Clinical trial results:
A Randomized, Double-Blind Trial Comparing the Effect of Dulaglutide 1.5 mg with Placebo on Glycemic Control in Patients with Type 2 Diabetes on Basal Insulin Glargine

Summary

EudraCT number	2012-004229-25
Trial protocol	IT HU CZ ES GB
Global end of trial date	15 October 2015

Results information

Result version number	v1 (current)
This version publication date	28 October 2016
First version publication date	28 October 2016

Trial information

Trial identification

Sponsor protocol code	13195

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02152371
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Alias: H9X-MC-GBDI, Trial ID : 13195

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 October 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main purpose of this study is to evaluate the use of the study drug known as dulaglutide in participants with type II diabetes who are taking once-daily insulin glargine. The study will last about 31 weeks for each participant.

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	28 May 2014
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	Czech Republic: 52
Country: Number of subjects enrolled	Puerto Rico: 28
Country: Number of subjects enrolled	Hungary: 72
Country: Number of subjects enrolled	United States: 61
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Spain: 55
Worldwide total number of subjects	300
EEA total number of subjects	211

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)	187
From 65 to 84 years	113
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who met all inclusion criteria and none of the exclusion criteria entered a 2-week lead-in period. Only those participants who required further up-titration of the insulin glargine dose per treat-to-target (TTT) algorithm were randomized to one of two treatment groups.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Dulaglutide + Insulin Glargine

Arm description:

1.5 milligrams (mg) dulaglutide administered subcutaneously (SQ) once weekly for 28 weeks. Titrated insulin glargine administered SQ once daily for 28 weeks. Participants who are taking metformin should remain on stable doses.

Dulaglutide: Administered SQ

Insulin Glargine: Administered SQ

Metformin: Administered orally

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

Dosage and administration details:

1.5 milligrams (mg) Dulaglutide administered subcutaneously (SQ) once weekly for 28 weeks.

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin administered orally daily.

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

Dosage and administration details:

Titrated insulin glargine administered SQ once weekly for 28 weeks.

Arm title	Placebo + Insulin Glargine

Arm description:

Placebo administered SQ once weekly for 28 weeks. Titrated insulin glargine administered SQ once daily for 28 weeks. Participants who are taking metformin should remain on stable doses.

Placebo: Administered SQ

Insulin Glargine: Administered SQ

Metformin: Administered orally

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

Dosage and administration details:

Insulin Glargine administered subcutaneous once daily for 28 weeks.

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

Dosage and administration details:

Placebo administered SQ once weekly for 28 weeks.

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Metformin administered orally daily.

Number of subjects in period 1	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine
Started	150	150
Received at least 1 dose of study drug.	150	150
Completed	138	134
Not completed	12	16
Consent withdrawn by subject	3	7
Physician decision	-	2
Adverse event, non-fatal	6	2
Reason Not Given	-	1
Lost to follow-up	1	-
Protocol deviation	2	3
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Dulaglutide + Insulin Glargine

Reporting group description:

1.5 milligrams (mg) dulaglutide administered subcutaneously (SQ) once weekly for 28 weeks. Titrated insulin glargine administered SQ once daily for 28 weeks. Participants who are taking metformin should remain on stable doses.

Dulaglutide: Administered SQ

Insulin Glargine: Administered SQ

Metformin: Administered orally

Reporting group title	Placebo + Insulin Glargine

Reporting group description:

Placebo administered SQ once weekly for 28 weeks. Titrated insulin glargine administered SQ once daily for 28 weeks. Participants who are taking metformin should remain on stable doses.

Placebo: Administered SQ

Insulin Glargine: Administered SQ

Metformin: Administered orally

Reporting group values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine	Total
Number of subjects	150	150	300
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)	95	92	187
From 65-84 years	55	58	113
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	60.2	60.6	
standard deviation	± 9.47	± 10.07	-
Gender, Male/Female Units: participants			
Female	65	62	127
Male	85	88	173
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	26	25	51
Not Hispanic or Latino	104	104	208
Unknown or Not Reported	20	21	41

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	1	2	3
Black or African American	5	6	11
White	143	138	281
More than one race	1	3	4
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Czech Republic	25	27	52
Puerto Rico	12	16	28
Hungary	37	35	72
United States	32	29	61
Italy	13	15	28
United Kingdom	2	2	4
Spain	29	26	55
Metformin Use			
Number of participants with Metformin use at baseline			
Units: Subjects			
Metformin Use	134	131	265
No Metformin Use	16	19	35
Mean Insulin Glargine Dose Units: Units			
arithmetic mean	40.71	36.59	
standard deviation	± 23.12	± 21.46	-

End points

End points reporting groups

Reporting group title	Dulaglutide + Insulin Glargine

Reporting group description:

1.5 milligrams (mg) dulaglutide administered subcutaneously (SQ) once weekly for 28 weeks. Titrated insulin glargine administered SQ once daily for 28 weeks. Participants who are taking metformin should remain on stable doses.

Dulaglutide: Administered SQ

Insulin Glargine: Administered SQ

Metformin: Administered orally

Reporting group title	Placebo + Insulin Glargine

Reporting group description:

Placebo administered SQ once weekly for 28 weeks. Titrated insulin glargine administered SQ once daily for 28 weeks. Participants who are taking metformin should remain on stable doses.

Placebo: Administered SQ

Insulin Glargine: Administered SQ

Metformin: Administered orally

Primary: Change from Baseline to 28 Weeks in Hemoglobin A1c (HbA1c)

End point title	Change from Baseline to 28 Weeks in Hemoglobin A1c (HbA1c)

End point description:

HbA1c is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. Least-squares (LS) mean and standard error (SE) changes from baseline in HbA1c at 28 weeks were measured using mixed model regression and restricted maximum likelihood (REML) with treatment, pooled country, visit, and treatment-by -visit interaction as fixed effects, baseline as covariate, and participant as a random effect.

End point type	Primary

End point timeframe:

Baseline, 28 Weeks

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: percentage of change				
least squares mean (standard error)	-1.44 (± 0.09)	-0.67 (± 0.09)		

Statistical analyses

Statistical analysis title	Change from Baseline to 28 Weeks HbA1c
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed-effect Model Repeated Measure
Parameter estimate	LS Means Diff
Point estimate	-0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	-0.56
Variability estimate	Standard error of the mean
Dispersion value	0.1

Secondary: Change from Baseline to 28 Weeks in Fasting Serum Glucose (FSG)

End point title	Change from Baseline to 28 Weeks in Fasting Serum Glucose (FSG)

End point description:

FSG is a test to determine glucose levels after an overnight fast and prior to any meal. LS means of the FSG change from baseline to primary endpoint at wee 28 was adjusted by treatment, country, metformin use, week, treatment-by-week interaction, and baseline FSG as covariate, via a MMRM analysis.

End point type	Secondary

End point timeframe:

Baseline, 28 Weeks

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: milligram per deciliter (mg/dL)				
least squares mean (standard error)	-44.63 (± 4.16)	-27.9 (± 4.08)		

Statistical analyses

Statistical analysis title	Change from Baseline to 28 Weeks in FSG
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine

Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Diff
Point estimate	-16.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.02
upper limit	-7.44
Variability estimate	Standard error of the mean
Dispersion value	4.72

Secondary: Change from Baseline to 28 Weeks in 7-Point Self Monitored Plasma Glucose (SMPG)

End point title	Change from Baseline to 28 Weeks in 7-Point Self Monitored Plasma Glucose (SMPG)

End point description:

The LS means of the 7-point SMPG change from baseline (BL) to primary endpoint at week 28 was measured using a MMRM analysis adjusted by treatment, country, metformin use, week, treatment-by-week interaction, and baseline SMPG as covariate.

End point type	Secondary

End point timeframe:

Baseline, 28 Weeks

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: mg/dL				
least squares mean (standard error)				
Pre-Morning Meal (n=133,129)	-44.03 (± 2.71)	-35.97 (± 2.64)		
Morning Meal 2-Hour Postprandial (n=123,119)	-64.16 (± 4.31)	-46.97 (± 4.27)		
Pre-Midday Meal (n=133,127)	-40.89 (± 3.72)	-25.34 (± 3.62)		
Midday Meal 2-Hour Post Prandial (n=123,117)	-51.13 (± 4.4)	-32.98 (± 4.33)		
Pre-Evening Meal (n=133,129)	-43.68 (± 4.21)	-28.71 (± 4.07)		
Evening Meal 2-Hour Postprandial (n=126,122)	-48.63 (± 5.22)	-27.35 (± 5.16)		
3:00 AM (n=124,117)	-39.77 (± 4.27)	-20.3 (± 4.23)		

Statistical analyses

Statistical analysis title	Change from BL to 28 Weeks SMPG Pre-Morning Meal
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.007
Method	Mixed models analysis
Parameter estimate	LS Mean Diff
Point estimate	-8.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.87
upper limit	-2.25
Variability estimate	Standard error of the mean
Dispersion value	2.95

Statistical analysis title	BL to 28 Wks SMPG Morning Meal 2hr Postprandial
Statistical analysis description: Change from Baseline to 28 Weeks SMPG Morning Meal 2-Hour Postprandial	
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Diff
Point estimate	-17.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.96
upper limit	-8.4
Variability estimate	Standard error of the mean
Dispersion value	4.45

Statistical analysis title	BL to 28 Weeks SMPG Pre-Midday Meal

Statistical analysis description:	
Change from Baseline to 28 Weeks SMPG Pre-Midday Meal	
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Diff
Point estimate	-15.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.58
upper limit	-7.52
Variability estimate	Standard error of the mean
Dispersion value	4.08

Statistical analysis title	BL to 28 Weeks SMPG Midday Meal 2-hr Postprandial
Statistical analysis description:	
Change from Baseline to 28 Weeks SMPG Midday Meal 2-Hour Postprandial	
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Diff
Point estimate	-18.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.18
upper limit	-9.12
Variability estimate	Standard error of the mean
Dispersion value	4.58

Statistical analysis title	BL to 28 Weeks SMPG Pre-Evening Meal
Statistical analysis description:	
Change from Baseline to 28 Weeks SMPG Pre-Evening Meal	
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine

Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Diff
Point estimate	-14.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-23.93
upper limit	-5.99
Variability estimate	Standard error of the mean
Dispersion value	4.55

Statistical analysis title	BL to 28 Weeks SMPG Evening Meal 2-hr Postprandial
Statistical analysis description:	
Change from Baseline to 28 Weeks SMPG Evening Meal 2-Hour Postprandial	
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Diff
Point estimate	-21.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.46
upper limit	-10.1
Variability estimate	Standard error of the mean
Dispersion value	5.68

Statistical analysis title	BL to 28 Weeks SMPG at 3:00AM
Statistical analysis description:	
Change from Baseline to 28 Weeks SMPG at 3:00AM	
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Mean Diff
Point estimate	-19.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.77
upper limit	-10.18
Variability estimate	Standard error of the mean
Dispersion value	4.72

Secondary: Change from Baseline to 28 Weeks in Body Weight

End point title	Change from Baseline to 28 Weeks in Body Weight

End point description:

LS means of the body weight change from baseline to primary endpoint at week 28 was adjusted by treatment, country, metformin use, week, treatment-by-week interaction, and baseline body weight as covariate, via a MMRM analysis.

End point type	Secondary

End point timeframe:

Baseline, 28 Weeks

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: kg				
least squares mean (standard error)	-1.91 (± 0.3)	0.5 (± 0.3)		

Statistical analyses

Statistical analysis title	Change From Baseline to 28 Wks Body Weight MMRM
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Means Difference
Point estimate	-2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.19
upper limit	-1.64
Variability estimate	Standard error of the mean
Dispersion value	0.39

Secondary: Change from Baseline to 28 Weeks in Daily Mean Insulin Glargine Dose

End point title	Change from Baseline to 28 Weeks in Daily Mean Insulin Glargine Dose

End point description:

LS means of the insulin dose change from baseline to primary endpoint at week 28 was adjusted by treatment, country, metformin use, week, treatment-by-week interaction, and baseline insulin dose as covariate, via a MMRM analysis.

End point type	Secondary

End point timeframe:

Baseline, 28 Weeks

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: units (u)				
least squares mean (standard error)				
Units (U)	12.75 (± 2.27)	25.94 (± 2.3)		

Statistical analyses

Statistical analysis title	Change From Baseline to 28 Wks Insulin Glargine
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	LS Means Diff
Point estimate	-13.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.55
upper limit	-6.84
Variability estimate	Standard error of the mean
Dispersion value	3.21

Secondary: Number of Participants with Investigator Reported and Adjudicated

Cardiovascular Events

End point title	Number of Participants with Investigator Reported and Adjudicated Cardiovascular Events

End point description:

Cardiovascular (CV) adverse events (AEs) were adjudicated by an independent committee of physicians with cardiology expertise external to the sponsor. Deaths occurring during the study treatment period and nonfatal CV AEs were to be adjudicated. Nonfatal CV events that were to be adjudicated were myocardial infarction; 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 (CVA/stroke), and transient ischemic attack (TIA).

End point type	Secondary

End point timeframe:

Baseline through 28 Weeks

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: participants				
number (not applicable)	3	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Self-Reported Events of Hypoglycemia

End point title	Percentage of Participants with Self-Reported Events of Hypoglycemia

End point description:

Hypoglycemic events (HE) were classified as severe (defined as episodes requiring the assistance of another person to actively administer resuscitative actions), documented symptomatic (defined as any time a participant feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia, and has a plasma glucose level of =<3.9 mmol/L), asymptomatic (defined as events not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose of =<3.9 mmol/L), nocturnal (defined as any hypoglycemic event that occurred between bedtime and waking), or probable symptomatic (defined as events during which symptoms of hypoglycemia were not accompanied by a plasma glucose determination). The percentage of participants with self-reported hypoglycemic events is presented. The percentage of participants with self-reported hypoglycemic events is presented.

End point type	Secondary

End point timeframe:

Baseline through 28 Weeks

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: percentage of particpants				
number (not applicable)				
Symptomatic	35.3	30		
Asymptomatic	42.7	39.3		
Severe	0.7	0		
Nocturnal	28	28.7		
Probable Symptomatic	2.7	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Discontinuing the Study Due to Severe, Persistent Hyperglycemia

End point title	Percentage of Participants Discontinuing the Study Due to Severe, Persistent Hyperglycemia

End point description:

Percentage of participants who discontinued due to severe, persistent hyperglycemia are presented.

End point type	Secondary

End point timeframe:

Baseline through 28 Weeks

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: percentage of participants				
number (not applicable)	0	0		

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 cases of acute pancreatitis confirmed by adjudication. A summary of serious and other non-serious AEs, regardless of causality, is located in the Reported Adverse Events module.

End point type	Secondary

End point timeframe:

Baseline through 28 Weeks

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Thyroid Tumors/Neoplasms (Including C-Cell Hyperplasia)

End point title	Number of Participants With Thyroid Tumors/Neoplasms (Including C-Cell Hyperplasia)

End point description:

Number of participants with one or more thyroid tumors/neoplasms of any type, including C-cell hyperplasia and thyroid cysts, is presented.

End point type	Secondary

End point timeframe:

Baseline through 28 Weeks

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: participants				
number (not applicable)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Dulaglutide Anti-Drug Antibodies

End point title	Number of Participants with Dulaglutide Anti-Drug Antibodies

End point description:

Dulaglutide anti-drug antibodies (ADA) were assessed at baseline, Weeks 12 and 28. A participant was considered to have treatment-emergent (TE) dulaglutide ADAs if the participant had at least 1 titer that was TE relative to baseline, defined as a 4-fold or greater increase in titer from baseline measurement.

End point type	Secondary

End point timeframe:

Baseline, Week 12 and Week 28

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149[1]	149[2]		
Units: participants				
number (not applicable)	0	2		

Notes:

[1] - Participants receiving at least 1 dose of study drug and had at least 1 Dulaglutide ADA test result.

[2] - Participants receiving at least 1 dose of study drug and had at least 1 Dulaglutide ADA test result.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Achieving HbA1c Targets of <7.0% or ≤6.5%

End point title	Percentage of Participants Achieving HbA1c Targets of <7.0% or ≤6.5%

End point description:

Percentage of participants who achieved a target HbA1c target of <7%, without weight gain and without documented symptomatic hypoglycemia at 28 weeks were analyzed using regression model, controlling for treatment, pre-treatment, baseline HbA1c and country.

End point type	Secondary

End point timeframe:

28 Weeks

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: percentage of participants				
number (not applicable)				
HbA1c <= 6.5	50.7	16.7		
HbA1c < 7.0	69.3	35.3		

Statistical analyses

Statistical analysis title	Participants Achieving HbA1c Targets ≤6.5%
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine

Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	6.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.7
upper limit	12

Statistical analysis title	Participants Achieving HbA1c Targets of <7.0%
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Log odds ratio
Point estimate	5.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.35
upper limit	9.73

Secondary: Percentage of Participants Achieving HbA1c Target of <7.0% and Without Weight Gain (<0.1 kilograms [kg]) at 28 Weeks and Without Documented Symptomatic Hypoglycemia During the Maintenance Period (Weeks 12-28)

End point title	Percentage of Participants Achieving HbA1c Target of <7.0% and Without Weight Gain (<0.1 kilograms [kg]) at 28 Weeks and Without Documented Symptomatic Hypoglycemia During the Maintenance Period (Weeks 12-28)

End point description:

End point type	Secondary

End point timeframe:

28 Weeks

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: percentage of participants				
number (not applicable)	40.7	16.7		

Statistical analyses

Statistical analysis title	HbA1c Target <7.0% w/o Wt Gain and Hypoglycemia
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.32
upper limit	7.47

Secondary: Percentage of Participants Achieving HbA1c Target of <7.0% at 28 Weeks and Without Documented Symptomatic Hypoglycemia during the Maintenance Period (Weeks 12-28)

End point title	Percentage of Participants Achieving HbA1c Target of <7.0% at 28 Weeks and Without Documented Symptomatic Hypoglycemia during the Maintenance Period (Weeks 12-28)

End point description:

Percentage of participants achieving target HbA1c of <7.0% at 28 weeks without documented symptomatic hypoglycemia are presented. Documented symptomatic hypoglycemia is defined as any time a participant experienced symptoms and or signs associated with hypoglycemia and had a plasma glucose of <=70 mg/dL.

End point type	Secondary

End point timeframe:

28 Weeks

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: percentage of participants				
number (not applicable)	52	28		

Statistical analyses

Statistical analysis title	HbA1c Target of <7.0% w/o Symptom Hypoglycemia
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.09
upper limit	6.23

Secondary: Percentage of Participants Achieving HbA1c Target of <7.0% and Without Weight Gain (<0.1 kg)

End point title	Percentage of Participants Achieving HbA1c Target of <7.0% and Without Weight Gain (<0.1 kg)
End point description:	
The percentage of participants achieving a target HbA1c of <7.0% without weight gain is presented.	
End point type	Secondary
End point timeframe:	
28 Weeks	

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: percentage of participants				
number (not applicable)	52.7	20		

Statistical analyses

Statistical analysis title	Achieving HbA1c Target of <7.0% W/O Weight Gain
Comparison groups	Dulaglutide + Insulin Glargine v Placebo + Insulin Glargine
Number of subjects included in analysis	300
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.26
upper limit	9.62

Secondary: Rate of Hypoglycemic Events up to 28 Weeks

End point title	Rate of Hypoglycemic Events up to 28 Weeks

End point description:

The rate of total hypoglycemic events any type per 30 days is presented. The hypoglycemia rate per 30 days during defined period is calculated by the number of hypoglycemia events within the period/number of days participant at risk within the period*30 days.

End point type	Secondary

End point timeframe:

Baseline through 28 Weeks

End point values	Dulaglutide + Insulin Glargine	Placebo + Insulin Glargine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	150	150		
Units: Rate				
arithmetic mean (standard deviation)	0.63 (± 1.24)	0.7 (± 1.32)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Entire Study	
Adverse event reporting additional description:	
H9X-MC-GBDI	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Dula_1.5
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Dula_1.5	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 150 (6.00%)	7 / 150 (4.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
hepatic cancer			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Injury, poisoning and procedural complications			
lower limb fracture			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
angina unstable			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 150 (0.67%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
atrial fibrillation			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
bradycardia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 150 (1.33%)	0 / 150 (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 18.1			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
myocardial infarction			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (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			
carotid artery stenosis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
cerebral infarction			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
transient ischaemic attack			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	2 / 150 (1.33%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
non-cardiac chest pain			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
granulomatous liver disease			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
skin ulcer			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
intervertebral disc protrusion			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
osteoarthritis			

alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
gastroenteritis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
viral infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	0 / 150 (0.00%)	1 / 150 (0.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
hypoglycaemia			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	1 / 150 (0.67%)	0 / 150 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dula_1.5	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 150 (34.00%)	29 / 150 (19.33%)	
Gastrointestinal disorders			
diarrhoea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	17 / 150 (11.33%)	6 / 150 (4.00%)	
occurrences (all)	19	6	
dyspepsia			
alternative dictionary used: MedDRA 18.1			

subjects affected / exposed	9 / 150 (6.00%)	0 / 150 (0.00%)	
occurrences (all)	9	0	
nausea			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	18 / 150 (12.00%)	2 / 150 (1.33%)	
occurrences (all)	23	3	
vomiting			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	9 / 150 (6.00%)	0 / 150 (0.00%)	
occurrences (all)	11	0	
Infections and infestations			
nasopharyngitis			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	6 / 150 (4.00%)	14 / 150 (9.33%)	
occurrences (all)	7	19	
upper respiratory tract infection			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	11 / 150 (7.33%)	10 / 150 (6.67%)	
occurrences (all)	18	10	
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 18.1			
subjects affected / exposed	10 / 150 (6.67%)	0 / 150 (0.00%)	
occurrences (all)	11	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported