Clinical trial results:
A 56-week, Multicenter, Open-label, Active-controlled, Randomized Study to Evaluate the Efficacy and Safety of Efpeglenatide Once Weekly Compared to Dulaglutide Once Weekly in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Metformin

Summary

EudraCT number	2017-002956-10
Trial protocol	PL HU
Global end of trial date	17 November 2020

Results information

Result version number	v1 (current)
This version publication date	14 November 2021
First version publication date	14 November 2021

Trial information

Trial identification

Sponsor protocol code	EFC14829

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03684642
WHO universal trial number (UTN)	U1111-1205-3150

Notes:

Sponsors

Sponsor organisation name	Sanofi-aventis Recherche & Développement
Sponsor organisation address	1, Avenue Pierre Brossolette, Chilly Mazarin, France, 91385
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.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	21 January 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 November 2020
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the noninferiority of once weekly injection of efpeglenatide 4 or 6 milligrams (mg) in comparison to once weekly injection of dulaglutide 1.5 mg on glycated hemoglobin (HbA1c) change from Baseline to Week 56 in subjects with Type 2 diabetes mellitus (T2DM) inadequately controlled with metformin.

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy:

Metformin oral tablet administered as per the Investigator’s prescription. Dose was kept stable throughout the study.

Evidence for comparator: -

Actual start date of recruitment	26 September 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 166
Country: Number of subjects enrolled	Hungary: 112
Country: Number of subjects enrolled	United States: 498
Country: Number of subjects enrolled	Ukraine: 132
Worldwide total number of subjects	908
EEA total number of subjects	278

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)	567
From 65 to 84 years	340
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 45 active sites in 4 countries. A total of 1608 subjects were screened between 26 September 2018 and 17 December 2019, out of which 700 were screen failures. Screen failures were mainly due to inclusion criteria not met.

Pre-assignment

Screening details:

A total of 908 subjects were randomized in 1:1:1 ratio to either efpeglenatide 4 mg, efpeglenatide 6 mg, or dulaglutide 1.5 mg treatment arms, stratified by screening HbA1c values (less than [<]8%, greater than or equal to [>=]8 percent [%]) and by body mass index (BMI) (<30 kilogram per meter square [kg/m^2] and >=30 kg/m^2) on Day 1.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Efpeglenatide 4 mg

Arm description:

Subjects received Efpeglenatide subcutaneous (SC) injection once weekly up to Week 56 on top of metformin. Subjects initiated dosing at 2 mg once weekly and increased every 2 weeks to the maximum of 4 mg once weekly for the treatment duration.

Arm type	Experimental
Investigational medicinal product name	Efpeglenatide
Investigational medicinal product code	SAR439977
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Efpeglenatide SC injection once weekly on top of metformin.

Arm title	Efpeglenatide 6 mg

Arm description:

Subjects received Efpeglenatide SC injection once weekly up to Week 56 on top of metformin. Subjects initiated dosing at 2 mg once weekly and increased every 2 weeks to the maximum of 6 mg once weekly for the treatment duration.

Arm type	Experimental
Investigational medicinal product name	Efpeglenatide
Investigational medicinal product code	SAR439977
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Efpeglenatide SC injection once weekly on top of metformin.

Arm title	Dulaglutide 1.5 mg

Arm description:

Subjects received Dulaglutide SC injection once weekly up to Week 56 on top of metformin. Subjects initiated dosing at 0.75 mg once weekly and increased after 2 weeks to 1.5 mg once weekly for the treatment duration.

Arm type	Active comparator
Investigational medicinal product name	Dulaglutide
Investigational medicinal product code	
Other name	Trulicity™
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dulaglutide SC injection once weekly on top of metformin.

Number of subjects in period 1	Efpeglenatide 4 mg	Efpeglenatide 6 mg	Dulaglutide 1.5 mg
Started	303	302	303
Treated	303	302	302
Completed	200	169	197
Not completed	103	133	106
Adverse Event	6	15	11
Randomized and not treated	-	-	1
Withdrawal by Subject	35	53	23
Other than specified	62	60	67
Poor compliance to protocol	-	4	1
Missing completion status but aliveat last contact	-	1	2
Lack of efficacy	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Efpeglenatide 4 mg
Reporting group description:	
Subjects received Efpeglenatide subcutaneous (SC) injection once weekly up to Week 56 on top of metformin. Subjects initiated dosing at 2 mg once weekly and increased every 2 weeks to the maximum of 4 mg once weekly for the treatment duration.	
Reporting group title	Efpeglenatide 6 mg
Reporting group description:	
Subjects received Efpeglenatide SC injection once weekly up to Week 56 on top of metformin. Subjects initiated dosing at 2 mg once weekly and increased every 2 weeks to the maximum of 6 mg once weekly for the treatment duration.	
Reporting group title	Dulaglutide 1.5 mg
Reporting group description:	
Subjects received Dulaglutide SC injection once weekly up to Week 56 on top of metformin. Subjects initiated dosing at 0.75 mg once weekly and increased after 2 weeks to 1.5 mg once weekly for the treatment duration.	

Reporting group values	Efpeglenatide 4 mg	Efpeglenatide 6 mg	Dulaglutide 1.5 mg
Number of subjects	303	302	303
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	60.3	60.0	59.4
standard deviation	± 9.6	± 10.1	± 10.1
Gender categorical Units: Subjects			
Female	142	157	153
Male	161	145	150
Race/Ethnicity Units: Subjects			
White	271	263	275
Black or African American	24	30	18
Asian	5	3	6
Other	3	4	2
Not reported	0	2	2
Body Mass Index (BMI) Units: kg/m^2			
arithmetic mean	33.4	33.4	33.4
standard deviation	± 6.1	± 6.2	± 6.4
Baseline Glycated Hemoglobin (HbA1c %) Units: percentage of HbA1c			
arithmetic mean	8.12	8.07	8.11
standard deviation	± 0.82	± 0.78	± 0.81

Reporting group values	Total		
Number of subjects	908		

Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	452		
Male	456		
Race/Ethnicity Units: Subjects			
White	809		
Black or African American	72		
Asian	14		
Other	9		
Not reported	4		
Body Mass Index (BMI) Units: kg/m^2 arithmetic mean standard deviation	 -		
Baseline Glycated Hemoglobin (HbA1c %) Units: percentage of HbA1c arithmetic mean standard deviation	 -		

End points

End points reporting groups

Reporting group title	Efpeglenatide 4 mg
Reporting group description:	
Subjects received Efpeglenatide subcutaneous (SC) injection once weekly up to Week 56 on top of metformin. Subjects initiated dosing at 2 mg once weekly and increased every 2 weeks to the maximum of 4 mg once weekly for the treatment duration.	
Reporting group title	Efpeglenatide 6 mg
Reporting group description:	
Subjects received Efpeglenatide SC injection once weekly up to Week 56 on top of metformin. Subjects initiated dosing at 2 mg once weekly and increased every 2 weeks to the maximum of 6 mg once weekly for the treatment duration.	
Reporting group title	Dulaglutide 1.5 mg
Reporting group description:	
Subjects received Dulaglutide SC injection once weekly up to Week 56 on top of metformin. Subjects initiated dosing at 0.75 mg once weekly and increased after 2 weeks to 1.5 mg once weekly for the treatment duration.	
Subject analysis set title	Efpeglenatide 4 mg
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received Efpeglenatide SC injection once weekly up to Week 56 on top of metformin. Subjects initiated dosing at 2 mg once weekly and increased every 2 weeks to the maximum of 4 mg once weekly for the treatment duration.	

Primary: Change From Baseline to Week 56 in HbA1c

End point title	Change From Baseline to Week 56 in HbA1c
End point description:	
Adjusted Least square (LS) means and Standard errors (SE) were obtained from analysis of covariance (ANCOVA) model to account for missing data. Missing values were imputed by baseline observation carried forward (BOCF)-like multiple imputation method. Analysis was performed on modified intent-to-treat (mITT) population which included subjects who completed study treatment; or who discontinued study treatment and completed/discontinued study before early termination; or who discontinued treatment before early termination and discontinued study due to early termination; or who discontinued treatment due to early termination within 30 days of target Week 56 visit.	
End point type	Primary
End point timeframe:	
Baseline to Week 56	

End point values	Efpeglenatide 4 mg	Efpeglenatide 6 mg	Dulaglutide 1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	257	254	250	
Units: percentage of HbA1c				
least squares mean (standard error)	-1.12 (± 0.06)	-1.17 (± 0.06)	-1.09 (± 0.06)	

Statistical analyses

Statistical analysis title	Efpeglenatide 4 mg versus Dulaglutide 1.5 mg

Statistical analysis description:

A hierarchical step-down testing procedure was used to control type 1 error. Analysis was performed using ANCOVA model with the treatment groups, randomisation strata, and geographical region as fixed classification effects, and Baseline HbA1c value as a continuous covariate.

Comparison groups	Efpeglenatide 4 mg v Dulaglutide 1.5 mg
Number of subjects included in analysis	507
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	LS Mean difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

[1] - Non-inferiority of Efpeglenatide vs. Dulaglutide was demonstrated if the upper bound of the two-sided 95% confidence interval (CI) for the difference between groups was <=0.3%.

Statistical analysis title	Efpeglenatide 6 mg versus Dulaglutide 1.5 mg

Statistical analysis description:

A hierarchical step-down testing procedure was used to control type 1 error. Analysis was performed using ANCOVA model with the treatment groups, randomisation strata, and geographical region as fixed classification effects, and Baseline HbA1c value as a continuous covariate.

Comparison groups	Efpeglenatide 6 mg v Dulaglutide 1.5 mg
Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	LS Mean Difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.09

Notes:

[2] - Non-inferiority of Efpeglenatide vs. Dulaglutide was demonstrated if the upper bound of the two-sided 95% CI for the difference between groups was <=0.3%.

Statistical analysis title	Efpeglenatide 4 mg versus Dulaglutide 1.5 mg
Comparison groups	Efpeglenatide 4 mg v Dulaglutide 1.5 mg

Number of subjects included in analysis	507
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7064 [3]
Method	ANCOVA

Notes:

[3] - Threshold for significance at the level of 0.05.

Statistical analysis title	Efpeglenatide 6 mg versus Dulaglutide 1.5 mg
Comparison groups	Efpeglenatide 6 mg v Dulaglutide 1.5 mg
Number of subjects included in analysis	504
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3427 [4]
Method	ANCOVA

Notes:

[4] - Threshold for significance at the level of 0.05.

Secondary: Change From Baseline to Week 56 in Body Weight

End point title	Change From Baseline to Week 56 in Body Weight

End point description:

Adjusted LS means and SE were obtained from ANCOVA model to account for missing data. Missing values were imputed by BOCF-like multiple imputation method. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 56

End point values	Efpeglenatide 4 mg	Efpeglenatide 6 mg	Dulaglutide 1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	257	254	250	
Units: kilogram				
least squares mean (standard error)	-2.87 (± 0.64)	-3.04 (± 0.67)	-2.81 (± 0.66)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With HbA1c <7.0%

End point title	Number of Subjects With HbA1c <7.0%

End point description:

Subjects who had no available assessment for HbA1c at Week 56 were considered as non-responders. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Week 56

End point values	Efpeglenatide 4 mg	Efpeglenatide 6 mg	Dulaglutide 1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	257	254	250	
Units: subjects	155	157	150	

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 56 in Fasting Plasma Glucose (FPG)

End point title	Change From Baseline to Week 56 in Fasting Plasma Glucose (FPG)

End point description:

Adjusted LS means and SE were obtained from ANCOVA model to account for missing data. Missing values were imputed by BOCF-like multiple imputation method. Analysis was performed on mITT population.

End point type	Secondary

End point timeframe:

Baseline to Week 56

End point values	Efpeglenatide 4 mg	Efpeglenatide 6 mg	Dulaglutide 1.5 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	257	254	250	
Units: millimoles per liter (mmol/L)				
least squares mean (standard error)	-1.81 (± 0.15)	-1.57 (± 0.15)	-1.71 (± 0.15)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With At Least One Hypoglycemic Events (Documented Symptomatic Hypoglycemia <3.0 mmol/ L [<54 mg/dL], Severe Hypoglycemia)

End point title	Number of Subjects With At Least One Hypoglycemic Events (Documented Symptomatic Hypoglycemia <3.0 mmol/ L [<54 mg/dL], Severe Hypoglycemia)[5]

End point description:

Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of <3.0 mmol/L (54 milligrams per

deciliter [mg/dL]). Severe hypoglycemia was an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Analysis was performed on safety population which included subjects who received at least 1 dose or part of a dose of the Investigational Medicinal Product (IMP), analyzed according to the treatment actually received. 10 subjects randomised to Efpeglenatide 6 mg received 4 mg dose for longer duration, and considered in the Efpeglenatide 4 mg group for safety analysis.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was reported for the arms applicable for the endpoint.

End point values	Efpeglenatide 6 mg	Dulaglutide 1.5 mg	Efpeglenatide 4 mg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	292	302	313	
Units: subjects				
Documented symptomatic hypoglycemia (<54 mg/dL)	1	0	3	
Severe hypoglycemia	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Hypoglycemic Events (Documented Symptomatic Hypoglycemia <3.0 mmol/L [<54 mg/dL] and Severe Hypoglycemia) Per Subject-Year

End point title	Number of Hypoglycemic Events (Documented Symptomatic Hypoglycemia <3.0 mmol/L [<54 mg/dL] and Severe Hypoglycemia) Per Subject-Year[6]

End point description:

Documented symptomatic hypoglycemia was an event during which typical symptoms of hypoglycemia were accompanied by a measured plasma glucose concentration of <3.0 mmol/L (<54 mg/dL). Severe hypoglycemia was an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Analysis was performed on safety population. 10 subjects randomised to Efpeglenatide 6 mg received 4 mg dose for longer duration, and considered in the Efpeglenatide 4 mg group for safety analysis.

End point type	Secondary

End point timeframe:

Baseline up to Week 56

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was reported for the arms applicable for the endpoint.

End point values	Efpeglenatide 6 mg	Dulaglutide 1.5 mg	Efpeglenatide 4 mg	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	292	302	313	
Units: events per subject-year				
number (not applicable)				

Documented symptomatic hypoglycemia (<54 mg/dL)	0.01	0	0.01	
Severe hypoglycemia	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from signature of informed consent up to end of study. Time frame for reporting of treatment emergent adverse events (TEAEs) was from first dose up to 30 days after last injection of the IMP (Week 60).

Adverse event reporting additional description:

TEAEs were defined as AEs that developed or worsened during the treatment-emergent period. Analysis was performed on safety population. For safety analysis, subjects were included in the treatment group in which they were exposed for longer duration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Efpeglenatide 4 mg

Reporting group description:

Subjects received Efpeglenatide SC injection once weekly up to Week 56 on top of metformin. Subjects initiated dosing at 2 mg once weekly and increased every 2 weeks to the maximum of 4 mg once weekly for the treatment duration. Included 10 subjects randomized to Efpeglenatide 6 mg who received 4 mg for longer duration and considered in the Efpeglenatide 4 mg for safety analysis.

Reporting group title	Efpeglenatide 6 mg

Reporting group description:

Subjects received Efpeglenatide SC injection once weekly up to Week 56 on top of metformin. Subjects initiated dosing at 2 mg once weekly and increased every 2 weeks to the maximum of 6 mg once weekly for the treatment duration. 10 subjects were excluded as they received 4 mg for longer duration and considered in the Efpeglenatide 4 mg group for safety analysis.

Reporting group title	Dulaglutide 1.5 mg

Reporting group description:

Subjects received Dulaglutide SC injection once weekly up to Week 56 on top of metformin. Subjects initiated dosing at 0.75 mg once weekly and increased after 2 weeks to 1.5 mg once weekly for the treatment duration.

Serious adverse events	Efpeglenatide 4 mg	Efpeglenatide 6 mg	Dulaglutide 1.5 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 313 (6.39%)	23 / 292 (7.88%)	20 / 302 (6.62%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign Salivary Gland Neoplasm			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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
Colon Cancer Metastatic			

subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (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 Melanoma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (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
Meningioma Benign			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (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
Papillary Renal Cell Carcinoma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (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
Renal Neoplasm			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
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 Meningioma Benign			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive Urgency			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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
Peripheral Arterial Occlusive Disease			

subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign Prostatic Hyperplasia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (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
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (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
Chronic Obstructive Pulmonary Disease			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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
Pulmonary Embolism			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	2 / 302 (0.66%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Mental Status Changes			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (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			
Concussion			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament Sprain			

subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Graft Occlusion			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Myocardial Infarction			
subjects affected / exposed	1 / 313 (0.32%)	2 / 292 (0.68%)	0 / 302 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina Pectoris			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (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
Angina Unstable			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial Fibrillation			
subjects affected / exposed	1 / 313 (0.32%)	1 / 292 (0.34%)	2 / 302 (0.66%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular Block Complete			
subjects affected / exposed	0 / 313 (0.00%)	2 / 292 (0.68%)	0 / 302 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac Failure			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Coronary Artery Disease			

subjects affected / exposed	2 / 313 (0.64%)	0 / 292 (0.00%)	0 / 302 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Ischaemia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus Node Dysfunction			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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
Supraventricular Tachycardia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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
Nervous system disorders			
Carpal Tunnel Syndrome			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (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
Cerebrovascular Accident			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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
Dizziness			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (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
Sciatica			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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
Syncope			

subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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
Transient Ischaemic Attack			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular Encephalopathy			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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
Blood and lymphatic system disorders			
Iron Deficiency Anaemia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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
Gastrointestinal disorders			
Colitis Ulcerative			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (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
Diverticulum Intestinal Haemorrhagic			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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
Enteritis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (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

Inguinal Hernia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (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
Omental Necrosis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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
Pancreatitis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis Chronic			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 313 (0.32%)	2 / 292 (0.68%)	0 / 302 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	1 / 313 (0.32%)	1 / 292 (0.34%)	0 / 302 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic Kidney Disease			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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

Nephrolithiasis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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
Subcapsular Renal Haematoma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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			
Covid-19 Pneumonia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis Infective			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 313 (0.32%)	1 / 292 (0.34%)	0 / 302 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia Urinary Tract Infection			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	1 / 313 (0.32%)	1 / 292 (0.34%)	0 / 302 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sialoadenitis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 292 (0.00%)	1 / 302 (0.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal Infection			
subjects affected / exposed	1 / 313 (0.32%)	0 / 292 (0.00%)	0 / 302 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 313 (0.00%)	1 / 292 (0.34%)	0 / 302 (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

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

Non-serious adverse events	Efpeglenatide 4 mg	Efpeglenatide 6 mg	Dulaglutide 1.5 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	202 / 313 (64.54%)	180 / 292 (61.64%)	178 / 302 (58.94%)
Investigations			
Lipase Increased			
subjects affected / exposed	27 / 313 (8.63%)	19 / 292 (6.51%)	24 / 302 (7.95%)
occurrences (all)	34	22	29

Nervous system disorders			
Dizziness			
subjects affected / exposed	18 / 313 (5.75%)	10 / 292 (3.42%)	10 / 302 (3.31%)
occurrences (all)	18	15	11
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	24 / 313 (7.67%)	30 / 292 (10.27%)	16 / 302 (5.30%)
occurrences (all)	32	39	25
Abdominal Pain Upper			
subjects affected / exposed	22 / 313 (7.03%)	16 / 292 (5.48%)	18 / 302 (5.96%)
occurrences (all)	22	20	18
Constipation			
subjects affected / exposed	32 / 313 (10.22%)	34 / 292 (11.64%)	19 / 302 (6.29%)
occurrences (all)	33	37	21
Diarrhoea			
subjects affected / exposed	93 / 313 (29.71%)	83 / 292 (28.42%)	90 / 302 (29.80%)
occurrences (all)	128	120	134
Dyspepsia			
subjects affected / exposed	26 / 313 (8.31%)	17 / 292 (5.82%)	15 / 302 (4.97%)
occurrences (all)	30	18	20
Nausea			
subjects affected / exposed	85 / 313 (27.16%)	83 / 292 (28.42%)	78 / 302 (25.83%)
occurrences (all)	116	109	111
Vomiting			
subjects affected / exposed	41 / 313 (13.10%)	45 / 292 (15.41%)	37 / 302 (12.25%)
occurrences (all)	57	65	64
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	21 / 313 (6.71%)	18 / 292 (6.16%)	20 / 302 (6.62%)
occurrences (all)	24	20	22
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	38 / 313 (12.14%)	50 / 292 (17.12%)	36 / 302 (11.92%)
occurrences (all)	39	56	40

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2019	Following changes were made: Post-dose Pharmacokinetic (PK) sampling time changed from 4 days (±1 day) to 3 days (±1 day) in order to collect more PK data in the absorption phase. Sample collection time points (only in efpeglenatide treated subjects) had been clarified; sample collection time points had been specified to allow higher flexibility with regard to post-dose sample collection window in order to facilitate additional post-dose sampling. A preferred interval for PK post-dose sampling (between Week 8 and Week 12) was defined considering the balance between two requirements: PK steady state and limited risk of anti-drug antibodies (ADA) formation. The PK endpoint had been updated to remove the operational instruction language; clarified the general PK sampling process; clarified the site of administration; reflected the changes made in PK endpoint; clarified studied population; schedule of activities -footnote updated; clarified sampling requirements; clarified reference source of information; clarified definition of fasting for purpose of sample collection for glycemic parameters; clarification to include DTP, a new process regarding IMP dispensation in case of emergency; clarified measure to minimise bias: randomisation and blinding; clarified randomisation code breaking during the study; clarification for specific IMP return process for autoinjectors that functioned normally; schedule of assessments after permanent IMP discontinuation; clarified that review and reconciliation by the Investigators of subjects responses to PROMIS GI symptom scale was not needed; adverse event of diabetic retinopathy complications were reviewed as per current medical review process without an independent ophthalmologist expert review.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Study was terminated early by Sponsor on 09 September 2020. Due to early termination of study, model-based efficacy analyses were performed in mITT population instead of the ITT population originally planned and data was carefully considered.

Notes: