determined using MMRM model with Baseline + HbA1c Stratum at Baseline + Country + GLP-1 RA Use at Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. APD: All randomized participants who took at least 1 dose of the study drug and had Dexcom G6 system CGM data collected at baseline and at least 1 post-baseline value were included. Participants who discontinued the study drug due to inadvertent enrollment were excluded. As pre-specified in the statistical analysis plan, outcome data were analyzed only from CGM data collected by the Dexcom G6 system.

End point type	Secondary

End point timeframe:

Week 8 to Week 12, Week 22 to Week 26 and Week 48 to Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	368	360		
Units: Percentage of time				
least squares mean (standard error)				
Week 8 to Week 12	1.06 (± 0.101)	0.93 (± 0.103)		
Week 22 to Week 26	1.55 (± 0.137)	1.25 (± 0.137)		
Week 48 to Week 52	1.49 (± 0.150)	1.19 (± 0.152)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Week 8 to Week 12 (Statistical Analysis)	
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.374
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.41

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Week 22 to Week 26 (Statistical Analysis)	
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0.67

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Week 48 to Week 52 (Statistical Analysis)	
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec

Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.162
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.72

Secondary: Percentage of Time in Hypoglycemia Range With Blood Glucose <54 mg/dL (3.0 mmol/L)

End point title	Percentage of Time in Hypoglycemia Range With Blood Glucose <54 mg/dL (3.0 mmol/L)

End point description:

Percentage of time spent in the hypoglycemia range with blood glucose < 54 mg/dL (3.0 mmol/L), as measured during the CGM session over a 24-hour period from Week 8 to Week 12, Week 22 to Week 26, and Week 48 to Week 52, was reported.LS mean was determined using MMRM model with Baseline + HbA1c Stratum at Baseline + Country + GLP-1 RA Use at Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. APD: All randomized participants who took at least 1 dose of the study drug and had Dexcom G6 system CGM data collected at baseline and at least 1 post-baseline value were included. Participants who discontinued the study drug due to inadvertent enrollment were excluded. As pre-specified in the statistical analysis plan, outcome data were analyzed only from CGM data collected by the Dexcom G6 system.

End point type	Secondary

End point timeframe:

Week 8 to Week 12, Week 22 to Week 26 and Week 48 to Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	368	360		
Units: Percentage of time				
least squares mean (standard error)				
Week 8 to Week 12	0.24 (± 0.041)	0.27 (± 0.041)		
Week 22 to Week 26	0.33 (± 0.037)	0.28 (± 0.037)		
Week 48 to Week 52	0.32 (± 0.043)	0.30 (± 0.043)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description: Week 8 to Week 12 (Statistical Analysis)	
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.594
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.08

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Week 22 to Week 26 (Statistical Analysis)	
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.266
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.04
upper limit	0.16

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Week 48 to Week 52 (Statistical Analysis)	
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.791
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.02

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.14

Secondary: Percentage of Time in Hyperglycemia Range With Blood Glucose >180 mg/dL (10.0 mmol/L)

End point title	Percentage of Time in Hyperglycemia Range With Blood Glucose >180 mg/dL (10.0 mmol/L)

End point description:

Percentage of time spent in the hyperglycemia range with blood glucose greater than (>) 180 mg/dL (10.0 mmol/L), as measured during the CGM session over a 24-hour period from Week 8 to Week 12, Week 22 to Week 26, and Week 48 to Week 52 was reported. LS mean was determined using MMRM model with Baseline + HbA1c Stratum at Baseline + Country + GLP-1 RA Use at Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. APD:All randomized participants who took at least 1 dose of the study drug and had Dexcom G6 system CGM data collected at baseline and at least 1 post-baseline value were included. Participants who discontinued the study drug due to inadvertent enrollment were excluded. As pre-specified in the statistical analysis plan, outcome data were analyzed only from CGM data collected by the Dexcom G6 system.

End point type	Secondary

End point timeframe:

Week 8 to Week 12, Week 22 to Week 26 and Week 48 to Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	368	360		
Units: Percentage of time				
least squares mean (standard error)				
Week 8 to Week 12	31.99 (± 0.925)	32.40 (± 0.939)		
Week 22 to Week 26	28.93 (± 0.999)	29.87 (± 1.007)		
Week 48 to Week 52	29.66 (± 1.074)	33.05 (± 1.086)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 8 to Week 12 (Statistical Analysis)

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec

Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.757
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	2.18

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Week 22 to Week 26 (Statistical Analysis)	
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.511
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.72
upper limit	1.85

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Week 48 to Week 52 (Statistical Analysis)	
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	728
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-3.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.39
upper limit	-0.39

Secondary: Change From Baseline in Treatment-Related Impact Measures for Diabetes (TRIM-D) -Total Score at Week 26 and Week 52

End point title	Change From Baseline in Treatment-Related Impact Measures for Diabetes (TRIM-D) -Total Score at Week 26 and Week 52

End point description:

The TRIM-D is a participant-reported measure designed to assess the impact of diabetes treatment on individuals' functioning and well-being across different diabetes treatments. The questionnaire includes 28 items grouped into 5 sub-domains: treatment burden, daily life, diabetes management, compliance, and psychological health. Each item is assessed on a 5-point scale, with higher scores indicating better health status. All items were summed to obtain a total raw score, which was transformed to a scale of 0 to 100 to obtain a total score. The total score range is 0-100, with a higher total score indicating better overall health and well-being, while a lower total score indicates worse health or well-being. APD:All randomized participants who received at least one dose of the study drug, had a baseline and at least one post- baseline value for this outcome.Participants who discontinued the study drug due to inadvertent enrollment were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 26, Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	445		
Units: score on a scale				
least squares mean (standard error)				
Week 26	8.84 (± 0.507)	7.18 (± 0.507)		
Week 52	8.82 (± 0.519)	6.81 (± 0.517)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Week 26 (Statistical Analysis) -LS mean was determined using MMRM model with Baseline + Country + HbA1c Stratum at Baseline + GLP-1 RA Use at Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables.

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	889
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.021
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	1.66

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	3.07

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Week 52 (Statistical Analysis) -LS mean was determined using MMRM model with Baseline + Country + HbA1c Stratum at Baseline + GLP-1 RA Use at Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables.

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	889
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	3.44

Secondary: Change From Baseline in Short Form-36 Health Survey Version 2 (SF-36v2) Acute Form (Physical-Component and Mental-Component) Scores at Week 26 and Week 52

End point title	Change From Baseline in Short Form-36 Health Survey Version 2 (SF-36v2) Acute Form (Physical-Component and Mental-Component) Scores at Week 26 and Week 52

End point description:

The SF-36v2 is a participant-reported measure designed to assess health status using 36 items across 8 domains: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health. Each domain is scored individually, and information from these 8 domains is further aggregated into 2 health component summary scores, the Physical Component Summary and Mental Component Summary. Scoring of each domain and both summary scores are norm based and presented in the form of T-scores, with a mean of 50 and a standard deviation of 10. Higher scores indicate better levels of function and/or better health. Range cannot be specified in norm-based scores. APD:All randomized participants who received at least one dose of the study drug, had a baseline and at least one post- baseline value for this outcome.Participants who discontinued the study drug due to inadvertent enrollment were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 26, Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	431	434		
Units: T-score				
least squares mean (standard error)				
Physical Component Score at Week 26	0.29 (± 0.344)	0.49 (± 0.345)		
Mental Component Score at Week 26	0.018 (± 0.380)	0.34 (± 0.381)		
Physical Component Score at Week 52	0.027 (± 0.349)	-0.14 (± 0.351)		
Mental Component Score at Week 52	0.014 (± 0.386)	0.25 (± 0.389)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Physical Component Score at Week 26 (Statistical Analysis) -LS mean was determined using MMRM model with Baseline + HbA1c Stratum at Baseline + Country + GLP-1 RA Use at Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables.

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	865
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.638
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.03
upper limit	0.63

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Mental Component Score at Week 26 (Statistical Analysis) - LS mean was determined using MMRM model with Baseline + HbA1c Stratum at Baseline + Country + GLP-1 RA Use at Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables.

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec

Number of subjects included in analysis	865
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.499
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.24
upper limit	0.6

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

Physical Component Score at Week 52 (Statistical Analysis) - LS mean was determined using MMRM model with Baseline + HbA1c Stratum at Baseline + Country + GLP-1 RA Use at Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables.

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	865
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.695
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.68
upper limit	1.01

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

Mental Component Score at Week 52 (Statistical Analysis) -LS mean was determined using MMRM model with Baseline + HbA1c Stratum at Baseline + Country + GLP-1 RA Use at Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables.

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	865
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.626
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	0.71

Secondary: Change from Baseline in EuroQuality of Life (EuroQol) -5 Dimensions-5 Levels (EQ-5D-5L) Health State Index and EQ visual analog scale (VAS) Scores at Week 26 and Week 52

End point title	Change from Baseline in EuroQuality of Life (EuroQol) -5 Dimensions-5 Levels (EQ-5D-5L) Health State Index and EQ visual analog scale (VAS) Scores at Week 26 and Week 52

End point description:

The EQ-5D-5L is a multidimensional, health-related, quality-of-life instrument. It includes 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that are assessed at 5 levels of response (no problems, slight problems, moderate problems, severe problems, and unable to perform or extreme problems). A single health- state index value was derived, which ranges from less than 0 (health state equivalent to death, negative values are valued as worse than death) to 1 (perfect health). The EQ VAS rates the participants' perceived health from 0 (the worst imaginable health) to 100 (the best imaginable health). This score provides a composite picture of the respondent's health status. APD:All randomized participants who received at least one dose of the study drug, had a baseline and at least one post- baseline value for this outcome.Participants who discontinued the study drug due to inadvertent enrollment were excluded.

End point type	Secondary

End point timeframe:

Baseline, Week 26, Week 52

End point values	500 U/mL - Insulin Efsitora Alfa	100 U/mL - Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	430	434		
Units: Score on a scale				
least squares mean (standard error)				
EQ-5D-5L Health State Index Score at Week 26	-0.018 (± 0.0078)	-0.004 (± 0.0078)		
EQ VAS Score at Week 26	1.07 (± 0.701)	2.18 (± 0.699)		
EQ-5D-5L Health State Index Score at Week 52	-0.018 (± 0.0077)	-0.008 (± 0.0077)		
EQ VAS Score at Week 52	1.56 (± 0.733)	1.91 (± 0.739)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

EQ-5D-5L Health State Index Score at Week 26 (Statistical Analysis) - LS mean was determined using MMRM model with Baseline + HbA1c Stratum at Baseline + Country + GLP-1 RA Use Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables.

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	864
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.128
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.015
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.034
upper limit	0.004

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
EQ VAS Score at Week 26 (Statistical Analysis) - LS mean was determined using MMRM model with Baseline + HbA1c Stratum at Baseline + Country + GLP-1 RA Use Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables.	
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	864
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.196
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	0.58

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
EQ-5D-5L Health State Index Score at Week 52 (Statistical Analysis) - LS mean was determined using MMRM model with Baseline + HbA1c Stratum at Baseline + Country + GLP-1 RA Use Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables.	
Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	864
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.285
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.01

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.029
upper limit	0.008

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

EQ VAS Score at Week 52 (Statistical Analysis) - LS mean was determined using MMRM model with Baseline + HbA1c Stratum at Baseline + Country + GLP-1 RA Use Randomization Flag + SU Use at Randomization Flag + Treatment + Time + Treatment*Time (Type III sum of squares) as variables.

Comparison groups	500 U/mL - Insulin Efsitora Alfa v 100 U/mL - Insulin Degludec
Number of subjects included in analysis	864
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.701
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.15
upper limit	1.44

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to end of follow-up (up to 57 weeks)

Adverse event reporting additional description:

All randomized participants who received at least one dose of study drug. Participants were analyzed based on the actual treatment they received. Gender specific events only occurring in male or female participants have had the number of participants At Risk adjusted accordingly.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	100 U/mL - Insulin Degludec

Reporting group description:

Participants received 100 U/mL insulin degludec administered SC QD over a 52-week treatment period, followed by a 5-week safety follow-up period.

Reporting group title	500 U/mL - Insulin Efsitora Alfa

Reporting group description:

Participants received 500 U/mL insulin efsitora alfa administered SC QW over a 52-week treatment period, followed by a 5-week safety follow-up period.

Serious adverse events	100 U/mL - Insulin Degludec	500 U/mL - Insulin Efsitora Alfa	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 462 (8.23%)	41 / 466 (8.80%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
bladder cancer			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
benign spleen tumour			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
basal cell carcinoma			

alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
clear cell renal cell carcinoma			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
colorectal adenocarcinoma			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
diffuse large b-cell lymphoma			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hormone receptor positive breast cancer			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
rectal adenocarcinoma			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancreatic neoplasm			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pancreatic carcinoma metastatic			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 462 (0.43%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
phlebitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral arterial occlusive disease			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
varicose vein			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
cardiac pacemaker insertion			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholecystectomy			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
coronary artery bypass			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
chest pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 462 (0.43%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
death			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
impaired healing			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (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			
abnormal uterine bleeding			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed[1]	0 / 197 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
benign prostatic hyperplasia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed[2]	0 / 265 (0.00%)	1 / 281 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
endometrial hyperplasia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed[3]	0 / 197 (0.00%)	1 / 185 (0.54%)	
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			
dyspnoea			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
cervical vertebral fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
clavicle fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ligament sprain			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
lumbar vertebral fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
meniscus injury			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 462 (0.43%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
traumatic renal injury			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
tibia fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
road traffic accident			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
rib fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
angina unstable			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
angina pectoris			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
acute myocardial infarction			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 462 (0.43%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
arteriosclerosis coronary artery			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 462 (0.65%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac arrest			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
cardiac failure			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiac ventricular thrombosis			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrioventricular block complete			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
coronary artery disease			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
coronary artery stenosis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
microvascular coronary artery disease			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
myocardial infarction			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	2 / 466 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
hypoglycaemic coma			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
intracranial aneurysm			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ischaemic stroke			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
peripheral nerve lesion			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
transient ischaemic attack			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
vertebrobasilar insufficiency			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
vertigo positional			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
glaucoma			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
rhegmatogenous retinal detachment			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
retinal ischaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 462 (0.65%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
intestinal polyp			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
large intestine polyp			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (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			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholelithiasis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	2 / 466 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
cholecystitis acute			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 462 (0.43%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
calculus urinary			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
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			
cervical spinal stenosis			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
chondropathy			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
intervertebral disc protrusion			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
lumbar spinal stenosis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteoarthritis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	4 / 462 (0.87%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteonecrosis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
spinal stenosis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
appendicitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
cellulitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
covid-19 pneumonia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
arthritis bacterial			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
chronic tonsillitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
diverticulitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyelonephritis acute			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pyelonephritis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
postoperative wound infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia bacterial			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
pilonidal disease			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 462 (0.22%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
urosepsis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 462 (0.00%)	1 / 466 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Metabolism and nutrition disorders hypoglycaemia alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	5 / 462 (1.08%)	0 / 466 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Gender-specific events occurring only in female participants have had the number of participants at risk adjusted accordingly.
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Gender-specific events occurring only in male participants have had the number of participants at risk adjusted accordingly.
[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Gender-specific events occurring only in female participants have had the number of participants at risk adjusted accordingly.

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

Non-serious adverse events	100 U/mL - Insulin Degludec	500 U/mL - Insulin Efsitora Alfa	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	224 / 462 (48.48%)	195 / 466 (41.85%)	
Investigations weight increased alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	20 / 462 (4.33%)	28 / 466 (6.01%)	
occurrences (all)	20	30	
Injury, poisoning and procedural complications drug titration error alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	55 / 462 (11.90%)	33 / 466 (7.08%)	
occurrences (all)	86	58	
Nervous system disorders headache alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	28 / 462 (6.06%)	21 / 466 (4.51%)	
occurrences (all)	47	30	
Gastrointestinal disorders diarrhoea alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	32 / 462 (6.93%)	31 / 466 (6.65%)	
occurrences (all)	48	36	
nausea			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	26 / 462 (5.63%)	26 / 466 (5.58%)	
occurrences (all)	29	27	
Infections and infestations			
covid-19			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	51 / 462 (11.04%)	37 / 466 (7.94%)	
occurrences (all)	51	38	
influenza			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	26 / 462 (5.63%)	18 / 466 (3.86%)	
occurrences (all)	31	22	
nasopharyngitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	41 / 462 (8.87%)	43 / 466 (9.23%)	
occurrences (all)	50	50	
upper respiratory tract infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	46 / 462 (9.96%)	37 / 466 (7.94%)	
occurrences (all)	63	52	
urinary tract infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	29 / 462 (6.28%)	17 / 466 (3.65%)	
occurrences (all)	35	20	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Outcome analyses related to Continuous Glucose Monitoring (CGM) were conducted using data from the Dexcom G6 system, which was used at all study sites except those in China. In China, CGM data were collected using the Libre FreeStyle H system.

Notes: