Clinical trial results:
A Phase 2, Randomized, Parallel, Open-Label Comparator-Controlled Trial to Evaluate the Safety and Efficacy of LY3209590 in Study Participants With Type 1 Diabetes Mellitus Previously Treated With Multiple Daily Injection Therapy

Summary

EudraCT number	2019-003589-41
Trial protocol	ES DE AT
Global end of trial date	01 October 2021

Results information

Result version number	v1 (current)
This version publication date	15 October 2022
First version publication date	15 October 2022

Trial information

Trial identification

Sponsor protocol code	I8H-MC-BDCP

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04450407
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 17183

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 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

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	01 October 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The reason for this study is to see if the study drug LY3209590 is safe and effective in participants with type 1 diabetes.

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	06 July 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Puerto Rico: 11
Country: Number of subjects enrolled	Austria: 12
Country: Number of subjects enrolled	United States: 179
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Spain: 30
Worldwide total number of subjects	266
EEA total number of subjects	76

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)	232

From 65 to 84 years	34
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was initially designed as 3 arms: LY3209590 Algorithm 1 (Paper), LY3209590 Algorithm 2 (Digital), and Insulin Degludec. However, it was amended to terminate the "LY3209590 Algorithm 2 (Digital)" arm during early enrollment phase due to technical issues with data entry.

Pre-assignment

Screening details:

(cont'd) Thus, this arm was excluded from the outcome measure analyses, but safety data was analysed and reported.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	LY3209590 Algorithm 1 (Paper)

Arm description:

Algorithm 1 is a paper-based algorithm where dose adjustments were manually determined by the investigator based on fasting glucose and hypoglycemia data. LY3209590 was provided in a 20 milligram (mg) vial of reconstitutable lyophilized powder. Participants received individualized LY3209590 loading dose based on the basal insulin dose prior randomization and baseline fasting glucose by subcutaneous (SC) injection on day 1 followed by weekly adjustments for the first 12 weeks, then every 4 weeks, of a 26-week treatment period, to achieve target fasting glucose of <=100 milligrams per deciliter (mg/dL).

Arm type	Experimental
Investigational medicinal product name	LY3209590
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

LY3209590 was provided in a 20 mg vial of reconstitutable lyophilized powder. Participants received individualized LY3209590 loading dose based on the basal insulin dose prior randomization and baseline fasting glucose by SC injection on day 1 followed by weekly adjustments for the first 12 weeks, then every 4 weeks, of a 26-week treatment period, to achieve target fasting glucose of <=100 mg/dL.

Arm title	LY3209590 Algorithm 2 (Digital)

Arm description:

Algorithm 2 is a computer-based algorithm to determine dose adjustments. LY3209590 was provided in a 20 mg vial of reconstitutable lyophilized powder. Participants received individualized LY3209590 loading dose based on the basal insulin dose prior randomization and baseline fasting glucose by SC injection on day 1 followed by weekly adjustments for the first 12 weeks, then every 4 weeks, of a 26-week treatment period, to achieve target fasting glucose of <=100 mg/dL.

Arm type	Experimental
Investigational medicinal product name	LY3209590
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

LY3209590 was provided in a 20 mg vial of reconstitutable lyophilized powder. Participants received individualized LY3209590 loading dose based on the basal insulin dose prior randomization and baseline

fasting glucose by SC injection on day 1 followed by weekly adjustments for the first 12 weeks, then every 4 weeks, of a 26-week treatment period, to achieve target fasting glucose of <=100 mg/dL.

Arm title	Insulin Degludec

Arm description:

Insulin degludec was provided as 100 units/milliliter (U/mL) in a prefilled pen. Participants received individually adjusted doses once daily by SC injection with a starting dose same as basal insulin dose prior randomization, during the 26-week treatment period, to achieve target fasting blood glucose of <=100 mg/dL.

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:

Insulin degludec was provided as 100 U/mL in a prefilled pen. Participants received individually adjusted doses once daily by SC injection with a starting dose same as basal insulin dose prior randomization, during the 26-week treatment period, to achieve target fasting blood glucose of <=100 mg/dL.

Number of subjects in period 1	LY3209590 Algorithm 1 (Paper)	LY3209590 Algorithm 2 (Digital)	Insulin Degludec
Started	124	16	126
Received at Least One Dose of Study Drug	123	16	126
Completed	107	15	118
Not completed	17	1	8
Consent withdrawn by subject	10	1	4
Physician decision	-	-	1
Adverse event, non-fatal	-	-	1
Investigational site terminated by sponsor	3	-	2
Pregnancy	1	-	-
Lost to follow-up	1	-	-
Protocol deviation	2	-	-

Baseline characteristics

Reporting groups	
Reporting group title	LY3209590 Algorithm 1 (Paper)

Reporting group description:

Algorithm 1 is a paper-based algorithm where dose adjustments were manually determined by the investigator based on fasting glucose and hypoglycemia data. LY3209590 was provided in a 20 milligram (mg) vial of reconstitutable lyophilized powder. Participants received individualized LY3209590 loading dose based on the basal insulin dose prior randomization and baseline fasting glucose by subcutaneous (SC) injection on day 1 followed by weekly adjustments for the first 12 weeks, then every 4 weeks, of a 26-week treatment period, to achieve target fasting glucose of <=100 milligrams per deciliter (mg/dL).

Reporting group title	LY3209590 Algorithm 2 (Digital)

Reporting group description:

Algorithm 2 is a computer-based algorithm to determine dose adjustments. LY3209590 was provided in a 20 mg vial of reconstitutable lyophilized powder. Participants received individualized LY3209590 loading dose based on the basal insulin dose prior randomization and baseline fasting glucose by SC injection on day 1 followed by weekly adjustments for the first 12 weeks, then every 4 weeks, of a 26-week treatment period, to achieve target fasting glucose of <=100 mg/dL.

Reporting group title	Insulin Degludec

Reporting group description:

Insulin degludec was provided as 100 units/milliliter (U/mL) in a prefilled pen. Participants received individually adjusted doses once daily by SC injection with a starting dose same as basal insulin dose prior randomization, during the 26-week treatment period, to achieve target fasting blood glucose of <=100 mg/dL.

Reporting group values	LY3209590 Algorithm 1 (Paper)	LY3209590 Algorithm 2 (Digital)	Insulin Degludec
Number of subjects	124	16	126
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	113	9	110
From 65-84 years	11	7	16
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	44.4	53.4	47.4
standard deviation	± 14.8	± 16.3	± 13.7
Gender categorical Units: Subjects			
Female	50	4	48
Male	74	12	78
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	23	5	10
Not Hispanic or Latino	100	11	116
Unknown or Not Reported	1	0	0

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	0	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	4
White	119	14	120
More than one race	1	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Puerto Rico	7	1	3
Austria	6	0	6
United States	80	15	84
Germany	16	0	18
Spain	15	0	15
Haemoglobin A1c (HbA1c)			
HbA1c is the glycosylated fraction of haemoglobin A. It is measured to identify average blood glucose concentration over prolonged periods of time.			
Units: Percentage of HbA1c			
arithmetic mean	7.52	7.64	7.45
standard deviation	± 0.85	± 0.70	± 0.87

Reporting group values	Total		
Number of subjects	266		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	232		
From 65-84 years	34		
85 years and over	0		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical Units: Subjects			
Female	102		
Male	164		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	38		
Not Hispanic or Latino	227		
Unknown or Not Reported	1		
Race (NIH/OMB)			

Units: Subjects			
American Indian or Alaska Native	0		
Asian	4		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	8		
White	253		
More than one race	1		
Unknown or Not Reported	0		
Region of Enrollment Units: Subjects			
Puerto Rico	11		
Austria	12		
United States	179		
Germany	34		
Spain	30		
Haemoglobin A1c (HbA1c)			
HbA1c is the glycosylated fraction of haemoglobin A. It is measured to identify average blood glucose concentration over prolonged periods of time.			
Units: Percentage of HbA1c			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	LY3209590 Algorithm 1 (Paper)

Reporting group description:

Algorithm 1 is a paper-based algorithm where dose adjustments were manually determined by the investigator based on fasting glucose and hypoglycemia data. LY3209590 was provided in a 20 milligram (mg) vial of reconstitutable lyophilized powder. Participants received individualized LY3209590 loading dose based on the basal insulin dose prior randomization and baseline fasting glucose by subcutaneous (SC) injection on day 1 followed by weekly adjustments for the first 12 weeks, then every 4 weeks, of a 26-week treatment period, to achieve target fasting glucose of <=100 milligrams per deciliter (mg/dL).

Reporting group title	LY3209590 Algorithm 2 (Digital)

Reporting group description:

Algorithm 2 is a computer-based algorithm to determine dose adjustments. LY3209590 was provided in a 20 mg vial of reconstitutable lyophilized powder. Participants received individualized LY3209590 loading dose based on the basal insulin dose prior randomization and baseline fasting glucose by SC injection on day 1 followed by weekly adjustments for the first 12 weeks, then every 4 weeks, of a 26-week treatment period, to achieve target fasting glucose of <=100 mg/dL.

Reporting group title	Insulin Degludec

Reporting group description:

Insulin degludec was provided as 100 units/milliliter (U/mL) in a prefilled pen. Participants received individually adjusted doses once daily by SC injection with a starting dose same as basal insulin dose prior randomization, during the 26-week treatment period, to achieve target fasting blood glucose of <=100 mg/dL.

Primary: Change from Baseline in Hemoglobin A1c (HbA1c)

End point title	Change from Baseline in Hemoglobin A1c (HbA1c)[1]

End point description:

HbA1c is the glycosylated fraction of haemoglobin A. It is measured to identify average blood glucose concentration over prolonged periods of time. Least squares (LS) mean change from baseline was analysed by mixed model repeated measures (MMRM) model with treatment, country, visit, and treatment by visit interaction as fixed effects and the baseline HbA1c as a covariate.

Analysis Population Description (APD): All participants randomized to either LY3209590 Algorithm 1 (Paper) or Insulin degludec, received at least one dose of study drug and had baseline, post-baseline HbA1c data prior to treatment discontinuation.

End point type	Primary

End point timeframe:

Baseline, Week 26

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The "LY3209590 Algorithm 2 (Digital)" arm was terminated during early enrollment phase due to technical issues with data entry. Thus, this arm was excluded from the outcome measure analyses.

End point values	LY3209590 Algorithm 1 (Paper)	Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	123		
Units: Percentage of HbA1c				
least squares mean (standard error)	0.04 (± 0.068)	-0.13 (± 0.065)		

Statistical analyses

Statistical analysis title	Change from Baseline in Hemoglobin A1c (HbA1c)
Comparison groups	LY3209590 Algorithm 1 (Paper) v Insulin Degludec
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	LS Mean Difference
Point estimate	0.17
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.01
upper limit	0.32

Notes:

[2] - The non-inferiority margin is 0.4%. Non-inferiority is achieved if the upper limit of the 90% CI (Confidence Interval) is below 0.4.

Secondary: Change from Baseline in Fasting Serum Glucose

End point title	Change from Baseline in Fasting Serum Glucose[3]

End point description:

LS mean change from baseline was analysed by mixed model repeated measures (MMRM) model with treatment, country, HbA1c stratum, visit, and treatment by visit interaction as fixed effects and the baseline fasting serum glucose as a covariate.

APD: All participants randomized to either LY3209590 Algorithm 1 (Paper) or Insulin degludec, received at least one dose of study drug and had baseline, post-baseline fasting serum glucose data prior to treatment discontinuation.

End point type	Secondary

End point timeframe:

Baseline, Week 26

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The "LY3209590 Algorithm 2 (Digital)" arm was terminated during early enrollment phase due to technical issues with data entry. Thus, this arm was excluded from the outcome measure analyses.

End point values	LY3209590 Algorithm 1 (Paper)	Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	118	124		
Units: milligrams per deciliter (mg/dL)				
least squares mean (standard error)	-5.9 (± 5.65)	-16.7 (± 5.21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Bolus Insulin Dose

End point title	Change from Baseline in Bolus Insulin Dose[4]

End point description:

Bolus insulin dose was the sum of doses for morning, midday, evening meals, snack and correction. LS mean change from baseline was analysed by MMRM model with treatment, country, HbA1c stratum, visit, and treatment by visit interaction as fixed effects and the baseline bolus insulin dose as a covariate.

APD: All participants randomized to either LY3209590 Algorithm 1 (Paper) or Insulin degludec, received at least one dose of study drug and had baseline, post-baseline bolus insulin dose data prior to treatment discontinuation.

End point type	Secondary

End point timeframe:

Baseline, Week 26

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The "LY3209590 Algorithm 2 (Digital)" arm was terminated during early enrollment phase due to technical issues with data entry. Thus, this arm was excluded from the outcome measure analyses.

End point values	LY3209590 Algorithm 1 (Paper)	Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	79	81		
Units: Units per kilogram per day (U/kg/day)				
least squares mean (standard error)	0.04 (± 0.019)	0.05 (± 0.018)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Documented Hypoglycemia

End point title	Rate of Documented Hypoglycemia[5]

End point description:

Documented hypoglycemia is defined as any time a participant reports a self-monitoring blood glucose <54 mg/dL (3.0 millimole per liter (mmol/L)). Negative binomial model using baseline hypoglycaemia incidence, baseline HbA1c and treatment as independent variables was performed to estimate the event rate. Data presented is group mean. Group Mean is estimated by first taking the inverse link function on individual participant covariates, then averaging over all participants.

APD: All participants randomized to either LY3209590 Algorithm 1 (Paper) or Insulin degludec, received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline through Week 26

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The "LY3209590 Algorithm 2 (Digital)" arm was terminated during early enrollment phase due to technical issues with data entry. Thus, this arm was excluded from the outcome measure analyses.

End point values	LY3209590 Algorithm 1 (Paper)	Insulin Degludec		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	126		
Units: Events per participant per year				
arithmetic mean (standard error)	20.7 (± 2.27)	18.4 (± 2.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Area Under the Concentration Time Curve (AUC) of LY3209590

End point title	Pharmacokinetics (PK): Area Under the Concentration Time Curve (AUC) of LY3209590[6]

End point description:

AUC of LY3209590 was calculated for individual participants using the participant's Week 26 LY3209590 dose amount and estimated clearance value.

APD: All participants randomized to LY3209590 Algorithm 1 (Paper), received at least one dose of study drug and had evaluable PK data at Week 26.

End point type	Secondary

End point timeframe:

Week 26

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK was evaluated only for experimental arm (i.e,) LY3209590 Algorithm 1 (Paper).
The "LY3209590 Algorithm 2 (Digital)" arm was terminated during early enrollment phase due to technical issues with data entry. Thus, this arm was excluded from the outcome measure analyses.

End point values	LY3209590 Algorithm 1 (Paper)			
Subject group type	Reporting group			
Number of subjects analysed	99			
Units: Nanomole*hour per Liter (nmol*hr/L)				
geometric mean (geometric coefficient of variation)	3520 (± 53)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to Follow-up (up to 31 weeks)

Adverse event reporting additional description:

APD: All randomized participants.
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	24.1

Reporting groups

Reporting group title	LY3209590 Algorithm 1 (Paper)

Reporting group description:

Algorithm 1 is a paper-based algorithm where dose adjustments were manually determined by the investigator based on fasting glucose and hypoglycemia data. LY3209590 was provided in a 20 mg vial of reconstitutable lyophilized powder. Participants received individualized LY3209590 loading dose based on the basal insulin dose prior randomization and baseline fasting glucose by SC injection on day 1 followed by weekly adjustments for the first 12 weeks, then every 4 weeks, of a 26-week treatment period, to achieve target fasting glucose of <=100 mg/dL.

Reporting group title	LY3209590 Algorithm 2 (Digital)

Reporting group description:

Algorithm 2 is a computer-based algorithm to determine dose adjustments. LY3209590 was provided in a 20 mg vial of reconstitutable lyophilized powder. Participants received individualized LY3209590 loading dose based on the basal insulin dose prior randomization and baseline fasting glucose by SC injection on day 1 followed by weekly adjustments for the first 12 weeks, then every 4 weeks, of a 26-week treatment period, to achieve target fasting glucose of <=100 mg/dL.

Reporting group title	Insulin Degludec

Reporting group description:

Insulin degludec was provided as 100 U/mL in a prefilled pen. Participants received individually adjusted doses once daily by SC injection with a starting dose same as basal insulin dose prior randomization, during the 26-week treatment period, to achieve target fasting blood glucose of <=100 mg/dL.

Serious adverse events	LY3209590 Algorithm 1 (Paper)	LY3209590 Algorithm 2 (Digital)	Insulin Degludec
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 124 (4.03%)	0 / 16 (0.00%)	4 / 126 (3.17%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
maternal exposure during pregnancy			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed[1]	1 / 50 (2.00%)	0 / 4 (0.00%)	0 / 48 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

patella fracture			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 124 (0.00%)	0 / 16 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
acute myocardial infarction			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 124 (0.00%)	0 / 16 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
coronary artery stenosis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 124 (0.00%)	0 / 16 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
depression			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 124 (0.81%)	0 / 16 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
facet joint syndrome			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 124 (0.81%)	0 / 16 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
intervertebral disc protrusion			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 124 (0.00%)	0 / 16 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			

pneumonia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 124 (0.81%)	0 / 16 (0.00%)	0 / 126 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
hypoglycaemia			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 124 (0.81%)	0 / 16 (0.00%)	1 / 126 (0.79%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	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: There are gender specific adverse events occurring only in male or female participants. The number of participants exposed has been adjusted accordingly.

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

Non-serious adverse events	LY3209590 Algorithm 1 (Paper)	LY3209590 Algorithm 2 (Digital)	Insulin Degludec
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 124 (16.94%)	7 / 16 (43.75%)	11 / 126 (8.73%)
Investigations			
hepatic enzyme increased			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 124 (0.00%)	1 / 16 (6.25%)	1 / 126 (0.79%)
occurrences (all)	0	2	1
sars-cov-2 test positive			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 124 (1.61%)	1 / 16 (6.25%)	0 / 126 (0.00%)
occurrences (all)	2	1	0
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	4 / 124 (3.23%)	1 / 16 (6.25%)	3 / 126 (2.38%)
occurrences (all)	4	1	3
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 24.1			

subjects affected / exposed	10 / 124 (8.06%)	0 / 16 (0.00%)	5 / 126 (3.97%)
occurrences (all)	14	0	5
General disorders and administration site conditions			
injection site bruising			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 124 (0.81%)	1 / 16 (6.25%)	0 / 126 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
nasal congestion			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	1 / 124 (0.81%)	1 / 16 (6.25%)	0 / 126 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
covid-19			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 124 (1.61%)	1 / 16 (6.25%)	2 / 126 (1.59%)
occurrences (all)	2	1	2
nasopharyngitis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	3 / 124 (2.42%)	1 / 16 (6.25%)	1 / 126 (0.79%)
occurrences (all)	4	1	1
onychomycosis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	0 / 124 (0.00%)	1 / 16 (6.25%)	0 / 126 (0.00%)
occurrences (all)	0	1	0
sinusitis			
alternative dictionary used: MedDRA 24.1			
subjects affected / exposed	2 / 124 (1.61%)	1 / 16 (6.25%)	1 / 126 (0.79%)
occurrences (all)	2	1	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2020	Amendment [a]: This amendment addresses Food and Drug Administration (FDA) feedback.
12 June 2020	Amendment [b]: This provides guidance if COVID-19 related local restrictions impact the participant's ability to attend their onsite study visits as originally scheduled.
20 August 2020	Amendment [c]: The amendment provides information to reflect and reinforce investigational medical device requirements absent in the initial study protocol for Algorithm 2. These requirements are consistent with country regulations where Algorithm 2 will be used.
28 October 2020	Amendment [d]: The amendment provides information to reflect termination of the investigational medical device study arm evaluating the individualized accruing data algorithm (Algorithm 2) investigational device in the study.

Notes:

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.

"LY3209590 Algorithm 2 (Digital)" arm was terminated during early enrollment phase due to technical issues with data entry. Thus, it was excluded from the outcome measure analyses, but safety data was analysed and reported.

Notes: