Clinical trial results:
A Randomized, Parallel-Arm, Double-Blind Study of Efficacy and Safety of Dulaglutide When Added to SGLT2 Inhibitors in Patients with Type 2 Diabetes Mellitus

Summary

EudraCT number	2015-002095-24
Trial protocol	DE HU CZ AT ES
Global end of trial date	02 February 2017

Results information

Result version number	v1 (current)
This version publication date	18 February 2018
First version publication date	18 February 2018

Trial information

Trial identification

Sponsor protocol code	H9X-MC-GBGE

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02597049
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 15361

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 877CTLilly, ClinicalTrials.gov@lilly.com
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559, ClinicalTrials.gov@lilly.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 February 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study was to evaluate the efficacy and safety of the study drug known as dulaglutide when added to sodium-glucose co-transporter 2 (SGLT2) inhibitors in participants with type 2 diabetes mellitus.

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	24 November 2015
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	Austria: 29
Country: Number of subjects enrolled	Hungary: 57
Country: Number of subjects enrolled	United States: 89
Country: Number of subjects enrolled	Czech Republic: 73
Country: Number of subjects enrolled	Mexico: 83
Country: Number of subjects enrolled	Israel: 18
Country: Number of subjects enrolled	Germany: 33
Country: Number of subjects enrolled	Spain: 42
Worldwide total number of subjects	424
EEA total number of subjects	234

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	326
From 65 to 84 years	98
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

No Text Entered

Period 1

Period 1 title	Period 1
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	1.5 mg Dulaglutide

Arm description:

Dulaglutide 1.5 milligrams (mg) given subcutaneously (SC) once a week (QW) for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	1.5 mg Dulaglutide
Investigational medicinal product code	
Other name	LY2189265
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dulaglutide 1.5 mg SC QW for 24 weeks.

Arm title	0.75 mg Dulaglutide

Arm description:

Dulaglutide 0.75 mg given SC QW for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	0.75 mg Dulaglutide
Investigational medicinal product code	
Other name	LY2189265
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dulaglutide 0.75 mg SC QW for 24 weeks.

Arm title	Placebo

Arm description:

Placebo given SC QW for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo given SC QW for 24 weeks.

Number of subjects in period 1	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo
Started	142	142	140
Received at least one dose of study drug	142	141	140
Completed	142	141	140
Not completed	0	1	0
Consent withdrawn by subject	-	1	-

Period 2	
Period 2 title	Period 2
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	1.5 mg Dulaglutide

Arm description:
Dulaglutide 1.5 milligrams (mg) given SC QW for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	Dulaglutide
Investigational medicinal product code	
Other name	LY2189265
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:
Dulaglutide 1.5 milligrams (mg) given subcutaneously (SC) once a week (QW) for 24 weeks.

Arm title	0.75 mg Dulaglutide

Arm description:
Dulaglutide 0.75 mg given subcutaneously (SC) once a week (QW) for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	0.75 mg Dulaglutide
Investigational medicinal product code	
Other name	LY2189265
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:
Dulaglutide 0.75 mg SC QW for 24 weeks.

Arm title	Placebo

Arm description:
Placebo given SC QW for 24 weeks.

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo given SC QW for 24 weeks.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Of the 424 participants who started the study and were randomized, one participant was withdrawn from treatment prior to dosing. The participant continued study participation and completed the study without study drug. This participant is not included in the overall number of baseline participants [intent-to-treat (ITT) population] for the Dulaglutide 0.75 mg reporting group.

Number of subjects in period 2[2]	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo
Started	142	141	140
Completed	135	137	137
Not completed	7	4	3
Consent withdrawn by subject	2	1	1
Adverse event, non-fatal	2	-	-
Death	2	-	-
Lost to follow-up	-	3	2
Noncompliant with study visits	1	-	-

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The worldwide number enrolled is represented in Period 1, however one participant was randomized into the study did not receive injectable study drug at the discretion of the investigator. This participant was not included in the efficacy or safety analysis; however, the participant continued participation in the study and completed all study activities.

Baseline characteristics

Reporting groups	
Reporting group title	1.5 mg Dulaglutide
Reporting group description:	
Dulaglutide 1.5 milligrams (mg) given SC QW for 24 weeks.	
Reporting group title	0.75 mg Dulaglutide
Reporting group description:	
Dulaglutide 0.75 mg given subcutaneously (SC) once a week (QW) for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
Placebo given SC QW for 24 weeks.	

Reporting group values	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo
Number of subjects	142	141	140
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	56.17	58.55	57.10
standard deviation	± 9.26	± 9.14	± 9.59
Gender categorical Units: Subjects			
Female	65	72	74
Male	77	69	66
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	51	44	44
Not Hispanic or Latino	90	97	94
Unknown or Not Reported	1	0	2
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	2	4
Asian	0	1	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	3	6
White	127	127	124
More than one race	11	8	6
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Austria	9	11	9
Hungary	19	19	19
United States	30	30	28
Czechia	25	23	25
Mexico	27	28	28
Israel	6	6	6

Germany	12	11	10
Spain	14	13	15

Mean Hemoglobin A1c (HbA1c)			
Units: percentage of HbA1c			
arithmetic mean	8.04	8.04	8.05
standard deviation	± 0.65	± 0.61	± 0.61
Mean A1c Efficacy Estimand			
Units: percentage of A1c			
arithmetic mean	1.00	1.1	1.2
standard deviation	± 0.1	± 0.2	± 0.3

Reporting group values	Total		
Number of subjects	423		
Age categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	211		
Male	212		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	139		
Not Hispanic or Latino	281		
Unknown or Not Reported	3		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	7		
Asian	1		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	12		
White	378		
More than one race	25		
Unknown or Not Reported	0		
Region of Enrollment			
Units: Subjects			
Austria	29		
Hungary	57		
United States	88		
Czechia	73		
Mexico	83		
Israel	18		
Germany	33		
Spain	42		

Mean Hemoglobin A1c (HbA1c) Units: percentage of HbA1c arithmetic mean standard deviation	- -		
Mean A1c Efficacy Estimand Units: percentage of A1c arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	1.5 mg Dulaglutide
Reporting group description: Dulaglutide 1.5 milligrams (mg) given subcutaneously (SC) once a week (QW) for 24 weeks.	
Reporting group title	0.75 mg Dulaglutide
Reporting group description: Dulaglutide 0.75 mg given SC QW for 24 weeks.	
Reporting group title	Placebo
Reporting group description: Placebo given SC QW for 24 weeks.	
Reporting group title	1.5 mg Dulaglutide
Reporting group description: Dulaglutide 1.5 milligrams (mg) given SC QW for 24 weeks.	
Reporting group title	0.75 mg Dulaglutide
Reporting group description: Dulaglutide 0.75 mg given subcutaneously (SC) once a week (QW) for 24 weeks.	
Reporting group title	Placebo
Reporting group description: Placebo given SC QW for 24 weeks.	

Primary: Change from Baseline in Hemoglobin A1c (HbA1c) at 24 Weeks (Treatment-regimen Estimand)

End point title	Change from Baseline in Hemoglobin A1c (HbA1c) at 24 Weeks (Treatment-regimen Estimand)

End point description:

Least Squares mean (LS) of the HbA1c change from baseline to primary endpoint at week 24 was adjusted by treatment, country, SGLT2 inhibitor dose, metformin use, treatment-by-visit interactions as fixed effects, and baseline HbA1c as a covariate and participant as a random effect, via a mixed-model repeated measure (MMRM) analysis. The intent-to-treat (ITT) estimand [treatment(Tx)-regimen estimand] used all data including post-rescue data and compared the benefit of treatment regimens as they were actually taken.

Analysis Population Description (APD): All randomized participants who received at least one dose of study medication and had post-rescue data.

End point type	Primary
End point timeframe: Baseline, Week 24	

End point values	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	132	134	133	
Units: percentage of HbA1c				
least squares mean (standard error)	-1.34 (± 0.064)	-1.21 (± 0.064)	-0.54 (± 0.064)	

Statistical analyses

Statistical analysis title	1.5 mg Dulaglutide, Placebo Tx-regimen Estimand
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	265
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.94
upper limit	-0.63

Statistical analysis title	0.75 mg Dulaglutide, Placebo Tx-regimen Estimand
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	-0.49

Primary: Change from Baseline in the HbA1c at 24 Weeks (Efficacy Estimand)

End point title	Change from Baseline in the HbA1c at 24 Weeks (Efficacy Estimand)

End point description:

LS mean of the HbA1c change from baseline to primary endpoint at week 24 was adjusted by treatment, country, SGLT2 inhibitor dose, metformin use, treatment-by-visit interactions as fixed effects, and baseline HbA1c as a covariate and participant as a random effect, via a MMRM analysis. The efficacy estimand excluded post-rescue data and compared the benefit of randomized treatments as they were assigned.

Analysis Population Description: All randomized participants who received at least one dose of study drug and did not require additional or alternative antihyperglycemic medications.

End point type	Primary
End point timeframe: Baseline, Week 24	

End point values	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	140	138	134	
Units: percentage of HbA1c				
least squares mean (standard error)	-1.30 (± 0.062)	-1.19 (± 0.062)	-0.49 (± 0.063)	

Statistical analyses

Statistical analysis title	1.5 mg Dulaglutide, Placebo Efficacy Estimand
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	274
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.98
upper limit	-0.63

Statistical analysis title	0.75 mg Dulaglutide, Placebo Efficacy Estimand
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	272
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.87
upper limit	-0.52

Secondary: Percentage of Participants with HbA1c <7%

End point title	Percentage of Participants with HbA1c <7%

End point description:

Number of participants with an HbA1c value of <7% at Week 24 is measured using longitudinal logistic regression with repeated measurements will. The model will include independent variables of treatment, country, SGLT2 inhibitor dose, metformin use, visit, baseline HbA1c-by-visit interaction, treatment-by-visit, and baseline HbA1c as a covariate.

End point type	Secondary

End point timeframe:

24 Weeks

End point values	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	140[1]	139[2]	137[3]	
Units: percentage of participants				
number (not applicable)				
Tx-regimen Estimand (132, 134, 133)	71.21	60.45	31.58	
Efficacy Estimand (130, 131, 123)	71.54	61.83	32.52	

Notes:

[1] - All participants who received at least one dose of Dulaglutide with HBA1c at Week 24.

[2] - All participants who received at least one dose of Dulaglutide with HBA1c at Week 24

[3] - All participants who received at least one dose of Dulaglutide with HBA1c at Week 24

Statistical analyses

Statistical analysis title	1.5 mg Dulaglutide, Placebo Tx-regimen Estimand
Statistical analysis description:	
Tx-regimen Estimand	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	11.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.69
upper limit	23.37

Statistical analysis title	0.75 mg Dulaglutide, Placebo Tx-regimen Estimand
Statistical analysis description: Tx-regimen Estimand	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.56
upper limit	13.16

Statistical analysis title	1.5 mg Dulaglutide, Placebo Efficacy Estimand
Statistical analysis description: Efficacy Estimand	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	277
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	12.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.86
upper limit	24.79

Statistical analysis title	0.75 mg Dulaglutide, Placebo Efficacy Estimand
Statistical analysis description: Efficacy Estimand	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.13

Confidence interval	
level	95 %
sides	2-sided
lower limit	3.67
upper limit	13.86

Secondary: Change from Baseline in Body Weight at 24 Weeks

End point title	Change from Baseline in Body Weight at 24 Weeks

End point description:

LS mean of the body weight change from baseline to primary endpoint at week 24 was adjusted by treatment, country, SGLT2 inhibitor dose, metformin use, baseline HbA1c strata, treatment-by-visit interactions as fixed effects, and baseline body weight as a covariate and participant as a random effect, via a MMRM analysis.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142[4]	141[5]	140[6]	
Units: kilograms (kg)				
least squares mean (standard error)				
Tx-regimen Estimand (135, 136, 137)	-3.1 (± 0.30)	-2.6 (± 0.30)	-2.1 (± 0.30)	
Efficacy Estimand (133, 133, 127)	-3.1 (± 0.30)	-2.6 (± 0.30)	-2.3 (± 0.31)	

Notes:

[4] - All participants who received at least one dose of study drug.

[5] - All participants who received at least one dose of study drug.

[6] - All participants who received at least one dose of study drug.

Statistical analyses

Statistical analysis title	1.5 mg Dulaglutide, Placebo Tx-regimen Estimand

Statistical analysis description:

Tx-regimen Estimand

Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.027
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	-0.1

Statistical analysis title	0.75 mg Dulaglutide, Placebo Tx-regimen Estimand
Statistical analysis description: Tx-regimen Estimand	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.264
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	0.4

Statistical analysis title	1.5 mg Dulaglutide, Placebo Efficacy Estimand
Statistical analysis description: Efficacy Estimand	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.034
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	-0.1

Statistical analysis title	0.75 mg Dulaglutide, Placebo Efficacy Estimand
Statistical analysis description: Efficacy Estimand	
Comparison groups	0.75 mg Dulaglutide v Placebo

Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.321
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	0.4

Secondary: Change from Baseline in Fasting Serum Glucose (Central Laboratory) at 24 Weeks

End point title	Change from Baseline in Fasting Serum Glucose (Central Laboratory) at 24 Weeks

End point description:

LS mean of change from baseline was calculated using last observation carried forward (LOCF) by treatment group, analysis of covariance (ANCOVA), and the intent-to-treat population [(ITT) those participants who were randomized and received at least one dose of study drug].

Analysis Population Description: All participants who received at least one dose of study drug and had baseline and at least one post-baseline value.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	141	140	
Units: milligram/deciliter (mg/dL)				
least squares mean (standard error)				
Tx-regimen Estimand (134, 133, 132)	-31.6 (± 2.17)	-26.5 (± 2.18)	-6.9 (± 2.21)	
Efficacy Estimand Data (132, 130, 122)	-31.9 (± 2.11)	-26.0 (± 2.12)	-5.3 (± 2.21)	

Statistical analyses

Statistical analysis title	1.5 mg Dulaglutide, Placebo Tx-regimen Estimand

Statistical analysis description:

Tx-regimen Estimand

Comparison groups	1.5 mg Dulaglutide v Placebo

Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-24.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.8
upper limit	-18.6

Statistical analysis title	0.75 mg Dulaglutide, Placebo Tx-regimen Estimand
Statistical analysis description: Tx-regimen Estimand	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-19.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.7
upper limit	-13.6

Statistical analysis title	1.5 mg Dulaglutide, Placebo Efficacy Estimand
Statistical analysis description: Efficacy Estimand	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-26.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.7
upper limit	-20.6

Statistical analysis title	0.75 mg Dulaglutide, Placebo Efficacy Estimand
Statistical analysis description: Efficacy Estimand	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-20.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.7
upper limit	-14.6

Secondary: Change from Baseline in 6-Point Self-Monitored Plasma Glucose (SMPG) Profile at 24 Weeks

End point title	Change from Baseline in 6-Point Self-Monitored Plasma Glucose (SMPG) Profile at 24 Weeks

End point description:

The self-monitored plasma glucose (SMPG) data were collected at the following 6 time points: pre-morning meal; 2 hours post-morning meal; pre-midday meal; 2 hours post-midday meal; pre-evening meal; 2 hours post-evening meal. Least Squares (LS) means of change from baseline were calculated using a mixed-effects model for repeated measures (MMRM) with treatment, metformin, country, SGLT2i dose, baseline HbA1c strata, visit, and treatment-by-visit interaction as fixed effects and baseline as a covariate.

Analysis Population Description: All participants who received at least one dose of study drug and had baseline SMPG value and at least one post-baseline SMPG value.

End point type	Secondary
End point timeframe: Baseline, Week 24	

End point values	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142	141	140	
Units: mg/dL				
least squares mean (standard error)				
Pre-morning Morning Meal (128, 124, 128)	-27.8 (± 2.13)	-23.2 (± 2.17)	-8.1 (± 2.14)	
2-Hour Postprandial Morning Meal (121, 121, 119)	-44.6 (± 3.31)	-41.1 (± 3.30)	-20.1 (± 3.33)	
Pre-Mid Day Meal (127, 124, 126)	-26.0 (± 2.91)	-22.0 (± 2.94)	-7.7 (± 2.93)	

2-Hour Postprandial Mid Day Meal (122, 121, 118)	-31.8 (± 3.47)	-25.5 (± 3.47)	-12.8 (± 3.63)	
Pre-Evening Meal (128, 121, 124)	-30.3 (± 2.85)	-30.1 (± 2.93)	-7.5 (± 2.91)	
2-Hour Postprandial Evening Meal (122, 121, 117)	-36.0 (± 3.30)	-30.6 (± 3.31)	-13.9 (± 3.38)	

Statistical analyses

Statistical analysis title	1.5 mg Dulaglutide, Placebo Pre-Morning
Statistical analysis description: Pre-morning meal.	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-19.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.7
upper limit	-13.8

Statistical analysis title	0.75 mg Dulaglutide, Placebo Pre-Morning
Statistical analysis description: Pre-morning meal	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-15.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.2
upper limit	-9.2

Statistical analysis title	1.5 mg Dulaglutide, Placebo 2-hour Post Morning
Statistical analysis description: 2-hour postprandial morning meal	

Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-24.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.8
upper limit	-15.3

Statistical analysis title	0.75 mg Dulaglutide, Placebo 2-hour Post Morning
Statistical analysis description: 2-hour postprandial morning meal	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-21.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.3
upper limit	-11.8

Statistical analysis title	1.5 mg Dulaglutide, Placebo Pre-Mid Day
Statistical analysis description: Pre-mid day meal	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-18.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.4
upper limit	-10.2

Statistical analysis title	1.5 mg Dulaglutide, Placebo Pre-Mid Day
Statistical analysis description: Pre-midday meal	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-18.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.5
upper limit	-6.2

Statistical analysis title	1.5 mg Dulaglutide, Placebo 2-hour Post Mid Day
Statistical analysis description: 2-hour postprandial after mid day meal	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.8
upper limit	-9.3

Statistical analysis title	0.75 mg Dulaglutide, Placebo 2-hour Post Mid Day
Statistical analysis description: 2-hour postprandial after midday meal	
Comparison groups	0.75 mg Dulaglutide v Placebo

Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-12.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-22.5
upper limit	-3.1

Statistical analysis title	1.5 mg Dulaglutide, Placebo Pre-Evening
Statistical analysis description: Pre-evening meal	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-22.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.7
upper limit	-14.7

Statistical analysis title	0.75 mg, Placebo Pre-Evening
Statistical analysis description: Pre-evening meal	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-22.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-30.7
upper limit	-14.4

Statistical analysis title	1.5 mg Dulaglutide, Placebo 2-hour Post Evening
Statistical analysis description: 2-hour postprandial after evening meal	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-22.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-31.4
upper limit	-12.9

Statistical analysis title	0.75 mg, Placebo 2-hour Post Evening
Statistical analysis description: 2-hour postprandial after evening meal	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-16.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26
upper limit	-7.4

Secondary: Change from Baseline in Fasting Glucagon at 24 Weeks

End point title	Change from Baseline in Fasting Glucagon at 24 Weeks

End point description:

Change from baseline in fasting glucagon was analyzed using an ANCOVA model with last observation carried forward (LOCF) included in treatment, country, SGLT2i dose, metformin use, and baseline HbA1c strata as fixed effects and baseline fasting glucagon as a covariate (with and without post rescue data).

Analysis Population Description: All participants who received at least one dose of study drug and with non-missing baseline values and at least one post-baseline value at the specified time point.

End point type	Secondary

End point timeframe: Baseline, Week 24

End point values	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	134	132	128	
Units: picomole per liter (pmol/L)				
least squares mean (standard error)				
Tx-regimen Estimand (134, 132, 128)	-2.1 (± 0.39)	-1.5 (± 0.39)	-0.9 (± 0.40)	
Efficacy Estimand (133, 129, 118)	-2.2 (± 0.39)	-1.4 (± 0.39)	-0.9 (± 0.41)	

Statistical analyses

Statistical analysis title	1.5 mg Dulaglutide, Placebo Tx-regimen Estimand
Statistical analysis description: Tx-regimen Estimand	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	-0.1

Statistical analysis title	0.75 mg Dulaglutide, Placebo Tx-regimen Estimand
Statistical analysis description: Tx-regimen Estimand	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.273
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	0.5

Statistical analysis title	1.5 mg Dulaglutide, Placebo Efficacy Estimand
Statistical analysis description: Efficacy Estimand	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	262
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.023
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	-0.2

Statistical analysis title	0.75 mg Dulaglutide, Placebo Efficacy Estimand
Statistical analysis description: Efficacy Estimand	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	260
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32
Method	Regression, Linear
Parameter estimate	Mean difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	0.6

Secondary: Rate of Hypoglycemic Events Adjusted Per 30 Days	
End point title	Rate of Hypoglycemic Events Adjusted Per 30 Days

End point description:

A hypoglycemic event is defined as any time a participant feels that he/she is experiencing symptoms

and/or signs associated with hypoglycemia, and has a PG level of ≤70 mg/dL [≤3.9 millimole per liter(mmol/L)].

End point type	Secondary

End point timeframe:

Baseline through 24 Weeks

End point values	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142[7]	141[8]	140[9]	
Units: Number of events/participant/30 days				
arithmetic mean (standard deviation)				
Total Hypoglycemia	0.026 (± 0.1827)	0.022 (± 0.1375)	0.017 (± 0.1320)	
Documented Symptomatic Hypoglycemia	0.013 (± 0.1406)	0.013 (± 0.1030)	0.010 (± 0.0893)	
Asymptomatic Hypoglycemia	0.013 (± 0.1180)	0.008 (± 0.0639)	0.006 (± 0.0540)	
Probable Symptomatic	0.000 (± 0.0000)	0.001 (± 0.0152)	0.001 (± 0.0147)	
Relative Hypoglycemia	0.003 (± 0.0311)	0.001 (± 0.0150)	0.005 (± 0.0493)	
Nocturnal Hypoglycemia	0.002 (± 0.0288)	0.009 (± 0.0821)	0.000 (± 0.0000)	

Notes:

[7] - All participants who received at least one dose of study drug.

[8] - All participants who received at least one dose of study drug.

[9] - All participants who received at least one dose of study drug.

Statistical analyses

Statistical analysis title	1.5 mg Dulaglutide, Placebo Total Hypoglycemia

Statistical analysis description:

Total hypoglycemia with glucose <= 70 mg/dL

Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	0.75 mg Dulaglutide, Placebo Total Hypoglycemia

Statistical analysis description:

Total hypoglycemia glucose with <= 70 mg/dL

Comparison groups	0.75 mg Dulaglutide v Placebo

Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	1.5 mg Dulaglutide, Placebo Symptomatic
Statistical analysis description:	
Documented symptomatic hypoglycemia glucose with <= 70 mg/dL	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.683
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	0.75 mg Dulaglutide, Placebo Symptomatic
Statistical analysis description:	
Documented symptomatic hypoglycemia glucose with <= 70 mg/dL	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	1.5 mg Dulaglutide, Placebo Asymptomatic
Statistical analysis description:	
Asymptomatic hypoglycemia with glucose <= 70 mg/dL	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	0.75 mg Dulaglutide, Placebo Asymptomatic
Statistical analysis description:	
Asymptomatic hypoglycemia with glucose <= 70 mg/dL	
Comparison groups	0.75 mg Dulaglutide v Placebo

Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	1.5 mg , Placebo Probable Symptomatic
Statistical analysis description: Probable symptomatic hypoglycemia with glucose <= 70 mg/dL	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.496
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	0.75 mg , Placebo Probable Symptomatic
Statistical analysis description: Probable symptomatic hypoglycemia with glucose <= 70 mg/dL	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	1.5 mg Dulaglutide, Placebo Relative
Statistical analysis description: Relative hypoglycemia with glucose <= 70 mg/dL	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.621
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	0.75 mg Dulaglutide, Placebo Relative
Statistical analysis description: Relative hypoglycemia with glucose <= 70 mg/dL	
Comparison groups	0.75 mg Dulaglutide v Placebo

Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.622
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	1.5 mg Dulaglutide, Placebo Nocturnal
Statistical analysis description: Nocturnal hypoglycemia with glucose <= 70 mg/dL	
Comparison groups	1.5 mg Dulaglutide v Placebo
Number of subjects included in analysis	282
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	Wilcoxon (Mann-Whitney)

Statistical analysis title	0.75 mg Dulaglutide, Placebo Nocturnal
Statistical analysis description: Nocturnal hypoglycemia with glucose <= 70 mg/dL	
Comparison groups	0.75 mg Dulaglutide v Placebo
Number of subjects included in analysis	281
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.498
Method	Wilcoxon (Mann-Whitney)

Secondary: Number of Participants Requiring Rescue Therapy Due to Severe Persistent Hyperglycemia

End point title	Number of Participants Requiring Rescue Therapy Due to Severe Persistent Hyperglycemia
End point description: Rescue therapy was defined as any additional therapeutic intervention in participants who developed persistent, severe hyperglycemia despite full compliance with the assigned therapeutic regimen, or initiation of an alternative antihyperglycemic medication following study drug discontinuation.	
End point type	Secondary
End point timeframe: Baseline through 24 Weeks	

End point values	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142[10]	141[11]	140[12]	
Units: Participants				
number (not applicable)	0	3	2	

Notes:

[10] - All participants who had at least one dose of study drug.

[11] - All participants who had at least one dose of study drug.

[12] - All participants who had at least one dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adjudicated Acute Pancreatitis Events

End point title	Number of Participants With Adjudicated Acute Pancreatitis Events

End point description:

The number of participants with events of pancreatitis confirmed by adjudication were summarized cumulatively at 24 weeks. Pancreatitis events were adjudicated by a committee of physicians external to the Sponsor. A summary of serious and other non-serious events regardless of causality is located in the Reported Adverse Events module.

End point type	Secondary

End point timeframe:

Baseline through 24 Weeks

End point values	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142[13]	141[14]	140[15]	
Units: Participants				
number (not applicable)	0	0	0	

Notes:

[13] - All participants who had at least one dose of study drug.

[14] - All participants who had at least one dose of study drug.

[15] - All participants who had at least one dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adjudicated Cardiovascular (CV) Events

End point title	Number of Participants With Adjudicated Cardiovascular (CV) Events

End point description:

Death and selected nonfatal CV adverse events (AEs) were adjudicated by an independent committee of physicians with cardiology expertise external to the Sponsor. Nonfatal CV events that were to be adjudicated were myocardial infarction (MI); hospitalization for unstable angina; hospitalization for heart failure; coronary interventions such as coronary artery bypass graft (CABG) or (percutaneous coronary intervention (PCI); and cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack (TIA).

End point type	Secondary

End point timeframe:

Baseline through 24 Weeks

End point values	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	142[16]	141[17]	140[18]	
Units: Participants				
number (not applicable)				
Any CV Event	0	0	3	
Fatal CV Event	0	0	0	
Non-fatal CV Event	0	0	3	

Notes:

[16] - All participants who had at least one dose of study drug.

[17] - All participants who had at least one dose of study drug.

[18] - All participants who had at least one dose of study drug.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Baseline to end of study (up to 24 weeks)	
Adverse event reporting additional description: H9X-MC-GBGE	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	1.5 mg Dulaglutide
Reporting group description: -	
Reporting group title	0.75 mg Dulaglutide
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 142 (3.52%)	3 / 141 (2.13%)	5 / 140 (3.57%)
number of deaths (all causes)	2	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
endometrial cancer			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed[1]	1 / 65 (1.54%)	0 / 72 (0.00%)	0 / 74 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
endometrial sarcoma			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed[2]	1 / 65 (1.54%)	0 / 72 (0.00%)	0 / 74 (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
malignant neoplasm of conjunctiva			
alternative dictionary used: MedDRA 20.0			

subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	0 / 140 (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
prostate cancer			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed[3]	1 / 77 (1.30%)	0 / 69 (0.00%)	0 / 66 (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
Injury, poisoning and procedural complications			
hip fracture			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
injury			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 142 (0.00%)	0 / 141 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
spinal cord injury lumbar			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	0 / 140 (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
Cardiac disorders			
angina unstable			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 142 (0.00%)	0 / 141 (0.00%)	2 / 140 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
atrial fibrillation			
alternative dictionary used: MedDRA 20.0			

subjects affected / exposed	0 / 142 (0.00%)	0 / 141 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
atrial tachycardia			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 142 (0.00%)	0 / 141 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
myocardial infarction			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 142 (0.00%)	0 / 141 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
gastrointestinal haemorrhage			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
dyspnoea			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 142 (0.00%)	1 / 141 (0.71%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
clostridium difficile colitis			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	0 / 140 (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
erysipelas			
alternative dictionary used: MedDRA 20.0			

subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	0 / 140 (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
pneumonia			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 142 (0.70%)	0 / 141 (0.00%)	0 / 140 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
sepsis			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 142 (0.00%)	0 / 141 (0.00%)	1 / 140 (0.71%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.
[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: This event is gender specific, only occurring in male or female subjects. The number of subjects exposed has been adjusted accordingly.

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

Non-serious adverse events	1.5 mg Dulaglutide	0.75 mg Dulaglutide	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 142 (30.28%)	34 / 141 (24.11%)	29 / 140 (20.71%)
Nervous system disorders			
headache			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	8 / 142 (5.63%)	5 / 141 (3.55%)	13 / 140 (9.29%)
occurrences (all)	13	8	16
Gastrointestinal disorders			
diarrhoea			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	8 / 142 (5.63%)	14 / 141 (9.93%)	4 / 140 (2.86%)
occurrences (all)	10	16	5

nausea alternative dictionary used: MedDRA 20.0 subjects affected / exposed occurrences (all)	21 / 142 (14.79%) 32	7 / 141 (4.96%) 13	5 / 140 (3.57%) 6
Musculoskeletal and connective tissue disorders back pain alternative dictionary used: MedDRA 20.0 subjects affected / exposed occurrences (all)	13 / 142 (9.15%) 15	12 / 141 (8.51%) 14	10 / 140 (7.14%) 14
Infections and infestations viral upper respiratory tract infection alternative dictionary used: MedDRA 20.0 subjects affected / exposed occurrences (all)	9 / 142 (6.34%) 12	8 / 141 (5.67%) 10	11 / 140 (7.86%) 12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 August 2015	Protocol A - All available data for the primary analysis, up to 24 weeks, will be included, except those collected after initiation of glucose-lowering rescue therapy. - If study drug is permanently discontinued for acute pancreatitis or for a severe or serious allergic reaction, the participant will continue in the study on another glucose-lowering regimen. - For participants diagnosed with acute pancreatitis or experience a severe or serious allergic reaction, the participant will continue in the study on another glucose-lowering regimen.
28 March 2016	Protocol B - Two primary estimands to compare the placebo and the dulaglutide arms in terms of the primary measure the change from baseline to 24 weeks for HbA1c. One primary estimand will be an efficacy estimand which will not use post-rescue data and the other will be an intent-to-treat (ITT) estimand which will use post-rescue data (treatment-regimen estimand). - Analysis of the key secondary efficacy outcome measures will include datasets with and without post-rescue data. - The primary analysis for primary and key secondary efficacy measures will be mixed-model repeated measure (MMRM) analysis using restricted maximum likelihood (REML).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported