Clinical trial results:
A Phase 2, Double-Blind, Placebo-Controlled, 18-Week Trial of Investigational Dulaglutide Doses versus Placebo in Patients with Type 2 Diabetes on Metformin Monotherapy

Summary

EudraCT number	2016-002494-34
Trial protocol	PL CZ
Global end of trial date	14 August 2017

Results information

Result version number	v1 (current)
This version publication date	30 July 2018
First version publication date	30 July 2018

Trial information

Trial identification

Sponsor protocol code	H9X-MC-GBGJ

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02973100
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 16568

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly, EU_Lilly_Clinical_Trials@lilly.com
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559, EU_Lilly_Clinical_Trials@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	14 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy and safety of investigational doses of dulaglutide in participants with type 2 diabetes on metformin monotherapy.

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	01 December 2016
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	Romania: 21
Country: Number of subjects enrolled	United States: 174
Country: Number of subjects enrolled	Czech Republic: 37
Country: Number of subjects enrolled	Poland: 44
Country: Number of subjects enrolled	Mexico: 41
Worldwide total number of subjects	317
EEA total number of subjects	102

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)	245

From 65 to 84 years	72
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study consisted of 3 periods: an approximately 2-week lead-in period, followed by an 18-week treatment period, and a 4-week safety follow-up period.

Pre-assignment

Screening details:

Not applicable

Period 1

Period 1 title	Overall Study
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	Placebo

Arm description:

Participants received placebo once weekly (QW) by subcutaneous (SC) injection.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo was administered through subcutaneous injection.

Arm title	Dulaglutide 1.5 milligrams (mg)

Arm description:

Participants received 1.5mg of dulaglutide QW by SC injection.

Arm type	Active comparator
Investigational medicinal product name	Dulaglutide
Investigational medicinal product code	LY2189265
Other name	Trulicity
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

1.5mg of Dulaglutide administered SC

Arm title	Dulaglutide 3.0 milligrams (mg)

Arm description:

Participants received 3.0mg of dulaglutide QW by SC injection.

Arm type	Experimental
Investigational medicinal product name	Dulaglutide
Investigational medicinal product code	LY2189265
Other name	Trulicity
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:
3.0mg of Dulaglutide administered SC

Arm title	Dulaglutide 4.5 milligrams (mg)

Arm description:
Participants received 4.5mg of dulaglutide QW by SC injection.

Arm type	Experimental
Investigational medicinal product name	Dulaglutide
Investigational medicinal product code	LY2189265
Other name	Trulicity
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:
4.5mg of Dulaglutide administered SC

Number of subjects in period 1	Placebo	Dulaglutide 1.5 milligrams (mg)	Dulaglutide 3.0 milligrams (mg)
Started	82	81	79
Received at Least 1 Dose of Study Drug	81	81	79
Completed	75	73	75
Not completed	7	8	4
Consent withdrawn by subject	3	5	1
Failed to attend Safety followup period	-	-	1
Adverse event, non-fatal	1	2	1
Notification of change in address	-	-	-
Lost to follow-up	3	1	1

Number of subjects in period 1	Dulaglutide 4.5 milligrams (mg)
Started	76
Received at Least 1 Dose of Study Drug	76
Completed	69
Not completed	7
Consent withdrawn by subject	4
Failed to attend Safety followup period	-
Adverse event, non-fatal	2
Notification of change in address	1
Lost to follow-up	-

Period 2

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

Arms

Are arms mutually exclusive?	No
Arm title	Placebo

Arm description:

Participants received placebo once weekly (QW) by subcutaneous (SC) injection.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Placebo was administered through subcutaneous injection.

Arm title	Dulaglutide 1.5 milligrams (mg)

Arm description:

Participants received 1.5mg of dulaglutide QW by SC injection.

Arm type	Active comparator
Investigational medicinal product name	Dulaglutide
Investigational medicinal product code	LY2189265
Other name	Trulicity
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

1.5mg of Dulaglutide administered SC

Arm title	Dulaglutide 3.0 milligrams (mg)

Arm description:

Participants received 3.0mg of dulaglutide QW by SC injection.

Arm type	Experimental
Investigational medicinal product name	Dulaglutide
Investigational medicinal product code	LY2189265
Other name	Trulicity
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

3.0mg of Dulaglutide administered SC

Arm title	Dulaglutide 4.5 milligrams (mg)

Arm description:

Participants received 4.5mg of dulaglutide QW by SC injection.

Arm type	Experimental

Investigational medicinal product name	Dulaglutide
Investigational medicinal product code	LY2189265
Other name	Trulicity
Pharmaceutical forms	Solution for injection/infusion in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

4.5mg of Dulaglutide administered SC

Notes:

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

Justification: The baseline characteristics are calculated for participants who received at least one dose of study drug as per SAP.

Number of subjects in period 2	Placebo	Dulaglutide 1.5 milligrams (mg)	Dulaglutide 3.0 milligrams (mg)
Started	81	81	79
Completed	75	73	75
Not completed	6	8	4
Consent withdrawn by subject	2	5	1
Failed to attend Safety followup period	-	-	1
Adverse event, non-fatal	1	2	1
Notification of change in address	-	-	-
Lost to follow-up	3	1	1

Number of subjects in period 2	Dulaglutide 4.5 milligrams (mg)
Started	76
Completed	69
Not completed	7
Consent withdrawn by subject	4
Failed to attend Safety followup period	-
Adverse event, non-fatal	2
Notification of change in address	1
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo once weekly (QW) by subcutaneous (SC) injection.	
Reporting group title	Dulaglutide 1.5 milligrams (mg)
Reporting group description:	
Participants received 1.5mg of dulaglutide QW by SC injection.	
Reporting group title	Dulaglutide 3.0 milligrams (mg)
Reporting group description:	
Participants received 3.0mg of dulaglutide QW by SC injection.	
Reporting group title	Dulaglutide 4.5 milligrams (mg)
Reporting group description:	
Participants received 4.5mg of dulaglutide QW by SC injection.	

Reporting group values	Placebo	Dulaglutide 1.5 milligrams (mg)	Dulaglutide 3.0 milligrams (mg)
Number of subjects	81	81	79
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)	65	59	62
From 65-84 years	16	22	17
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	56.52	57.65	55.90
standard deviation	± 8.93	± 9.79	± 10.74
Gender categorical Units: Subjects			
Female	33	42	44
Male	48	39	35
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	35	32	38
Not Hispanic or Latino	46	49	40
Unknown or Not Reported	0	0	1
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	10	6	9
Asian	0	0	1

Native Hawaiian or Other Pacific Islander	1	0	0
Black or African American	6	6	6
White	59	68	58
More than one race	5	1	4
Unknown or Not Reported	0	0	1
Region of Enrollment Units: Subjects			
Romania	6	6	5
United States	42	45	44
Czech Republic	10	9	10
Poland	13	11	10
Mexico	10	10	10
Baseline Hemoglobin A1c (HbA1c) Units: Percentage of glycosylated hemoglobin			
arithmetic mean	8.08	8.02	8.16
standard deviation	± 0.79	± 0.80	± 0.92

Reporting group values	Dulaglutide 4.5 milligrams (mg)	Total	
Number of subjects	76	317	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	59	245	
From 65-84 years	17	72	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	57.13		
standard deviation	± 9.63	-	
Gender categorical Units: Subjects			
Female	40	159	
Male	36	158	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	30	135	
Not Hispanic or Latino	45	180	
Unknown or Not Reported	1	2	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	6	31	
Asian	3	4	
Native Hawaiian or Other Pacific Islander	0	1	

Black or African American	6	24	
White	59	244	
More than one race	2	12	
Unknown or Not Reported	0	1	
Region of Enrollment Units: Subjects			
Romania	4	21	
United States	43	174	
Czech Republic	8	37	
Poland	10	44	
Mexico	11	41	
Baseline Hemoglobin A1c (HbA1c) Units: Percentage of glycosylated hemoglobin			
arithmetic mean	8.12		
standard deviation	± 0.81	-	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received placebo once weekly (QW) by subcutaneous (SC) injection.	
Reporting group title	Dulaglutide 1.5 milligrams (mg)
Reporting group description:	
Participants received 1.5mg of dulaglutide QW by SC injection.	
Reporting group title	Dulaglutide 3.0 milligrams (mg)
Reporting group description:	
Participants received 3.0mg of dulaglutide QW by SC injection.	
Reporting group title	Dulaglutide 4.5 milligrams (mg)
Reporting group description:	
Participants received 4.5mg of dulaglutide QW by SC injection.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo once weekly (QW) by subcutaneous (SC) injection.	
Reporting group title	Dulaglutide 1.5 milligrams (mg)
Reporting group description:	
Participants received 1.5mg of dulaglutide QW by SC injection.	
Reporting group title	Dulaglutide 3.0 milligrams (mg)
Reporting group description:	
Participants received 3.0mg of dulaglutide QW by SC injection.	
Reporting group title	Dulaglutide 4.5 milligrams (mg)
Reporting group description:	
Participants received 4.5mg of dulaglutide QW by SC injection.	

Primary: Change from Baseline in Hemoglobin A1c (HbA1c)

End point title	Change from Baseline in Hemoglobin A1c (HbA1c)
End point description:	
HbA1c is the glycosylated fraction of hemoglobin A. HbA1c is measured to identify average plasma glucose concentration over prolonged periods of time. Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with baseline as a covariate, pooled country, treatment, time, treatment*time as fixed effects. Analysis Population Description (APD): All randomized participants who received at least one dose of study drug and had postbaseline values, excluding post rescue data for Hemoglobin A1c.	
End point type	Primary
End point timeframe:	
Baseline, Week 18	

End point values	Placebo	Dulaglutide 1.5 milligrams (mg)	Dulaglutide 3.0 milligrams (mg)	Dulaglutide 4.5 milligrams (mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	73	73	66
Units: Percentage of glycosylated hemoglobin				
least squares mean (standard error)	-0.44 (± 0.101)	-1.23 (± 0.099)	-1.31 (± 0.099)	-1.40 (± 0.103)

Statistical analyses

Statistical analysis title	Change from Baseline in HbA1c
Comparison groups	Placebo v Dulaglutide 1.5 milligrams (mg)
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.07
upper limit	-0.53

Statistical analysis title	Change from Baseline in HbA1c
Comparison groups	Placebo v Dulaglutide 3.0 milligrams (mg)
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.14
upper limit	-0.6

Statistical analysis title	Change from Baseline in HbA1c
Comparison groups	Placebo v Dulaglutide 4.5 milligrams (mg)

Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.24
upper limit	-0.69

Secondary: Percentage of Participants with HbA1c of <7.0%

End point title	Percentage of Participants with HbA1c of <7.0%

End point description:

Hemoglobin A1c (HbA1c) is the glycosylated fraction of hemoglobin A. HbA1c is measured primarily to identify average plasma glucose concentration over prolonged periods of time.
Analysis Population Description: All randomized participants who received at least one dose of study drug and had postbaseline values, excluding post rescue data for Hemoglobin A1c.

End point type	Secondary

End point timeframe:

Week 18

End point values	Placebo	Dulaglutide 1.5 milligrams (mg)	Dulaglutide 3.0 milligrams (mg)	Dulaglutide 4.5 milligrams (mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	73	73	66
Units: Percentage of Participants				
number (not applicable)	20	71.2	71.2	68.2

Statistical analyses

Statistical analysis title	Percentage of Participants with HbA1c of <7.0%
Comparison groups	Placebo v Dulaglutide 1.5 milligrams (mg)
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	24.489

Confidence interval	
level	95 %
sides	2-sided
lower limit	8.368
upper limit	71.667

Statistical analysis title	Percentage of Participants with HbA1c of <7.0%
Comparison groups	Placebo v Dulaglutide 3.0 milligrams (mg)
Number of subjects included in analysis	143
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	27.906
Confidence interval	
level	95 %
sides	2-sided
lower limit	9.238
upper limit	84.3

Statistical analysis title	Percentage of Participants with HbA1c of <7.0%
Comparison groups	Placebo v Dulaglutide 4.5 milligrams (mg)
Number of subjects included in analysis	136
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	21.852
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.672
upper limit	62.242

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

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

End point description:

Fasting serum glucose (FSG) is a test to determine how much glucose (sugar) is in a serum sample after an overnight fast. Least Squares (LS) means was determined by MMRM methodology with baseline as a covariate, pooled country, baseline HbA1c strata using >=8% as cutoff, treatment, time, treatment*time as fixed effects.
Analysis Population Description: All randomized participants who received at least one dose of study drug and had postbaseline values, excluding post rescue data for FSG.

End point type	Secondary
End point timeframe: Baseline, Week 18	

End point values	Placebo	Dulaglutide 1.5 milligrams (mg)	Dulaglutide 3.0 milligrams (mg)	Dulaglutide 4.5 milligrams (mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	62	67	61
Units: millimole/liter (mmol/L)				
least squares mean (standard error)	-0.69 (± 0.257)	-2.01 (± 0.261)	-1.92 (± 0.250)	-2.11 (± 0.263)

Statistical analyses

Statistical analysis title	Change from Baseline in FSG
Comparison groups	Placebo v Dulaglutide 1.5 milligrams (mg)
Number of subjects included in analysis	125
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.02
upper limit	-0.62

Statistical analysis title	Change from Baseline in FSG
Comparison groups	Placebo v Dulaglutide 3.0 milligrams (mg)
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.91
upper limit	-0.54

Statistical analysis title	Change from Baseline in FSG
Comparison groups	Placebo v Dulaglutide 4.5 milligrams (mg)
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.12
upper limit	-0.72

Secondary: Change from Baseline in Body Weight

End point title	Change from Baseline in Body Weight

End point description:

Least Squares (LS) mean was determined by mixed-model repeated measures (MMRM) model with baseline as a covariate, pooled country, baseline HbA1c strata using >=8% as cutoff, treatment, time, treatment*time as fixed effects.
Analysis Population Description: All randomized participants who received at least one dose of study drug and had postbaseline values, excluding post rescue data for body weight.

End point type	Secondary

End point timeframe:

Baseline, Week 18

End point values	Placebo	Dulaglutide 1.5 milligrams (mg)	Dulaglutide 3.0 milligrams (mg)	Dulaglutide 4.5 milligrams (mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	70	72	74	67
Units: Kilograms (Kg)				
least squares mean (standard error)	-1.6 (± 0.39)	-2.8 (± 0.39)	-3.9 (± 0.39)	-4.1 (± 0.41)

Statistical analyses

Statistical analysis title	Change from Baseline in Body Weight
Comparison groups	Placebo v Dulaglutide 1.5 milligrams (mg)

Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.025
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	-0.2

Statistical analysis title	Change from Baseline in Body Weight
Comparison groups	Placebo v Dulaglutide 3.0 milligrams (mg)
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	-1.3

Statistical analysis title	Change from Baseline in Body Weight
Comparison groups	Placebo v Dulaglutide 4.5 milligrams (mg)
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	-1.5

Secondary: Percentage of Participants Discontinuing Study Drug Due to Adverse

Events

End point title	Percentage of Participants Discontinuing Study Drug Due to Adverse Events

End point description:

Adverse event (AE) defined as any unfavorable medical event, newly emerged or a deterioration of a preexisting condition, in other words any untoward medical occurrence in a patient administered a pharmaceutical product, without regard to the possibility of a causal relationship, that occurred after the visit for informed consent and up to the visit for completion of administration, or discontinuation.
Analysis Population Description: All randomized participants who received study drug and had postbaseline data for safety analyses.

End point type	Secondary

End point timeframe:

Baseline through Week 18

End point values	Placebo	Dulaglutide 1.5 milligrams (mg)	Dulaglutide 3.0 milligrams (mg)	Dulaglutide 4.5 milligrams (mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	81	79	76
Units: Percentage of Participants				
number (not applicable)	4.9	6.2	10.1	13.2

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Documented Symptomatic Hypoglycemia

End point title	Rate of Documented Symptomatic Hypoglycemia

End point description:

Hypoglycemic events (HE) were classified as severe, documented symptomatic (defined as an HE with typical symptoms of hypoglycemia and a blood glucose level of ≤3.9 millimoles per liter [mmol/L]). Hypoglycemia rate per 30 days was summarized at each visit by treatment group. The rate of hypoglycemia was analyzed using a generalized estimation equations model with a negative binomial distribution and a Log link. LS mean was determined by MMRM methodology with baseline hypoglycemia rate, pooled country, HbA1c at Baseline, treatment, with log of exposure in days divided by 365.25 as the offset.
APD: All randomized participants who received at least one dose of study drug and had postbaseline values, excluding post rescue values for hypoglycemic Episodes.

End point type	Secondary

End point timeframe:

Week 18

End point values	Placebo	Dulaglutide 1.5 milligrams (mg)	Dulaglutide 3.0 milligrams (mg)	Dulaglutide 4.5 milligrams (mg)
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	81	79	76
Units: Episodes/participant/365.25 days				
least squares mean (standard error)	0.00 (± 0.000)	0.00 (± 0.000)	0.00 (± 0.000)	0.00 (± 0.001)

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): The Maximum Drug Concentration at Steady State (Cmax,ss) of Dulaglutide

End point title	Pharmacokinetics (PK): The Maximum Drug Concentration at Steady State (Cmax,ss) of Dulaglutide

End point description:

Plasma samples for PK analysis were combined measure obtained from 0, 2, 4, 6, 10, 18, 22 weeks and until early termination of the visit. Cmax takes all time points post dose into account and one value was reported.
Analysis Population Description: All randomized participants who received at least one dose of the study drug and have evaluable PK data.

End point type	Secondary

End point timeframe:

Predose, 0, 2, 4, 6, 10, 18, 22 weeks and early termination

End point values	Dulaglutide 1.5 milligrams (mg)	Dulaglutide 3.0 milligrams (mg)	Dulaglutide 4.5 milligrams (mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	79	76	
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (confidence interval 90%)	90.4 (38.9 to 170)	151 (64.3 to 277)	204 (87.2 to 377)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics: Area Under the Concentration-Time Curve at Steady State From Time Zero to 168 Hours (AUC[0-168], ss) of Dulaglutide

End point title	Pharmacokinetics: Area Under the Concentration-Time Curve at Steady State From Time Zero to 168 Hours (AUC[0-168], ss) of Dulaglutide

End point description:

AUC[0-168h] is a combined measure obtained from 0, 2, 4, 6, 10, 18, 22 weeks and until early termination of the visit.
Analysis Population Description: All randomized participants who received at least one dose of the study drug and have evaluable PK data.

End point type	Secondary

End point timeframe:

Predose, 0, 2, 4, 6, 10, 18, 22 weeks and early termination

End point values	Dulaglutide 1.5 milligrams (mg)	Dulaglutide 3.0 milligrams (mg)	Dulaglutide 4.5 milligrams (mg)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	81	79	76	
Units: nanogram*hour per milliliter (ng*h/mL)				
arithmetic mean (confidence interval 90%)	11800 (5300 to 21300)	26700 (15300 to 41400)	36600 (21100 to 56500)	

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-GBGJ	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Dulaglutide 4.5 milligrams (mg)
Reporting group description: -	
Reporting group title	Dulaglutide 3.0 milligrams (mg)
Reporting group description: -	
Reporting group title	Dulaglutide 1.5 milligrams (mg)
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Dulaglutide 4.5 milligrams (mg)	Dulaglutide 3.0 milligrams (mg)	Dulaglutide 1.5 milligrams (mg)
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 76 (3.95%)	7 / 79 (8.86%)	3 / 81 (3.70%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
invasive ductal breast carcinoma			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 79 (1.27%)	0 / 81 (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, poisoning and procedural complications			
traumatic intracranial haemorrhage			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

hypotension			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Cardiac disorders			
acute myocardial infarction			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
atrioventricular block second degree			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Myocardial infarction			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pericarditis			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
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			
abdominal pain upper			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 76 (1.32%)	0 / 79 (0.00%)	0 / 81 (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
pancreatitis			
alternative dictionary used: MedDRA 20.0			

subjects affected / exposed	1 / 76 (1.32%)	0 / 79 (0.00%)	0 / 81 (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
vomiting			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Hepatobiliary disorders			
cholecystitis			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 76 (1.32%)	0 / 79 (0.00%)	0 / 81 (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
cholecystitis acute			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 76 (1.32%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cholelithiasis			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	0 / 79 (0.00%)	1 / 81 (1.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
pulmonary oedema			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Renal and urinary disorders			
renal failure			
alternative dictionary used: MedDRA 20.0			

subjects affected / exposed	0 / 76 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Musculoskeletal and connective tissue disorders			
spinal pain			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
bronchitis			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 76 (1.32%)	0 / 79 (0.00%)	0 / 81 (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
cholecystitis infective			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
fungal oesophagitis			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
peritonsillar abscess			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
Metabolism and nutrition disorders			
hyperglycaemic hyperosmolar nonketotic syndrome			
alternative dictionary used: MedDRA 20.0			

subjects affected / exposed	0 / 76 (0.00%)	0 / 79 (0.00%)	0 / 81 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hyponatraemia			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 79 (1.27%)	0 / 81 (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
hypovolaemia			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 79 (1.27%)	0 / 81 (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

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 81 (4.94%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
invasive ductal breast carcinoma			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
traumatic intracranial haemorrhage			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
hypotension			
alternative dictionary used: MedDRA 20.0			

subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
acute myocardial infarction			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
atrioventricular block second degree			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
pericarditis			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
abdominal pain upper			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
pancreatitis			
alternative dictionary used: MedDRA 20.0			

subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
vomiting				
alternative dictionary used: MedDRA 20.0				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
cholecystitis				
alternative dictionary used: MedDRA 20.0				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
cholecystitis acute				
alternative dictionary used: MedDRA 20.0				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
cholelithiasis				
alternative dictionary used: MedDRA 20.0				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
pulmonary oedema				
alternative dictionary used: MedDRA 20.0				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
renal failure				
alternative dictionary used: MedDRA 20.0				

subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
spinal pain			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
bronchitis			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
cholecystitis infective			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
fungal oesophagitis			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
peritonsillar abscess			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
hyperglycaemic hyperosmolar nonketotic syndrome			
alternative dictionary used: MedDRA 20.0			

subjects affected / exposed	1 / 81 (1.23%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
hyponatraemia				
alternative dictionary used: MedDRA 20.0				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
hypovolaemia				
alternative dictionary used: MedDRA 20.0				
subjects affected / exposed	0 / 81 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Dulaglutide 4.5 milligrams (mg)	Dulaglutide 3.0 milligrams (mg)	Dulaglutide 1.5 milligrams (mg)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 76 (51.32%)	49 / 79 (62.03%)	36 / 81 (44.44%)
Investigations			
weight decreased			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	2 / 76 (2.63%)	5 / 79 (6.33%)	3 / 81 (3.70%)
occurrences (all)	2	6	6
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	4 / 79 (5.06%)	1 / 81 (1.23%)
occurrences (all)	0	4	1
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	4 / 76 (5.26%)	5 / 79 (6.33%)	4 / 81 (4.94%)
occurrences (all)	5	6	6
headache			

alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	5 / 76 (6.58%)	10 / 79 (12.66%)	4 / 81 (4.94%)
occurrences (all)	8	13	4
General disorders and administration site conditions			
fatigue			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	7 / 76 (9.21%)	4 / 79 (5.06%)	1 / 81 (1.23%)
occurrences (all)	7	4	1
Gastrointestinal disorders			
abdominal discomfort			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	4 / 76 (5.26%)	2 / 79 (2.53%)	0 / 81 (0.00%)
occurrences (all)	10	2	0
abdominal pain			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	7 / 76 (9.21%)	1 / 79 (1.27%)	3 / 81 (3.70%)
occurrences (all)	7	1	4
constipation			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	6 / 76 (7.89%)	4 / 79 (5.06%)	5 / 81 (6.17%)
occurrences (all)	6	4	5
diarrhoea			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	16 / 76 (21.05%)	18 / 79 (22.78%)	9 / 81 (11.11%)
occurrences (all)	32	34	17
dyspepsia			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	8 / 76 (10.53%)	5 / 79 (6.33%)	6 / 81 (7.41%)
occurrences (all)	13	5	10
eructation			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	6 / 76 (7.89%)	1 / 79 (1.27%)	3 / 81 (3.70%)
occurrences (all)	6	1	3
gastrooesophageal reflux disease			
alternative dictionary used:			

MedDRA 20.0			
subjects affected / exposed	0 / 76 (0.00%)	1 / 79 (1.27%)	5 / 81 (6.17%)
occurrences (all)	0	1	5
nausea			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	23 / 76 (30.26%)	20 / 79 (25.32%)	18 / 81 (22.22%)
occurrences (all)	40	32	45
vomiting			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	10 / 76 (13.16%)	9 / 79 (11.39%)	9 / 81 (11.11%)
occurrences (all)	16	15	20
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	4 / 76 (5.26%)	1 / 79 (1.27%)	0 / 81 (0.00%)
occurrences (all)	4	2	0
Infections and infestations			
influenza			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 76 (1.32%)	4 / 79 (5.06%)	1 / 81 (1.23%)
occurrences (all)	1	4	1
upper respiratory tract infection			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 76 (1.32%)	5 / 79 (6.33%)	1 / 81 (1.23%)
occurrences (all)	1	5	1
viral upper respiratory tract infection			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	3 / 76 (3.95%)	6 / 79 (7.59%)	2 / 81 (2.47%)
occurrences (all)	4	6	2
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	6 / 76 (7.89%)	13 / 79 (16.46%)	3 / 81 (3.70%)
occurrences (all)	6	17	3

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 81 (35.80%)		
Investigations			
weight decreased			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
Vascular disorders			
hypertension			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	6		
headache			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	7 / 81 (8.64%)		
occurrences (all)	11		
General disorders and administration site conditions			
fatigue			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	2 / 81 (2.47%)		
occurrences (all)	3		
Gastrointestinal disorders			
abdominal discomfort			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
abdominal pain			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		

constipation			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
diarrhoea			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	9 / 81 (11.11%)		
occurrences (all)	10		
dyspepsia			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
eructation			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
nausea			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	5		
vomiting			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	4 / 81 (4.94%)		
occurrences (all)	6		
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		
Infections and infestations			

influenza			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	0 / 81 (0.00%)		
occurrences (all)	0		
upper respiratory tract infection			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	3 / 81 (3.70%)		
occurrences (all)	5		
viral upper respiratory tract infection			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	5 / 81 (6.17%)		
occurrences (all)	7		
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 20.0			
subjects affected / exposed	1 / 81 (1.23%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 August 2016	Amendment (a): Supraventricular arrhythmias and cardiac conduction disorders were added as adverse events of special interest.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported