Clinical trial results:
A Phase 3, Multicenter, Randomized, Parallel-Design, Open-Label Study to Evaluate the Efficacy and Safety of LY3209590 as a Weekly Basal Insulin Compared with Insulin Degludec in Participants with Type 1 Diabetes Treated with Multiple Daily Injection Therapy

Summary

EudraCT number	2021-005892-38
Trial protocol	SK PL
Global end of trial date	07 May 2024

Results information

Result version number	v1 (current)
This version publication date	22 May 2025
First version publication date	22 May 2025

Trial information

Trial identification

Sponsor protocol code	I8H-MC-BDCY

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05463744
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 18263

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, 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	07 May 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 May 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

A Study of Insulin Efsitora Alfa (LY3209590) Compared with Insulin Degludec in Participants with Type 1 Diabetes Treated with Multiple Daily Injection Therapy

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	12 August 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	Poland: 132
Country: Number of subjects enrolled	Slovakia: 32
Country: Number of subjects enrolled	Argentina: 197
Country: Number of subjects enrolled	Japan: 101
Country: Number of subjects enrolled	Taiwan: 32
Country: Number of subjects enrolled	United States: 198
Worldwide total number of subjects	692
EEA total number of subjects	164

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)	631
From 65 to 84 years	61
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Not Applicable

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 who were treated with prestudy basal insulin and prandial insulin therapy (100 units per milliliter (U/mL) Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered once weekly (QW) for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

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

Dosage and administration details:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered QW for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

Arm title	100 U/mL Insulin Degludec

Arm description:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered once daily (QD) for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

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 who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered QD for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

Number of subjects in period 1	500 U/mL Insulin Efsitora Alfa	100 U/mL Insulin Degludec
Started	343	349
Received at Least one Dose of Study Drug	343	349
Completed	316	319
Not completed	27	30
Non-compliance with Study Drug	1	-
Consent withdrawn by subject	19	16
Physician decision	-	1
Adverse event, non-fatal	4	4
Death	-	1
Pregnancy	-	3
Inadvertent enrollment	2	1
Lost to follow-up	1	3
Subject Terminated by Sponsor	-	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 were treated with prestudy basal insulin and prandial insulin therapy (100U/mL Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered QW for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

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

Dosage and administration details:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered QW for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

Arm title	100 U/mL Insulin Degludec

Arm description:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered QD for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

Arm type	Experimental

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 who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered QD for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

Number of subjects in period 2	500 U/mL Insulin Efsitora Alfa	100 U/mL Insulin Degludec
Started	332	326
Completed	328	324
Not completed	4	2
Consent withdrawn by subject	3	1
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	500 U/mL Insulin Efsitora Alfa
Reporting group description:	
Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 units per milliliter (U/mL) Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered once weekly (QW) for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.	
Reporting group title	100 U/mL Insulin Degludec
Reporting group description:	
Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered once daily (QD) for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.	

Reporting group values	500 U/mL Insulin Efsitora Alfa	100 U/mL Insulin Degludec	Total
Number of subjects	343	349	692
Age categorical Units: Subjects			
Age continuous			
Analysis Population Description (APD): All randomized participants who received at least one dose of the study drug.			
Units: years			
arithmetic mean	44.40	43.60	
standard deviation	± 14.22	± 14.01	-
Gender categorical Units: Subjects			
Female	150	158	308
Male	193	191	384
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	121	116	237
Not Hispanic or Latino	221	230	451
Unknown or Not Reported	1	3	4
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	69	73	142
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	11	13	24
White	259	262	521
More than one race	2	1	3
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Argentina	98	99	197
Japan	48	53	101
Poland	66	66	132
Slovakia	15	17	32

Taiwan	15	17	32
United States	101	97	198

HemoglobinA1c (HbA1c)			
HbA1c is the glycosylated fraction of hemoglobin A. It is measured primarily to identify the average plasma glucose concentration over prolonged periods of time.			
Units: Percentage of HbA1c			
arithmetic mean	7.88	7.94	
standard deviation	± 0.75	± 0.72	-

End points

End points reporting groups

Reporting group title	500 U/mL Insulin Efsitora Alfa
Reporting group description:	
Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 units per milliliter (U/mL) Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered once weekly (QW) for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.	
Reporting group title	100 U/mL Insulin Degludec
Reporting group description:	
Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered once daily (QD) for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.	
Reporting group title	500 U/mL Insulin Efsitora Alfa
Reporting group description:	
Participants who were treated with prestudy basal insulin and prandial insulin therapy (100U/mL Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered QW for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.	
Reporting group title	100 U/mL Insulin Degludec
Reporting group description:	
Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered QD for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.	

Primary: Change from Baseline in Hemoglobin A1c (HbA1c) at Week 26 [Noninferiority Analysis]

End point title	Change from Baseline in Hemoglobin A1c (HbA1c) at Week 26 [Noninferiority Analysis]
End point description:	
HbA1c is the glycosylated fraction of hemoglobin A. It is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. Least Squares (LS) mean was determined using Analysis of Covariance (ANCOVA) model treatment + country + CGM use prior to study entry [yes/no]+ carbohydrate counting for prandial insulin[yes/no] + baseline value of the dependent variable (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	Primary
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	341	348		
Units: millimoles per mole (mmol/mol)				
least squares mean (standard error)	-5.53 (± 0.512)	-6.10 (± 0.506)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	689
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	1.98

Notes:

[1] - 0.4% noninferiority margin (NIM)

Secondary: Change from Baseline in Hemoglobin A1c (HbA1c) at Week 26 [Superiority Analysis]

End point title	Change from Baseline in Hemoglobin A1c (HbA1c) at Week 26 [Superiority Analysis]

End point description:

HbA1c is the glycosylated fraction of hemoglobin A. It is measured primarily to identify the average plasma glucose concentration over prolonged periods of time.
LS mean was determined using ANCOVA model with treatment + country + CGM use prior to study entry [yes/no] + carbohydrate counting for prandial insulin[yes/no] + baseline value of the dependent variable (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	341	348		
Units: mmol/mol				
least squares mean (standard error)	-5.53 (± 0.512)	-6.10 (± 0.506)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	689
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.432
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	1.98

Secondary: Percentage of Time-in-Glucose Range Between 70 and 180 mg/dL [3.9 and 10.0 mmol/L]

End point title	Percentage of Time-in-Glucose Range Between 70 and 180 mg/dL [3.9 and 10.0 mmol/L]

End point description:

Time in glucose range between 70 and 180 milligram per deciliter (mg/dL) [3.9 and 10.0 millimole per liter (mmol/L)], measured by continued glucose monitoring (CGM) from week 23-26 inclusive over a 24-Hour Period. The time component of the time-in-range statistic was calculated using the display time recorded by the CGM device.
LS mean was determined using ANCOVA model with treatment+country+CGM use prior to study entry [yes/no]+carbohydrate counting for prandial insulin dosing [yes/no]+Hemoglobin A1c Stratum at Baseline and baseline value of the dependent variable (Type III sum of squares) as variables.Missing data at Week 23-26 were imputed by return-to-baseline multiple imputations approach.
APD:All randomized participants who took at least one dose of study drug and had evaluable data for this outcome at baseline or Week 23-26 were included. Participants who discontinued study drug due to inadvertent enrollment were excluded

End point type	Secondary

End point timeframe:

Week 23 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	339	347		
Units: Percentage of time				
least squares mean (standard error)	52.54 (± 0.691)	52.85 (± 0.684)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	686
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.751
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.22
upper limit	1.6

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 = Baseline hypoglycemia rate + 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 and had evaluable data for this outcome.

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	343	349		
Units: events per year				
arithmetic mean (standard error)	1.99 (± 0.180)	1.96 (± 0.177)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9
Method	Negative binomial model
Parameter estimate	Relative Rate
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.31

Secondary: 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 primarily to identify the average plasma glucose concentration over prolonged periods of time.
LS mean was determined using ANCOVA model with treatment + country + CGM use prior to study entry [yes/no]+ carbohydrate counting for prandial insulin[yes/no] + baseline value of the dependent variable (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	341	348		
Units: mmol/mol				
least squares mean (standard error)	-4.10 (± 0.529)	-4.36 (± 0.524)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	689
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	1.72

Notes:

[2] - 0.4% noninferiority margin (NIM)

Secondary: Change from Baseline in Fasting Blood Glucose

End point title	Change from Baseline in Fasting Blood Glucose

End point description:

Change from baseline in fasting glucose measured by self-monitoring blood glucose (SMBG).
LS mean was determined using ANCOVA model with treatment, country, CGM use prior to study entry [yes/no], carbohydrate counting for prandial insulin dosing [yes/no]) and baseline value of the dependent variable as variables. Missing data at Baseline were imputed with multiple imputation with assumption of missing at random. Missing data 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 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 or Week 26 were considered, while for the Week 52 analysis, data from Baseline or 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, 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	341	348		
Units: millimoles per liter				
least squares mean (standard error)				
Week 26	-1.48 (± 0.125)	-1.41 (± 0.123)		
Week 52	-1.38 (± 0.138)	-1.11 (± 0.136)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1: Week 26
Comparison groups	100 U/mL Insulin Degludec v 500 U/mL Insulin Efsitora Alfa
Number of subjects included in analysis	689
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.697
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	0.27

Statistical analysis title	Statistical Analysis 2: Week 52
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	689
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.163
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.65
upper limit	0.11

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 23 to Week 26 and Week 49 to Week 52 was reported.
LS mean was determined using mixed model repeated measures (MMRM) model with BASELINE + Country + Prior CGM use + Carbohydrate counting for Prandial Dose + Hemoglobin A1c Stratum at Baseline + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. Unstructured variance-covariance structure was used.
APD: All randomized participants who took 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 23 to Week 26 and Week 49 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	331	332		
Units: percentage of CV				
least squares mean (standard error)				
Week 23 to Week 26	33.72 (± 0.230)	33.69 (± 0.229)		
Week 49 to Week 52	33.69 (± 0.233)	33.18 (± 0.233)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1: Week 23 to Week 26
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.939
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.61
upper limit	0.66

Statistical analysis title	Statistical Analysis 2: Week 49 to Week 52
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec

Number of subjects included in analysis	663
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.116
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	1.17

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

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

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 49 to Week 52.
LS mean was determined using ANCOVA model with treatment, country, CGM use prior to study entry [yes/no], carbohydrate counting for prandial insulin dosing [yes/no]) and Hemoglobin A1c Stratum at baseline and baseline value of the dependent variable as variables. Missing data at Baseline were imputed with multiple imputation with assumption of missing at random. Missing data 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 evaluable data for this outcome at baseline or Week 49-52 were included in the analysis. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

End point type	Secondary

End point timeframe:

Week 49 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	338	347		
Units: percentage of time				
least squares mean (standard error)	50.28 (± 0.755)	49.74 (± 0.744)		

Statistical analyses

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

Number of subjects included in analysis	685
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.61
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.54
upper limit	2.62

Secondary: Basal Insulin Dose

End point title	Basal Insulin Dose

End point description:

The insulin dose was recorded daily or weekly 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 BASELINE + Hemoglobin A1c Stratum at Baseline + Country + Prior CGM use + Carbohydrate counting for Prandial Dose + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. Variance-covariance structure was set as compound symmetry.
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	341	347		
Units: Units per week (U/week)				
least squares mean (standard error)				
Week 26	199.51 (± 4.47)	208.47 (± 4.43)		
Week 52	204.37 (± 4.50)	211.25 (± 4.46)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1: Week 26
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec

Number of subjects included in analysis	688
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.155
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-8.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.3
upper limit	3.38

Statistical analysis title	Statistical Analysis 2: Week 52
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	688
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.278
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-6.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.31
upper limit	5.55

Secondary: Bolus Insulin Dose

End point title	Bolus Insulin Dose

End point description:

The insulin dose was recorded daily or weekly in an electronic diary. The average daily bolus insulin dose at Week 26 and Week 52 was reported.
LS mean was determined using MMRM model with BASELINE + Hemoglobin A1c Stratum at Baseline + Country + Prior CGM use + Carbohydrate counting for Prandial Dose + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. Variance-covariance structure was set as compound symmetry.
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	307	327		
Units: Units per day (U/day)				
least squares mean (standard error)				
Week 26	21.48 (± 0.64)	25.25 (± 0.62)		
Week 52	22.62 (± 0.65)	26.10 (± 0.63)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1: Week 26
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-3.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.52
upper limit	-2.03

Statistical analysis title	Statistical Analysis 2: Week 52
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-3.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.26
upper limit	-1.71

Secondary: Total Insulin Dose

End point title	Total Insulin Dose

End point description:

The average weekly total insulin dose is the sum of the average weekly basal and bolus doses. LS mean was determined using MMRM model with BASELINE + Hemoglobin A1c Stratum at Baseline + Country + Prior CGM use + Carbohydrate counting for Prandial Dose + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. Variance-covariance structure was set as compound symmetry.
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	305	327		
Units: Units per week (U/week)				
least squares mean (standard error)				
Week 26	343.91 (± 6.72)	383.19 (± 6.47)		
Week 52	355.66 (± 6.81)	391.60 (± 6.53)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1: Week 26
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	632
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-39.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-57.59
upper limit	-20.98

Statistical analysis title	Statistical Analysis 2: Week 52
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec

Number of subjects included in analysis	632
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	-35.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	-54.44
upper limit	-17.43

Secondary: Basal Insulin Dose to Total Insulin Dose Ratio

End point title	Basal Insulin Dose to Total Insulin Dose Ratio

End point description:

The basal/total insulin dose ratio is the average weekly basal dose divided by the average weekly total dose.
LS mean was determined using MMRM model with BASELINE + Hemoglobin A1c Stratum at Baseline + Country + Prior CGM use + Carbohydrate counting for Prandial Dose + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. Variance-covariance structure was set as compound symmetry.
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	305	327		
Units: Ratio				
least squares mean (standard error)				
Week 26	56.4 (± 0.69)	53.2 (± 0.66)		
Week 52	55.4 (± 0.70)	52.6 (± 0.67)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1: Week 26
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec

Number of subjects included in analysis	632
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	3.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.32
upper limit	5.06

Statistical analysis title	Statistical Analysis 2: Week 52
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	632
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	4.7

Secondary: Hypoglycemia Event Rate

End point title	Hypoglycemia Event Rate

End point description:

Rate of Composite Level 2 and 3 Hypoglycemia Events were reported. Hypoglycemia with glucose <54 mg/dL (Level 2) or Severe Hypoglycemia confirmed by the investigator to be an event that required assistance for treatment (Level 3) was reported. A severe hypoglycemic event is characterized by altered mental or physical status requiring 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 = Baseline hypoglycemia rate + 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	343	349		
Units: Events per year				
arithmetic mean (standard error)	14.03 (± 0.816)	11.59 (± 0.681)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	692
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	Negative binomial model
Parameter estimate	LS Mean Difference
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	1.41

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 using Baseline + Treatment + Time + Treatment*Time (Type III sum of squares) as variables. Variance-covariance structure was set as compound symmetry.
APD: All randomized participants who received at least one dose of the study drug and had baseline, at least one post-baseline evaluable data for this outcome.

End point type	Secondary

End point timeframe:

Baseline, 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	342	348		
Units: kilograms (kg)				
least squares mean (standard error)				
Baseline, Week 26	1.71 (± 0.159)	1.62 (± 0.158)		

Baseline, Week 52	1.96 (± 0.160)	1.85 (± 0.159)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1: Week 26
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	690
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.702
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.086
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.35
upper limit	0.53

Statistical analysis title	Statistical Analysis 2: Week 52
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	690
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.609
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.56

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 23 to week 26 and week 49 to week 52 was reported. LS Mean was determined by ANCOVA model using treatment + country + CGM use prior to study entry [yes/no] + carbohydrate counting for prandial insulin dosing [yes/no] + Hemoglobin A1c Stratum at Baseline and baseline value of the dependent variable (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 23-week 26 and week 49-week 52 were imputed by return-to-baseline multiple imputations approach.
APD: For the Week 23-26 analysis, data from Baseline or Week 23-26 were considered, while for the Week 49-52 analysis, data from Baseline or Week 49-52 were included. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

End point type	Secondary

End point timeframe:

Week 23 to Week 26 and Week 49 to Week 52
APD: All randomized participants who received at least one dose of the study drug and had evaluable data for this outcome at Baseline, Week 23-26, or Week 49-52 were included in the analysis.

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	339	347		
Units: percentage of time				
least squares mean (standard error)				
Week 23 to Week 26	0.75 (± 0.058)	0.72 (± 0.057)		
Week 49 to Week 52	0.74 (± 0.053)	0.64 (± 0.052)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1: Week 23 to Week 26
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	686
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.681
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.19

Statistical analysis title	Statistical Analysis 2: Week 49 to Week 52
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec

Number of subjects included in analysis	686
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.182
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.24

Secondary: Percentage of Time in Hyperglycemia Range With Blood Glucose >180 mg/dL (10.0 mmol/L) from Week 23 to Week 26

End point title	Percentage of Time in Hyperglycemia Range With Blood Glucose >180 mg/dL (10.0 mmol/L) from Week 23 to Week 26

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 23 to Week 26 was reported.
LS Mean was determined by ANCOVA model using treatment + country + CGM use prior to study entry [yes/no] + carbohydrate counting for prandial insulin dosing [yes/no] + Hemoglobin A1c Stratum at Baseline and baseline value of the dependent variable (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 23-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 evaluable data for this outcome at baseline or Week 23-26 were included in the analysis. Participants who discontinued the study drug due to inadvertent enrollment were excluded

End point type	Secondary

End point timeframe:

Week 23 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	339	347		
Units: percentage of time				
least squares mean (standard error)	44.29 (± 0.743)	44.29 (± 0.735)		

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	686
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.999
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.06
upper limit	2.05

Secondary: Diabetes Treatment Satisfaction as Measured by the Diabetes Treatment Satisfaction Questionnaire, Change Version (DTSQc) at Week 26

End point title	Diabetes Treatment Satisfaction as Measured by the Diabetes Treatment Satisfaction Questionnaire, Change Version (DTSQc) at Week 26

End point description:

The DTSQc score is used to assess relative change in participant satisfaction from baseline. The questionnaire consists of 8 items, 6 of which measure Treatment Satisfaction, dealing with: 1. satisfaction with current treatment; 2. convenience of the treatment; 3. flexibility; 4. satisfaction with own understanding of participant's diabetes; 5. how likely to recommend their present treatment; and 6. how satisfied to continue with their present treatment. Each item is rated on a 7-point Likert scale (which ranges from -3 (much less satisfied) to +3 (much more satisfied). The scores from the 6 treatment satisfaction items are summed to a Total Treatment Satisfaction Score, which ranges from -18 (much less satisfied) to +18 (much more satisfied). Higher the score the greater the improvement in satisfaction with treatment. The lower the score the greater the deterioration in satisfaction with treatment.

End point type	Secondary

End point timeframe:

Week 26
APD: All randomized participants who received at least one dose of the study drug and had evaluable data for this outcome. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

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	306	314		
Units: score on a scale				
least squares mean (standard error)	14.4 (± 4.53)	13.2 (± 5.20)		

Statistical analyses

Statistical analysis title	Statistical Analysis: Week 26
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	620
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.008
Method	Wilcoxon (Mann-Whitney)

Secondary: Diabetes Treatment Satisfaction as Measured by the Diabetes Treatment Satisfaction Questionnaire, Change Version (DTSQc) at Week 52

End point title	Diabetes Treatment Satisfaction as Measured by the Diabetes Treatment Satisfaction Questionnaire, Change Version (DTSQc) at Week 52

End point description:

The DTSQc score is used to assess relative change in participant satisfaction from baseline. The questionnaire consists of 8 items, 6 of which measure Treatment Satisfaction, dealing with: 1. satisfaction with current treatment; 2. convenience of the treatment; 3. flexibility; 4. satisfaction with own understanding of participant's diabetes; 5. how likely to recommend their present treatment; and 6. how satisfied to continue with their present treatment. Each item is rated on a 7-point Likert scale (which ranges from -3 (much less satisfied) to +3 (much more satisfied). The scores from the 6 treatment satisfaction items are summed to a Total Treatment Satisfaction Score, which ranges from -18 (much less satisfied) to +18 (much more satisfied). Higher the score the greater the improvement in satisfaction with treatment. The lower the score the greater the deterioration in satisfaction with treatment.

End point type	Secondary

End point timeframe:

Week 52
APD: All randomized participants who received at least one dose of the study drug and had evaluable data for this outcome. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

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	310	312		
Units: score on a scale				
arithmetic mean (standard deviation)	14.4 (± 5.31)	12.8 (± 5.67)		

Statistical analyses

Statistical analysis title	Statistical Analysis: Week 52
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec

Number of subjects included in analysis	622
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: Change From Baseline in Short Form-36 Version 2 (SF-36 v2) Acute Form (Physical-Component and Mental-Component) Scores

End point title	Change From Baseline in Short Form-36 Version 2 (SF-36 v2) Acute Form (Physical-Component and Mental-Component) Scores

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. The 8 health domains are aggregated into two summary scores known as the physical component summary (PCS) score and the mental component summary (MCS) score. 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.
LS Mean was determined by MMRM model with Baseline + Country + Carbohydrate counting for Prandial Dose + Prior CGM use + Hemoglobin A1c Stratum at Baseline + Treatment + Time + Treatment*Time (Type III sum of squares). as variables. Unstructured variance-covariance structure was used.

End point type	Secondary

End point timeframe:

Baseline, Week 26, and Week 52
APD:All randomized participants who received at least one dose of study drug,had baseline and atleast one post-baseline value for this outcome.Participants discontinued study drug due to inadvertent enrollment were excluded

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	327	330		
Units: score on a scale				
least squares mean (standard error)				
Physical Component Score: Baseline, Week 26	0.19 (± 0.275)	-0.24 (± 0.272)		
Physical Component Score: Baseline, Week 52	0.48 (± 0.262)	-0.25 (± 0.260)		
Mental Component Score: Baseline, Week 26	0.58 (± 0.419)	0.36 (± 0.415)		
Mental Component Score: Baseline, Week 52	0.61 (± 0.419)	0.16 (± 0.417)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1: PCS: Baseline, Week 26
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec

Number of subjects included in analysis	657
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	1.19

Statistical analysis title	Statistical Analysis 2: PCS: Baseline, Week 52
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	657
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	1.45

Statistical analysis title	Statistical Analysis 3: MCS: Baseline, Week 26
Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	657
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.71
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	1.38

Statistical analysis title	Statistical Analysis 4: MCS: Baseline, Week 52

Comparison groups	500 U/mL Insulin Efsitora Alfa v 100 U/mL Insulin Degludec
Number of subjects included in analysis	657
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.447
Method	Mixed models analysis
Parameter estimate	LS Mean Difference
Point estimate	0.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.71
upper limit	1.61

Secondary: Percentage of Time in Hyperglycemia Range With Blood Glucose >180 mg/dL (10.0 mmol/L) From Week 49 to Week 52

End point title	Percentage of Time in Hyperglycemia Range With Blood Glucose >180 mg/dL (10.0 mmol/L) From Week 49 to Week 52

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 49 to Week 52 was reported.
LS Mean was determined by ANCOVA model using treatment + country + CGM use prior to study entry [yes/no] + carbohydrate counting for prandial insulin dosing [yes/no] + Hemoglobin A1c Stratum at Baseline and baseline value of the dependent variable (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 49-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 evaluable data for this outcome at baseline or Week 49-52 were included in the analysis. Participants who discontinued the study drug due to inadvertent enrollment were excluded.

End point type	Secondary

End point timeframe:

Week 49 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	338	347		
Units: percentage of time				
least squares mean (standard error)	46.73 (± 0.811)	47.56 (± 0.797)		

Statistical analyses

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

Number of subjects included in analysis	685
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.468
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.06
upper limit	1.41

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

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 who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL Insulin Lispro) received 100 U/mL of Insulin Degludec administered once QW for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

Reporting group title	500 U/mL Insulin Efsitora Alfa

Reporting group description:

Participants who were treated with prestudy basal insulin and prandial insulin therapy (100 U/mL) Insulin Lispro) received 500 U/mL of insulin efsitora alfa administered QD for 52 weeks as subcutaneous injection, followed by a 5-week safety follow-up.

Serious adverse events	100 U/mL Insulin Degludec	500 U/mL Insulin Efsitora Alfa	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 349 (6.88%)	45 / 343 (13.12%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Vascular disorders			
aortic stenosis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 349 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
abortion spontaneous			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed[1]	0 / 158 (0.00%)	2 / 150 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
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	1 / 349 (0.29%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
completed suicide			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 349 (0.29%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
ankle fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 349 (0.29%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
limb injury			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 349 (0.29%)	0 / 343 (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	1 / 349 (0.29%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
road traffic accident			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 349 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
chronic granulomatous disease			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 349 (0.29%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
limb reduction defect			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 349 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
angina pectoris			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 349 (0.57%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
angina unstable			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 349 (0.29%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
coronary artery disease			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 349 (0.57%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
acute myocardial infarction			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 349 (0.29%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
aphasia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 349 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
dizziness			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 349 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
seizure			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 349 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
epilepsy			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 349 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
generalised tonic-clonic seizure			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 349 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoglycaemic seizure			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 349 (0.29%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoglycaemic unconsciousness			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	4 / 349 (1.15%)	10 / 343 (2.92%)	
occurrences causally related to treatment / all	3 / 5	4 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
vertigo			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 349 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
gastritis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 349 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 349 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
costochondritis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 349 (0.29%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
abscess limb			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 349 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
appendicitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 349 (0.29%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
bronchitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 349 (0.29%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
sepsis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 349 (0.57%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteomyelitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 349 (0.57%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
pneumonia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 349 (0.29%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
tooth infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 349 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

sinusitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 349 (0.00%)	1 / 343 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
diabetic ketoacidosis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 349 (0.57%)	0 / 343 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
hypoglycaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	7 / 349 (2.01%)	27 / 343 (7.87%)	
occurrences causally related to treatment / all	3 / 7	16 / 33	
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 male or 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	119 / 349 (34.10%)	117 / 343 (34.11%)	
Skin and subcutaneous tissue disorders			
dermatitis contact			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	16 / 349 (4.58%)	19 / 343 (5.54%)	
occurrences (all)	16	20	
Infections and infestations			
covid-19			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	23 / 349 (6.59%)	16 / 343 (4.66%)	
occurrences (all)	24	16	
urinary tract infection			
alternative dictionary used:			

MedDRA 27.0			
subjects affected / exposed	11 / 349 (3.15%)	21 / 343 (6.12%)	
occurrences (all)	16	24	
nasopharyngitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	42 / 349 (12.03%)	40 / 343 (11.66%)	
occurrences (all)	54	45	
upper respiratory tract infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	30 / 349 (8.60%)	24 / 343 (7.00%)	
occurrences (all)	35	29	
influenza			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	18 / 349 (5.16%)	27 / 343 (7.87%)	
occurrences (all)	22	30	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 May 2022	- Objectives, Endpoints, and Estimands were modified. - Inclusion and Exclusion Criteria were modified. - Updated the analysis populations/sets. - Statistical Considerations: Made updates to endpoint word order throughout section and subsections for clarity - Primary Endpoint(s)/Estimand(s) Analysis: Replaced the stratification factor "prestudy basal insulin glargine U-300 or other basal insulin" with a new stratification factor "CGM use prior to study entry [yes/no]" in ANCOVA and MMRM models. - Safety Analyses: Removed inadvertently hidden text format applied to hypoglycemia time period definitions.
21 June 2022	- Schedule of Activities (SoA) have been updated. - Deleted text "Potential intrinsic and extrinsic factors" from tertiary endpoints for PK/PD of LY3209590. - Edited text to describe use of the unblinded Continuous glucose monitoring (CGM) system receive
12 October 2022	- SoA updated for clarity - Inclusion and Exclusion Criteria were modified - Added "if the participants can safely do this" for participants advised to check SMBG readings for suspected hypoglycemia for clarification. - Added a note for participants to not manually calibrate the study CGM with fingerstick blood glucose readings for clarification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported