Clinical trial results:
A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of the Continuation of Sitagliptin Compared with the Withdrawal of Sitagliptin During Initiation and Titration of Insulin Glargine (LANTUS®) in Subjects with Type 2 Diabetes Mellitus

Summary

EudraCT number	2015-004990-34
Trial protocol	EE HU LV CZ ES DK RO PL
Global end of trial date	30 January 2018

Results information

Result version number	v1 (current)
This version publication date	03 February 2019
First version publication date	03 February 2019

Trial information

Trial identification

Sponsor protocol code	0431-845

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02738879
WHO universal trial number (UTN)	-
Other trial identifiers	MK-0431-845: Merck Protocol Number

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	30 January 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is a trial of continuing sitagliptin versus withdrawing sitagliptin in participants with type 2 diabetes mellitus (T2DM) and inadequate glycemic control who initiate and titrate insulin glargine (LANTUS®) based on a treat-to-target algorithm to achieve fasting glucose levels of 72-100 mg/dL (4-5.6 mmol/L). A primary hypothesis of this trial is that after 30 weeks, continuing sitagliptin results in a greater reduction of hemoglobin A1C (A1C) relative to withdrawing sitagliptin.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy:

The following medications were given to all participants: Metformin: at least 1500 mg/day, oral, twice daily for participants entering the study on immediate-release metformin + sitagliptin or a fixed dose combination (FDC). Metformin XR: at least 1500 mg/day, oral, once daily for participants entering the study on extended-release metformin + sitagliptin or a FDC. Insulin glargine (LANTUS®) initiated at 10 units and titrated based on a treat-to-target algorithm to achieve fasting glucose levels of 72-100 mg/dL (4-5.6 mmol/L); administered once daily subcutaneously.

Evidence for comparator: -

Actual start date of recruitment	09 May 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	Philippines: 52
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Romania: 30
Country: Number of subjects enrolled	Russian Federation: 59
Country: Number of subjects enrolled	Spain: 46
Country: Number of subjects enrolled	Turkey: 19
Country: Number of subjects enrolled	United States: 144
Country: Number of subjects enrolled	Argentina: 69
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Czech Republic: 24
Country: Number of subjects enrolled	Denmark: 18
Country: Number of subjects enrolled	Estonia: 13

Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Guatemala: 58
Country: Number of subjects enrolled	Hungary: 37
Country: Number of subjects enrolled	Israel: 21
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Latvia: 25
Country: Number of subjects enrolled	Mexico: 41
Country: Number of subjects enrolled	New Zealand: 19
Worldwide total number of subjects	746
EEA total number of subjects	231

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)	547
From 65 to 84 years	199
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 746 participants were randomized across 149 study sites in 22 countries.

Pre-assignment

Screening details:

Male and female participants with Type 2 diabetes mellitus (T2DM) ≥18 years of age were enrolled in this trial.

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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Sitagliptin

Arm description:

Sitagliptin 100 mg, oral, once daily for 30 weeks

Arm type	Experimental
Investigational medicinal product name	Sitagliptin
Investigational medicinal product code	
Other name	MK-0431 Januvia
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Sitagliptin 100 mg, oral, once daily for 30 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 as a background medication of at least 1500 mg/day, oral, twice daily for participants entering the study on immediate-release metformin + sitagliptin or a FDC.

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

Dosage and administration details:

Metformin XR as a background medication of at least 1500 mg/day, oral, once daily for participants entering the study on extended-release metformin + sitagliptin or a FDC.

Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	
Other name	LANTUS®
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Basal insulin therapy of insulin glargine (LANTUS®) initiated at 10 units and titrated based on a treat-to-target algorithm to achieve fasting glucose levels of 72-100 mg/dL (4-5.6 mmol/L); administered once daily subcutaneously.

Arm title	Placebo

Arm description:

Placebo to sitagliptin, 100 mg, oral, once daily for 30 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo to sitagliptin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo to sitagliptin 100 mg, oral, once daily for 30 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 as a background medication of at least 1500 mg/day, oral, twice daily for participants entering the study on immediate-release metformin + sitagliptin or a FDC.

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

Dosage and administration details:

Metformin XR as a background medication of at least 1500 mg/day, oral, once daily for participants entering the study on extended-release metformin + sitagliptin or a FDC.

Investigational medicinal product name	Insulin glargine
Investigational medicinal product code	
Other name	LANTUS®
Pharmaceutical forms	Concentrate and solvent for solution for injection
Routes of administration	Intradermal use

Dosage and administration details:

Basal insulin therapy of insulin glargine (LANTUS®) initiated at 10 units and titrated based on a treat-to-target algorithm to achieve fasting glucose levels of 72-100 mg/dL (4-5.6 mmol/L); administered once daily subcutaneously.

Number of subjects in period 1	Sitagliptin	Placebo
Started	374	372
Treated	373	370
Completed	361	347
Not completed	13	25
Consent withdrawn by subject	5	7

Physician decision	3	4
Screen Failure	1	2
Adverse event, non-fatal	1	1
Death	-	2
Site Discontinued Study Participation	1	-
Pregnancy	-	1
Lost to follow-up	1	5
Protocol deviation	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Sitagliptin
Reporting group description:	
Sitagliptin 100 mg, oral, once daily for 30 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo to sitagliptin, 100 mg, oral, once daily for 30 weeks	

Reporting group values	Sitagliptin	Placebo	Total
Number of subjects	374	372	746
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)	275	272	547
From 65-84 years	99	100	199
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	58.5	58.1	
standard deviation	± 9.5	± 9.7	-
Gender Categorical Units: Subjects			
Female	204	181	385
Male	170	191	361
Race Units: Subjects			
American Indian Or Alaska	19	18	37
Asian	42	37	79
Black Or African American	12	12	24
Multiple	34	34	68
Native Hawaiian Or Other	6	1	7
White	259	270	529
Missing	2	0	2
Anti-Hyperglycemic Agent			
Background Anti-Hyperglycemic Agent (AHA) at Screening metformin = Met dipeptidyl peptidase 4 inhibitor = DPP-4i			
Units: Subjects			
Met + DPP-4i	184	184	368
Met + DPP-4i + sulfonylurea (SU)	87	86	173
Met + SU	103	102	205
Geographic Region			

Units: Subjects			
Asia	36	26	62
Europe	158	172	330
Latin America	85	83	168
North America	80	78	158
Other	15	13	28
Hemoglobin A1C (A1C)			
Percent A1C= Glycated hemoglobin/total hemoglobin x 100 (N= 373; 370)			
Units: Percent A1C			
arithmetic mean	8.8	8.8	
standard deviation	± 0.9	± 1.0	-
Fasting Plasma Glucose (FPG)			
Fasting plasma glucose level after a 10-hour overnight fast. (N= 373; 370)			
Units: mg/dL			
arithmetic mean	199.0	201.2	
standard deviation	± 50.8	± 51.8	-
Estimated Glomercular Filtration Rate			
Estimated Glomercular Filtration Rate (eGFR) is a test of renal function. (N= 373; 370)			
Units: mL/min/1.73 m^2			
arithmetic mean	103.7	106.4	
standard deviation	± 30.3	± 28.1	-
Body Weight			
(N= 373; 370)			
Units: Kilograms			
arithmetic mean	84.8	85.6	
standard deviation	± 19.8	± 18.9	-

End points

End points reporting groups	
Reporting group title	Sitagliptin
Reporting group description: Sitagliptin 100 mg, oral, once daily for 30 weeks	
Reporting group title	Placebo
Reporting group description: Placebo to sitagliptin, 100 mg, oral, once daily for 30 weeks	

Primary: Change from Baseline in A1C at Week 30	
End point title	Change from Baseline in A1C at Week 30
End point description: A1C is blood marker used to report average blood glucose levels over prolonged periods of time. Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. Thus, this change from baseline reflects the Week 30 A1C minus the Week 0 A1C. The analysis population consisted of all randomized participants who received at least one dose of study treatment and had at least one measurement of the respective endpoint (baseline or post-baseline).	
End point type	Primary
End point timeframe: Baseline and Week 30	

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	370		
Units: Pecent A1C				
least squares mean (confidence interval 95%)	-1.88 (-1.98 to -1.78)	-1.42 (-1.52 to -1.32)		

Statistical analyses

Statistical analysis title	A1C Non-inferiority Analysis
Statistical analysis description: A longitudinal data analysis (LDA) model included terms for treatment, AHA treatment at screening (Met + DPP-4i, Met + DPP-4i + SU, Met + SU), time, and the interactions of time by treatment and of time by AHA treatment at screening. Least Squares Means = LSM	
Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Method	LDA
Parameter estimate	Between Group Difference in the LSM
Point estimate	-0.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	-0.34

Notes:

[1] - Hypothesis A: After 30 weeks, continuing sitagliptin is non-inferior relative to withdrawing sitagliptin on the change from baseline in A1C. Non-inferiority is declared if the upper bound of the two-sided 95% CI for the difference is less than 0.3%.

Statistical analysis title	A1C Superiority Analysis

Statistical analysis description:

A LDA model included terms for treatment, AHA treatment at screening (Met + DPP-4i, Met + DPP-4i + SU, Met + SU), time, and the interactions of time by treatment and of time by AHA treatment at screening.

Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	< 0.001
Method	LDA
Parameter estimate	Between Group Difference in the LSM
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.58
upper limit	-0.34

Notes:

[2] - Hypothesis B: After 30 weeks, continuing sitagliptin results in a greater reduction of A1C relative to withdrawing sitagliptin.

Primary: Event Rate of Documented Symptomatic Hypoglycemia with Blood Glucose ≤70 mg/dL (≤3.9 mmol/L)

End point title	Event Rate of Documented Symptomatic Hypoglycemia with Blood Glucose ≤70 mg/dL (≤3.9 mmol/L)

End point description:

Documented symptomatic hypoglycemia is defined as an event during which typical symptoms of hypoglycemia are accompanied by a measured (e.g., by fingerstick) plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L). The event rate was the number of events divided by follow-up time (participant-years). The analysis population consisted of all randomized participants who received at least one dose of study treatment. Two participants in the sitagliptin group were not included in the primary analysis due to a missing value of a model covariate (race).

End point type	Primary

End point timeframe:

Up to 30 weeks

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	370		
Units: Total Number of Events/Participant-Years				
number (confidence interval 95%)	1.55 (1.22 to 1.96)	2.12 (1.70 to 2.66)		

Statistical analyses

Statistical analysis title	Event Rate Ratio (Sitagliptin vs. Placebo)

Statistical analysis description:

Calculated via the Negative Binomial Model including terms for treatment, race (i.e., White and Other), region (i.e., Europe, North America, and Other), AHA treatment at screening, baseline A1C value and baseline body weight and an offset for follow-up time (on the natural log scale).

Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	741
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	Negative Binomial Model
Parameter estimate	Event Rate Ratio
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	0.98

Primary: Percentage of Participants Who Experienced One or More Adverse Events (AEs)

End point title	Percentage of Participants Who Experienced One or More Adverse Events (AEs)

End point description:

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study. The analysis population consisted all randomized participants who received at least one dose of study treatment.

End point type	Primary

End point timeframe:

Up to 32 weeks

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	370		
Units: Percentage of participants				
number (not applicable)	57.9	60.0		

Statistical analyses

Statistical analysis title	Between Group Difference in Percentages
Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	superiority
Method	Miettinen & Nurminen
Parameter estimate	Between Group Difference in Percentages
Point estimate	-2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.1
upper limit	5

Primary: Percentage of Participants Who Discontinued Study Drug Due to an AE

End point title	Percentage of Participants Who Discontinued Study Drug Due to an AE

End point description:

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure, that occurs during the course of the study. The analysis population consisted all randomized participants who received at least one dose of study treatment.

End point type	Primary

End point timeframe:

Up to 30 weeks

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	370		
Units: Percentage of participants				
number (not applicable)	1.3	1.6		

Statistical analyses

Statistical analysis title	Between Group Difference in Percentages
Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	superiority
Method	Miettinen & Nurminen
Parameter estimate	Between Group Difference in Percentages
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	1.7

Secondary: Percentage of Participants with Events of Documented Symptomatic Hypoglycemia with Blood Glucose ≤70 mg/dL (≤3.9 mmol/L)

End point title	Percentage of Participants with Events of Documented Symptomatic Hypoglycemia with Blood Glucose ≤70 mg/dL (≤3.9 mmol/L)

End point description:

Documented symptomatic hypoglycemia is defined as an event during which typical symptoms of hypoglycemia are accompanied by a measured (e.g., by fingerstick) plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L). The incidence (number of participants with ≥1 event divided by number of participants) of documented symptomatic hypoglycemia was determined. The analysis population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 30 weeks

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	370		
Units: Percentage of participants				
number (confidence interval 95%)	33.5 (28.5 to 38.6)	37.7 (32.7 to 42.6)		

Statistical analyses

Statistical analysis title	Between Group Difference in Percentages
Comparison groups	Sitagliptin v Placebo

Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	Miettinen and Nurminen
Parameter estimate	Between Group Difference in Percentages
Point estimate	-4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.2
upper limit	2.9

Secondary: Event Rate of Documented Symptomatic Hypoglycemia with Blood Glucose <56 mg/dL (≤3.1 mmol/L)

End point title	Event Rate of Documented Symptomatic Hypoglycemia with Blood Glucose <56 mg/dL (≤3.1 mmol/L)

End point description:

Documented symptomatic hypoglycemia is defined as an event during which typical symptoms of hypoglycemia are accompanied by a measured (e.g., by fingerstick) plasma glucose concentration <56 mg/dL (≤3.1 mmol/L). The event rate was the number of events divided by follow-up time (participant-years). The analysis population consisted of all randomized participants who received at least one dose of study treatment. Two participants in the sitagliptin group were not included in the primary analysis due to a missing value of a model covariate (race).

End point type	Secondary

End point timeframe:

Up to 30 weeks

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	370		
Units: Total Number of Events/Participant-Years				
number (confidence interval 95%)	0.17 (0.10 to 0.28)	0.22 (0.14 to 0.36)		

Statistical analyses

Statistical analysis title	Event Rate Ratio

Statistical analysis description:

The analysis was calculated via the Negative Binomial Model including terms for treatment, race (i.e., White and Other), region (i.e., Europe, North America, and Other), AHA treatment at screening, baseline A1C value and baseline body weight and an offset for follow-up time (on the natural log scale).

Comparison groups	Sitagliptin v Placebo

Number of subjects included in analysis	741
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.394
Method	Negative Binomial Model
Parameter estimate	Event Rate Ratio
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.44

Secondary: Percentage of Participants with Documented Hypoglycemia with Blood Glucose ≤70 mg/dL (≤3.9 mmol/L)

End point title	Percentage of Participants with Documented Hypoglycemia with Blood Glucose ≤70 mg/dL (≤3.9 mmol/L)

End point description:

Documented hypoglycemia is defined by a measured (e.g., by fingerstick) plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L). The analysis population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 30 weeks

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	370		
Units: Percentage of participants				
number (confidence interval 95%)	66.8 (61.9 to 71.7)	68.0 (63.2 to 72.9)		

Statistical analyses

Statistical analysis title	Between Group Difference in Percentages

Statistical analysis description:

The analysis included imputed events after participants discontinued from the study medication, using a Gamma frailty model. Proportions and difference in proportions were calculated via the Miettinen and Nurminen stratified by AHA treatment at screening. The bootstrap method was used to obtain the CI and p-value.

Comparison groups	Sitagliptin v Placebo

Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74
Method	Miettinen and Nurminen
Parameter estimate	Between Group Difference in Percentages
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.2
upper limit	5.8

Secondary: Percentage of Participants with Documented Symptomatic Hypoglycemia with Blood Glucose <56 mg/dL (≤3.1 mmol/L)

End point title	Percentage of Participants with Documented Symptomatic Hypoglycemia with Blood Glucose <56 mg/dL (≤3.1 mmol/L)

End point description:

Documented symptomatic hypoglycemia is defined as an event during which typical symptoms of hypoglycemia are accompanied by a measured (e.g., by fingerstick) plasma glucose concentration <56 mg/dL (≤3.1 mmol/L). The analysis population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 30 weeks

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	370		
Units: Percentage of participants				
number (confidence interval 95%)	7.6 (4.9 to 10.3)	8.3 (5.4 to 11.2)		

Statistical analyses

Statistical analysis title	Between Group Difference in Percentages

Statistical analysis description:

Percentages and difference in percentages were calculated via the Miettinen and Nurminen stratified by AHA treatment at screening. The analysis included imputed events after subjects discontinued from the study medication, using a Gamma frailty model. The bootstrap method was used to obtain the CI and p-value.

Comparison groups	Sitagliptin v Placebo

Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.712
Method	Miettinen and Nurminen
Parameter estimate	Between Group Difference in Percentages
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.7
upper limit	3.2

Secondary: Change from Baseline in Total Daily Insulin Dose (Units) at Week 30

End point title	Change from Baseline in Total Daily Insulin Dose (Units) at Week 30

End point description:

Change from baseline reflects the Week 30 total daily insulin dose minus the Week 0 total daily insulin dose. The Week 0 total daily insulin dose was 0, by definition, because insulin was not administered at baseline. The analysis population consisted of all randomized participants who received at least one dose of study treatment and had at least one measurement of the respective endpoint (baseline or post-baseline).

End point type	Secondary

End point timeframe:

Baseline and Week 30

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	365	367		
Units: Insulin Units				
least squares mean (confidence interval 95%)	53.2 (48.5 to 58.0)	61.3 (56.5 to 66.0)		

Statistical analyses

Statistical analysis title	Between Group Difference in the LSM

Statistical analysis description:

The analysis is based on a LDA model including terms for treatment, AHA treatment at screening (Met + DPP-4i, Met + DPP-4i + SU, Met + SU), time, and the interactions of time by treatment and of time by AHA treatment at screening.

Comparison groups	Sitagliptin v Placebo

Number of subjects included in analysis	732
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.016
Method	LDA model
Parameter estimate	Between Group Difference in the LSM
Point estimate	-8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.6
upper limit	-1.5

Secondary: Event Rate of Documented Hypoglycemia with Blood Glucose ≤70 mg/dL (≤3.9 mmol/L)

End point title	Event Rate of Documented Hypoglycemia with Blood Glucose ≤70 mg/dL (≤3.9 mmol/L)

End point description:

Documented hypoglycemia is defined by a measured (e.g., by fingerstick) plasma glucose concentration ≤70 mg/dL (≤3.9 mmol/L). The event rate was the number of events divided by follow-up time (participant-years). The analysis population consisted of all randomized participants who received at least one dose of study treatment and had at least one measurement of the respective endpoint (baseline or post-baseline). Two participants (both in the sitagliptin group) were not included in the analysis due to a missing value of a model covariate (race).

End point type	Secondary

End point timeframe:

Up to 30 weeks

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	370		
Units: Total Number of Events/Participant-Years				
number (confidence interval 95%)	5.05 (4.34 to 5.88)	6.21 (5.33 to 7.24)		

Statistical analyses

Statistical analysis title	Event Rate Ratio

Statistical analysis description:

Negative Binomial Model including terms for treatment, race (i.e., White and Other), region (i.e., Europe, North America, and Other), AHA treatment at screening, baseline A1C value and baseline body weight and an offset for follow-up time (on the natural log scale).

Comparison groups	Sitagliptin v Placebo

Number of subjects included in analysis	741
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041
Method	Negative Binomial Model
Parameter estimate	Event Rate Ratio
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	0.99

Secondary: Event Rate of Documented Hypoglycemia with Blood Glucose <56 mg/dL (≤3.1 mmol/L)

End point title	Event Rate of Documented Hypoglycemia with Blood Glucose <56 mg/dL (≤3.1 mmol/L)

End point description:

Documented hypoglycemia is defined by a measured (e.g., by fingerstick) plasma glucose concentration <56 mg/dL (≤3.1 mmol/L). The event rate was the number of events divided by follow-up time (participant-years). The analysis population consisted of all randomized participants who received at least one dose of study treatment and had at least one measurement of the respective endpoint (baseline or post-baseline). Two participants (both in the sitagliptin group) were not included in the analysis due to a missing value of a model covariate (race).

End point type	Secondary

End point timeframe:

Up to 30 weeks

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	371	370		
Units: Total Number of Events/Participant-Years				
number (confidence interval 95%)	0.30 (0.20 to 0.45)	0.36 (0.25 to 0.53)		

Statistical analyses

Statistical analysis title	Event Rate Ratio

Statistical analysis description:

Negative Binomial Model including terms for treatment, race (i.e., White and Other), region (i.e., Europe, North America, and Other), AHA treatment at screening, baseline A1C value and baseline body weight and an offset for follow-up time (on the natural log scale).

Comparison groups	Sitagliptin v Placebo

Number of subjects included in analysis	741
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.473
Method	Negative Binomial Model
Parameter estimate	Event Rate Ratio
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.37

Secondary: Percentage of Participants with Documented Hypoglycemia with Blood Glucose <56 mg/dL (≤3.1 mmol/L)

End point title	Percentage of Participants with Documented Hypoglycemia with Blood Glucose <56 mg/dL (≤3.1 mmol/L)

End point description:

Documented hypoglycemia is defined by a measured (e.g., by fingerstick) plasma glucose concentration <56 mg/dL (≤3.1 mmol/L). The analysis population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 30 weeks

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	370		
Units: Percentage of Participants				
number (confidence interval 95%)	12.4 (8.9 to 15.8)	13.6 (10.0 to 17.2)		

Statistical analyses

Statistical analysis title	Between Group Difference in Percentages

Statistical analysis description:

Percentages and difference in percentages were calculated via the Miettinen and Nurminen stratified by AHA treatment at screening. Includes imputed events after participants discontinued from the study medication, using a Gamma frailty model. The bootstrap method was used to obtain the CI and p-value.

Comparison groups	Sitagliptin v Placebo

Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.624
Method	Miettinen and Nurminen
Parameter estimate	Between Group Difference in Percentages
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.2
upper limit	3.7

Secondary: Percentage of Participants with A1C goal <7.0% (<53 mmol/mol) at Week 30

End point title	Percentage of Participants with A1C goal <7.0% (<53 mmol/mol) at Week 30

End point description:

A1C is blood marker used to report average blood glucose levels over prolonged periods of time. Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. The analysis population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Week 30

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	370		
Units: Percentage of participants				
number (not applicable)	54.2	35.4		

Statistical analyses

Statistical analysis title	Between Group Difference in Percentages
Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Miettinen and Nurminen
Parameter estimate	Between Group Difference in Percentages
Point estimate	18.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	11.6
upper limit	25.7

Secondary: Percentage of Participants with A1C goal <7.0% (<53 mmol/mol at Week 30 and No Documented Hypoglycemia with Blood Glucose ≤70 mg/dL (≤3.9 mmol/L) up to Week 30

End point title	Percentage of Participants with A1C goal <7.0% (<53 mmol/mol at Week 30 and No Documented Hypoglycemia with Blood Glucose ≤70 mg/dL (≤3.9 mmol/L) up to Week 30

End point description:

A1C is blood marker used to report average blood glucose levels over prolonged periods of time. Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. The analysis population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Week 30

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	370		
Units: Percentage of participants				
number (not applicable)	15.3	10.0		

Statistical analyses

Statistical analysis title	Between Group Difference in Percentages
Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.03
Method	Miettinen and Nurminen
Parameter estimate	Between Group Difference in Percentages
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	10.1

Secondary: Change from Baseline in Fasting Plasma Glucose (FPG) at Week 30

End point title	Change from Baseline in Fasting Plasma Glucose (FPG) at Week 30

End point description:

Blood glucose was measured on a fasting basis. Blood was drawn at predose on Day 1 and after 30 weeks of treatment to determine change in plasma glucose levels (i.e., FPG at Week 30 minus FPG at Week 0). The analysis population consisted of all randomized participants who received at least one dose of study treatment and had at least one measurement of the respective endpoint (baseline or post-baseline).

End point type	Secondary

End point timeframe:

Baseline and Week 30

End point values	Sitagliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	373	370		
Units: mg/dL				
least squares mean (confidence interval 95%)	-84.8 (-90.0 to -79.6)	-78.3 (-83.5 to -73.1)		

Statistical analyses

Statistical analysis title	Between Group Difference in the LSM

Statistical analysis description:

Analysis was based on a LDA model including terms for treatment, AHA treatment at screening (Met + DPP-4i, Met + DPP-4i + SU, Met + SU), time, and the interactions of time by treatment and of time by AHA treatment at screening.

Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	743
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	LDA
Parameter estimate	Between Group Difference in the LSM
Point estimate	-6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.9
upper limit	-1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 32 weeks

Adverse event reporting additional description:

The analysis population consisted all randomized participants who received at least one dose of study treatment. Events of hypoglycemia of any type were collected as efficacy endpoints in this study. AEs of symptomatic hypoglycemia could also be reported by investigators.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Sitagliptin

Reporting group description:

Sitagliptin 100 mg, oral, once daily for 30 weeks

Reporting group title	Placebo

Reporting group description:

Placebo to sitagliptin, 100 mg, oral, once daily for 30 weeks

Serious adverse events	Sitagliptin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 373 (3.75%)	18 / 370 (4.86%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	0	
Investigations			
Heart rate irregular			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 373 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 373 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fibula fracture			
subjects affected / exposed	1 / 373 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament rupture			
subjects affected / exposed	1 / 373 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 373 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 373 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	1 / 373 (0.27%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 373 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 373 (0.00%)	2 / 370 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar radiculopathy			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			

subjects affected / exposed	1 / 373 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated umbilical hernia			
subjects affected / exposed	1 / 373 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 373 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 373 (0.27%)	0 / 370 (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			
Diabetic foot			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 373 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin abscess			
subjects affected / exposed	1 / 373 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sialoadenitis			
subjects affected / exposed	1 / 373 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheitis			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 373 (0.27%)	0 / 370 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 373 (0.00%)	1 / 370 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Sitagliptin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 373 (21.18%)	72 / 370 (19.46%)	
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 373 (6.70%)	19 / 370 (5.14%)	
occurrences (all)	36	23	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	24 / 373 (6.43%)	32 / 370 (8.65%)	
occurrences (all)	30	35	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	35 / 373 (9.38%)	24 / 370 (6.49%)	
occurrences (all)	96	74	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 April 2016	AM1: The participant population was expanded to include eligible patients on metformin and a sulfonylurea with an A1C of 7.5% to 11.0% at Screening in the study.
11 July 2016	AM2: 1. Metformin dosing was removed and the text was updated to allow the dose frequency to be defined by local labels or clinical practice guidelines. 2. Added text and footnote to state that participants participating in the continuous glucose monitoring (CGM) sub-study cannot use acetaminophen and/or medications containing acetaminophen for at least 24 hours prior to sensor insertion and while the sensor is being used.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported