Clinical trial results:
A Phase III, Multicenter, Randomized, Double-Blind, Active-Comparator Controlled Clinical Trial to Study the Safety and Efficacy of the Addition of Sitagliptin Compared with the Addition of Dapagliflozin in Subjects with Type 2 Diabetes Mellitus and Mild Renal Impairment Who Have Inadequate Glycemic Control on Metformin With or Without a Sulfonylurea

Summary

EudraCT number	2014-005525-13
Trial protocol	LT LV FI IE EE HU ES GB
Global end of trial date	10 October 2017

Results information

Result version number	v1 (current)
This version publication date	04 October 2018
First version publication date	04 October 2018

Trial information

Trial identification

Sponsor protocol code	0431-838

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02532855
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-0431-838

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	10 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study is to assess the effect of the addition of sitagliptin to metformin with or without a sulfonylurea compared with the addition of dapagliflozin to metformin with or without a sulfonylurea on hemoglobin A1c (A1C) over 24 weeks of treatment as well as the overall safety and tolerability of sitagliptin in comparison to that of dapagliflozin after 24 weeks of treatment. The primary hypothesis is that the change from baseline in A1C in participants treated with the addition of sitagliptin is non-inferior compared to that in participants treated with the addition of dapagliflozin after 24 weeks of treatment.

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: -

Evidence for comparator: -

Actual start date of recruitment	20 October 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 32
Country: Number of subjects enrolled	Brazil: 23
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Colombia: 27
Country: Number of subjects enrolled	Estonia: 16
Country: Number of subjects enrolled	Finland: 4
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Hungary: 36
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Korea, Republic of: 6
Country: Number of subjects enrolled	Latvia: 17
Country: Number of subjects enrolled	Lithuania: 21
Country: Number of subjects enrolled	Mexico: 51
Country: Number of subjects enrolled	New Zealand: 19
Country: Number of subjects enrolled	Norway: 18
Country: Number of subjects enrolled	Peru: 11

Country: Number of subjects enrolled	Romania: 27
Country: Number of subjects enrolled	Russian Federation: 68
Country: Number of subjects enrolled	South Africa: 22
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 150
Worldwide total number of subjects	614
EEA total number of subjects	179

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)	203
From 65 to 84 years	407
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 183 medical centers in 24 countries.

Pre-assignment

Screening details:

Male and female participants, 25 years or older, with Type 2 diabetes mellitus (T2DM) and mild renal impairment on metformin alone or in combination with a sulfonylurea (SU) agent were enrolled in this trial.

Period 1

Period 1 title	Pre-Treatment 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:

Participants receive sitagliptin 100 mg once daily plus matching placebo for dapagliflozin 5 mg once daily for 4 weeks followed by sitagliptin 100 mg once daily plus matching placebo for dapagliflozin 10 mg once daily for 20 weeks. Participants continue pre-study metformin (at least 1500 mg daily) alone or in combination with a sulfonylurea agent (at a dose of ≥ 50% maximum labeled dose in the country of the investigational site) throughout the duration of the study.

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

Dosage and administration details:

Sitagliptin, 100 mg, once daily (q.d.), oral, for 24 weeks

Investigational medicinal product name	Matching placebo for dapagliflozin 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo, q.d. for 4 weeks (Day 1 to Week 4)

Investigational medicinal product name	Matching placebo for dapagliflozin 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo, q.d. for 20 weeks (Week 4 to Week 24)

Investigational medicinal product name	Metformin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Metformin, oral tablet(s), at least 1500 mg daily

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

Dosage and administration details:

Sulfonylurea agent, dose required to be at least 50% of maximum labeled dose, consistent with near maximum efficacy of the sulfonylurea agent.

Arm title	Dapagliflozin

Arm description:

Participants receive dapagliflozin 5 mg once daily plus matching placebo for sitagliptin 100 mg once daily for 4 weeks followed by dapagliflozin 10 mg once daily plus matching placebo for sitagliptin 100 mg once daily for 20 weeks. Participants continue pre-study metformin (at least 1500 mg daily) alone or in combination with a sulfonylurea agent (at a dose of ≥ 50% maximum labeled dose in the country of the investigational site) throughout the duration of the study.

Arm type	Active comparator
Investigational medicinal product name	Dapagliflozin 10 mg group
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin, 5 mg, q.d., for 4 weeks (Day 1 to Week 4)

Investigational medicinal product name	Dapagliflozin 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 10 mg, oral, q.d. for 20 weeks (Week 4 to Week 24)

Investigational medicinal product name	Matching placebo for sitagliptin 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo, q.d. for 24 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, oral tablet(s), at least 1500 mg daily

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

Dosage and administration details:

Sulfonylurea agent, dose required to be at least 50% of maximum labeled dose, consistent with near maximum efficacy of the sulfonylurea agent.

Number of subjects in period 1	Sitagliptin	Dapagliflozin
Started	307	307
Completed	307	306
Not completed	0	1
One participant was randomized but not treated	-	1

Period 2

Period 2 title	Treatment Period
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	Sitagliptin

Arm description:

Participants receive sitagliptin 100 mg once daily plus matching placebo for dapagliflozin 5 mg once daily for 4 weeks followed by sitagliptin 100 mg once daily plus matching placebo for dapagliflozin 10 mg once daily for 20 weeks. Participants continue pre-study metformin (at least 1500 mg daily) alone or in combination with a sulfonylurea agent (at a dose of ≥ 50% maximum labeled dose in the country of the investigational site) throughout the duration of the study.

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

Dosage and administration details:

Sitagliptin, 100 mg once daily (q.d.), oral, for 24 weeks

Investigational medicinal product name	Matching placebo for dapagliflozin 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo, q.d. for 4 weeks (Day 1 to Week 4)

Investigational medicinal product name	Matching placebo for dapagliflozin 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo, q.d. for 20 weeks (Week 4 to Week 24)

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

Dosage and administration details:

Metformin, oral tablet(s), at least 1500 mg daily

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

Dosage and administration details:

Sulfonylurea agent, dose required to be at least 50% of maximum labeled dose, consistent with near maximum efficacy of the sulfonylurea agent.

Arm title	Dapagliflozin

Arm description:

Participants receive dapagliflozin 5 mg once daily plus matching placebo for sitagliptin 100 mg once daily for 4 weeks followed by dapagliflozin 10 mg once daily plus matching placebo for sitagliptin 100 mg once daily for 20 weeks. Participants continue pre-study metformin (at least 1500 mg daily) alone or in combination with a sulfonylurea agent (at a dose of ≥ 50% maximum labeled dose in the country of the investigational site) throughout the duration of the study.

Arm type	Active comparator
Investigational medicinal product name	Dapagliflozin 10 mg group
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 5 mg, q.d., for 4 weeks (Day 1 to Week 4)

Investigational medicinal product name	Dapagliflozin 10 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Dapagliflozin 10 mg, oral, q.d. for 20 weeks (Week 4 to Week 24)

Investigational medicinal product name	Matching placebo for sitagliptin 100 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo, q.d. for 24 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, oral tablet(s), at least 1500 mg daily

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

Dosage and administration details:

Sulfonylurea agent, dose required to be at least 50% of maximum labeled dose, consistent with near maximum efficacy of the sulfonylurea agent.

Number of subjects in period 2	Sitagliptin	Dapagliflozin
Started	307	306
Completed	299	295
Not completed	8	11
Consent withdrawn by subject	4	8
Lost to follow-up	4	3

Baseline characteristics

Reporting groups	
Reporting group title	Sitagliptin
Reporting group description:	
Participants receive sitagliptin 100 mg once daily plus matching placebo for dapagliflozin 5 mg once daily for 4 weeks followed by sitagliptin 100 mg once daily plus matching placebo for dapagliflozin 10 mg once daily for 20 weeks. Participants continue pre-study metformin (at least 1500 mg daily) alone or in combination with a sulfonylurea agent (at a dose of ≥ 50% maximum labeled dose in the country of the investigational site) throughout the duration of the study.	
Reporting group title	Dapagliflozin
Reporting group description:	
Participants receive dapagliflozin 5 mg once daily plus matching placebo for sitagliptin 100 mg once daily for 4 weeks followed by dapagliflozin 10 mg once daily plus matching placebo for sitagliptin 100 mg once daily for 20 weeks. Participants continue pre-study metformin (at least 1500 mg daily) alone or in combination with a sulfonylurea agent (at a dose of ≥ 50% maximum labeled dose in the country of the investigational site) throughout the duration of the study.	

Reporting group values	Sitagliptin	Dapagliflozin	Total
Number of subjects	307	307	614
Age categorical			
All randomized participants			
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)	97	106	203
From 65-84 years	206	201	407
85 years and over	4	0	4
Age Continuous			
All randomized participants			
Units: years			
arithmetic mean	67.7	66.6	
standard deviation	± 8.5	± 8.6	-
Sex: Female, Male			
All randomized participants			
Units: Subjects			
Female	138	120	258
Male	169	187	356
Background Antihyperglycemic Agent (AHA)			
All randomized participants			
Units: Subjects			
Metformin Alone	212	225	437
Metformin and Sulfonylurea	95	81	176
Unknown	0	1	1
Race (NIH/OMB)			

All randomized participants			
Units: Subjects			
American Indian or Alaska Native	18	14	32
Asian	11	7	18
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	8	11	19
White	240	235	475
More than one race	30	39	69
Unknown or Not Reported	0	0	0
Hemoglobin A1C			
All randomized and treated participants. N=307, 306			
Units: Percentage			
arithmetic mean	7.7	7.8	
standard deviation	± 0.7	± 0.7	-
Fasting Plasma Glucose (FPG)			
All randomized and treated participants. N=307, 306			
Units: mg/dL			
arithmetic mean	162.3	165.2	
standard deviation	± 40.4	± 40.6	-
Incremental 2-hour Postprandial Glucose Excursion (PPGE)			
All randomized and treated participants who underwent MMTT analysis and had a baseline measurement for this endpoint. N=295, 290			
Units: mg/dL			
arithmetic mean	96.2	95.7	
standard deviation	± 55.3	± 47.1	-
2-hr Postprandial Glucose			
All randomized and treated participants who underwent MMTT analysis and had a baseline measurement for this endpoint. N=296, 292			
Units: mg/dL			
arithmetic mean	257.7	259.9	
standard deviation	± 67.1	± 64.4	-
Glucagon Area Under the Curve (AUC0-120 minutes)			
All randomized and treated participants who underwent MMTT analysis and had a baseline measurement for this endpoint. N=108, 109			
Units: pmol.hr/L			
arithmetic mean	49.6	51.8	
standard deviation	± 44.7	± 45.1	-
Insulin AUC0-120 minutes			
All randomized and treated participants who underwent MMTT analysis and had a baseline measurement for this endpoint. N=113, 112			
Units: mIU.hr/L			
arithmetic mean	155.0	139.9	
standard deviation	± 121.8	± 93.5	-
Insulin AUC0-120 minutes to Glucagon AUC0-120 minutes Ratio			
All randomized and treated participants who underwent MMTT analysis and had a baseline measurement for this endpoint. N=104, 102			
Units: Ratio			
arithmetic mean	4.0	3.5	
standard deviation	± 3.7	± 3.0	-

End points

End points reporting groups

Reporting group title	Sitagliptin

Reporting group description:

Participants receive sitagliptin 100 mg once daily plus matching placebo for dapagliflozin 5 mg once daily for 4 weeks followed by sitagliptin 100 mg once daily plus matching placebo for dapagliflozin 10 mg once daily for 20 weeks. Participants continue pre-study metformin (at least 1500 mg daily) alone or in combination with a sulfonylurea agent (at a dose of ≥ 50% maximum labeled dose in the country of the investigational site) throughout the duration of the study.

Reporting group title	Dapagliflozin

Reporting group description:

Participants receive dapagliflozin 5 mg once daily plus matching placebo for sitagliptin 100 mg once daily for 4 weeks followed by dapagliflozin 10 mg once daily plus matching placebo for sitagliptin 100 mg once daily for 20 weeks. Participants continue pre-study metformin (at least 1500 mg daily) alone or in combination with a sulfonylurea agent (at a dose of ≥ 50% maximum labeled dose in the country of the investigational site) throughout the duration of the study.

Reporting group title	Sitagliptin

Reporting group description:

Participants receive sitagliptin 100 mg once daily plus matching placebo for dapagliflozin 5 mg once daily for 4 weeks followed by sitagliptin 100 mg once daily plus matching placebo for dapagliflozin 10 mg once daily for 20 weeks. Participants continue pre-study metformin (at least 1500 mg daily) alone or in combination with a sulfonylurea agent (at a dose of ≥ 50% maximum labeled dose in the country of the investigational site) throughout the duration of the study.

Reporting group title	Dapagliflozin

Reporting group description:

Participants receive dapagliflozin 5 mg once daily plus matching placebo for sitagliptin 100 mg once daily for 4 weeks followed by dapagliflozin 10 mg once daily plus matching placebo for sitagliptin 100 mg once daily for 20 weeks. Participants continue pre-study metformin (at least 1500 mg daily) alone or in combination with a sulfonylurea agent (at a dose of ≥ 50% maximum labeled dose in the country of the investigational site) throughout the duration of the study.

Primary: Change from Baseline in A1C at Week 24

End point title	Change from Baseline in A1C at Week 24

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 24 A1C minus the Week 0 A1C. The analysis population included all randomized and treated participants who had at least one observation for the analysis endpoint, at baseline or subsequent to at least one dose of study treatment.

End point type	Primary

End point timeframe:

Baseline and Week 24

End point values	Sitagliptin	Dapagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	306		
Units: Percentage				
least squares mean (confidence interval 95%)	-0.51 (-0.60 to -0.43)	-0.36 (-0.45 to -0.27)		

Statistical analyses

Statistical analysis title	Difference in the LSM (sitagliptin-dapagliflozin)

Statistical analysis description:

Based on a Longitudinal Data Analysis (LDA) model including terms for treatment, time, background antihyperglycemic agent (AHA), the interaction of time and background AHA, and the interaction of time by treatment. Least squares means (LSM)

Comparison groups	Sitagliptin v Dapagliflozin
Number of subjects included in analysis	613
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in the LSM (Sit.-Dap.)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	-0.04

Notes:

[1] - For the primary hypothesis, sitagliptin will be considered non-inferior to dapagliflozin if the upper bound of the two-sided 95% confidence interval (CI) of the between-group difference in least squares mean change from baseline in A1C (sitagliptin minus dapagliflozin) is less than 0.3% (the non-inferiority margin).

Statistical analysis title	Difference in the LSM (Sit. - Dap.)

Statistical analysis description:

Based on a LDA model including terms for treatment, time, background AHA, the interaction of time and background AHA, and the interaction of time by treatment.

Comparison groups	Sitagliptin v Dapagliflozin
Number of subjects included in analysis	613
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Longitudinal data analysis
Parameter estimate	Difference in the LSM (Sit. - Dap.)
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	-0.04

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

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

End point description:

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product. The AE does not have to have a causal relationship with this treatment. The AE can include any unfavourable and unintended sign, symptom, or disease or any worsening (change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the pharmaceutical product. The population analyzed included all randomized and treated participants.

End point type	Primary

End point timeframe:

Up to 26 weeks

End point values	Sitagliptin	Dapagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	306		
Units: Percentage of participants				
number (not applicable)	48.9	51.6		

Statistical analyses

Statistical analysis title	Difference in % (Sit. - Dap.)
Statistical analysis description:	
Based on Miettinen & Nurminen method.	
Comparison groups	Sitagliptin v Dapagliflozin
Number of subjects included in analysis	613
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in % (Sit. - Dap.)
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.7
upper limit	5.1

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 adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product. The AE does not have to have a causal relationship with this treatment. The AE can include any unfavourable and unintended sign, symptom, or disease or any worsening (change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the pharmaceutical product. The analysis population included all randomized and treated participants.

End point type	Primary

End point timeframe:

Up to 24 weeks

End point values	Sitagliptin	Dapagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	306		
Units: Percentage of participants				
number (not applicable)	3.3	3.3		

Statistical analyses

Statistical analysis title	Difference in % (Sit. - Dap.)
Statistical analysis description:	
Based on Miettinen & Nurminen method.	
Comparison groups	Sitagliptin v Dapagliflozin
Number of subjects included in analysis	613
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in % (Sit. - Dap.)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3
upper limit	3

Secondary: Change from Baseline in Incremental 2-hour (2-hr) Postprandial Glucose Excursion (PPGE) at Week 24

End point title	Change from Baseline in Incremental 2-hour (2-hr) Postprandial Glucose Excursion (PPGE) at Week 24

End point description:

The 2hr PPGE is defined as T-120 minus T-0 for each participant: change from baseline PPGE = Week 24 mean (T-120 minus T-0) minus Baseline mean (T-120 minus T-0). The 2-point MMTT measured values at T-0 and T-120 while the 3-point MMTT measured values at T-0, T-60, and T-120: although only a subset of participants had the 3-point MMTT performed, all participants had a T-0 and T-120 time point. A negative (-) change from baseline to Week 24 indicates better control of postprandial glucose. The analysis population consisted of all randomized and treated participants who underwent MMTT for the analysis endpoint, had both baseline and Week 24 endpoint measurements, without: drug compliance <75%, use of prohibited AHA medications or pharmacologic doses of corticosteroids or incorrect double-blind study drug or a change in metformin or sulfonylurea dose.

End point type	Secondary

End point timeframe:

Immediately before and 120 minutes after the standard meal at Baseline and Week 24

End point values	Sitagliptin	Dapagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	298	296		
Units: mg/dL				
least squares mean (confidence interval 95%)	-24.2 (-30.4 to -18.0)	-18.5 (-24.9 to -12.1)		

Statistical analyses

Statistical analysis title	Difference in the LSM Change from Baseline (CFB)

Statistical analysis description:

Based on a LDA model including terms for treatment, time, background AHA, the interaction of time and background AHA, and the interaction of time by treatment.

Comparison groups	Sitagliptin v Dapagliflozin
Number of subjects included in analysis	594
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.138
Method	LDA
Parameter estimate	Difference in LSM (Sit. - Dap.)
Point estimate	-5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.3
upper limit	1.8

Secondary: Change from Baseline in 2-hr Postprandial Glucose (PPG) at Week 24

End point title	Change from Baseline in 2-hr Postprandial Glucose (PPG) at Week 24

End point description:

The 2hr change from baseline in mean PPG = Week 24 mean T-120 glucose minus Baseline mean T-120 glucose) and shows each drugs impact on PPG. The 2-point MMTT measured values at T-0 and T-120 while the 3-point MMTT measured values at T-0, T-60, and T-120: although only a subset of the study had the 3-point MMTT performed, all participants had a T-0 and T-120 time point. A negative (-) change from baseline to Week 24 indicates better control of postprandial glucose. The analysis population consisted of all randomized and treated participants who underwent MMTT for the analysis endpoint, had both baseline and Week 24 endpoint measurements, without: drug compliance <75%, use of prohibited AHA medications or pharmacologic doses of corticosteroids or incorrect double blind study drug or a change in metformin or sulfonylurea dose.

End point type	Secondary

End point timeframe:

Immediately before and 120 minutes after the standard meal at Baseline and Week 24

End point values	Sitagliptin	Dapagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	258	248		
Units: mg/dL				
least squares mean (confidence interval 95%)	-40.4 (-46.9 to -33.9)	-37.0 (-43.7 to -30.3)		

Statistical analyses

Statistical analysis title	Difference in the LSM CFB at Week 24

Statistical analysis description:

The ANCOVA model included terms for treatment, background AHA, and the baseline 2-hour PPG value as a covariate.

Comparison groups	Sitagliptin v Dapagliflozin
Number of subjects included in analysis	506
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in the LSM (Sit. - Dap.)
Point estimate	-3.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.1
upper limit	5.3

Secondary: Change from Baseline in Glucagon Area Under the Curve (AUC0-120 minutes) at Week 24

End point title	Change from Baseline in Glucagon Area Under the Curve (AUC0-120 minutes) at Week 24

End point description:

Participants who underwent the 3-point MMTT had a first blood sample (T=0 minutes) drawn immediately prior to a standard meal and 60 and 120 minutes after the standard meal. The AUC curve was generated with the 3 time points. Change in postprandial glucagon AUC was calculated from the glucagon AUC over the first 120 minutes following the morning meal at baseline minus glucagon AUC over the first 120 minutes following the morning meal at Week 24. A negative (-) change from baseline to Week 24 indicates better control of postprandial glucose. All randomized and treated participants who underwent MMTT for the analysis endpoint, had both baseline and Week 24 endpoint measurements, without: drug compliance <75%, use of prohibited AHA medications or pharmacologic doses of corticosteroids or incorrect double-blind study drug or a change in metformin or sulfonylurea dose.

End point type	Secondary

End point timeframe:

Immediately before and 60 and 120 minutes after the standard meal at Baseline and Week 24

End point values	Sitagliptin	Dapagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85	88		
Units: pmol.hr/L				
least squares mean (confidence interval 95%)	-4.2 (-8.8 to 0.4)	0.2 (-4.4 to 4.8)		

Statistical analyses

Statistical analysis title	Difference in LSM (Sit. - Dap.)

Statistical analysis description:

The ANCOVA model included terms for treatment, background AHA, and the baseline glucagon AUC value as a covariate.

Comparison groups	Sitagliptin v Dapagliflozin
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in the LSM (Sit. - Dap.)
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.1
upper limit	1.4

Secondary: Change from Baseline in Insulin AUC0-120 minutes at Week 24

End point title	Change from Baseline in Insulin AUC0-120 minutes at Week 24

End point description:

Participants who underwent the 3-point MMTT had a first blood sample (T=0 minutes) drawn immediately prior to a standard meal and 60 and 120 minutes after the standard meal. The AUC curve was generated with the 3 time points. Change in postprandial insulin AUC was calculated from the insulin AUC over the first 120 minutes following the morning meal at baseline minus insulin AUC over the first 120 minutes following the morning meal at Week 24. A negative (-) change from baseline to Week 24 indicates better control of postprandial glucose. The analysis population included all randomized and treated participants who underwent MMTT for the analysis endpoint, had both baseline and Week 24 endpoint measurements, without: drug compliance <75%, use of prohibited AHA medications or pharmacologic doses of corticosteroids or incorrect double-blind study drug or a change in metformin or sulfonylurea dose.

End point type	Secondary

End point timeframe:

Immediately before and 60 and 120 minutes after the standard meal at Baseline and Week 24

End point values	Sitagliptin	Dapagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	96	94		
Units: mIU.hr/L				
least squares mean (confidence interval 95%)	-23.4 (-36.8 to -9.9)	-28.2 (-42.1 to -14.4)		

Statistical analyses

Statistical analysis title	Difference in the LSM (Sit. - Dap.)

Statistical analysis description:

The ANCOVA model included terms for treatment, background AHA, and the baseline insulin AUC value as a covariate.

Comparison groups	Sitagliptin v Dapagliflozin
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in the LSM (Sit. - Dap.)
Point estimate	4.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.2
upper limit	22

Secondary: Change from Baseline in Postprandial Insulin AUC0-120 minutes to Glucagon AUC0-120 minutes Ratio at Week 24

End point title	Change from Baseline in Postprandial Insulin AUC0-120 minutes to Glucagon AUC0-120 minutes Ratio at Week 24

End point description:

Participants who underwent the 3-point MMTT had a first blood sample (T=0 minutes) drawn immediately prior to a standard meal and 60 and 120 minutes after the standard meal. The AUC curve was generated with the 3 time points. The endpoint was calculated from the ratio of (insulin AUC / glucagon AUC) over the first 120 minutes following the morning meal at baseline minus AUC over the first 120 minutes following the morning meal at Week 24. A negative (-) change from baseline to Week 24 indicates better control of postprandial glucose. The analysis population consisted of all randomized and treated participants who underwent MMTT for the analysis endpoint, had both baseline and Week 24 endpoint measurements, without: drug compliance <75%, use of prohibited AHA medications or pharmacologic doses of corticosteroids or incorrect double-blind study drug or a change in metformin or sulfonylurea dose.

End point type	Secondary

End point timeframe:

Immediately before and 60 and 120 minutes after the standard meal at Baseline and Week 24

End point values	Sitagliptin	Dapagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	81		
Units: Ratio				
least squares mean (confidence interval 95%)	-0.6 (-1.1 to -0.0)	-1.2 (-1.8 to -0.7)		

Statistical analyses

Statistical analysis title	Difference in LSM (Sit. - Dap.)
Statistical analysis description:	
The ANCOVA model included terms for treatment, background AHA, and the baseline insulin AUC to glucagon AUC ratio value as a covariate.	
Comparison groups	Sitagliptin v Dapagliflozin
Number of subjects included in analysis	164
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Difference in the LSM (Sit. - Dap.)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	1.3

Secondary: Percentage of Participants with A1C <7% (53 mmol/mol) at Week 24.

End point title	Percentage of Participants with A1C <7% (53 mmol/mol) at Week 24.
End point description:	
A1C is blood marker used to report average blood glucose levels over prolonged periods of time and is reported as a percentage (%). Percentage A1C is the ratio of glycated hemoglobin to total hemoglobin x 100. The percentage of participants was estimated using standard multiple imputation techniques from cLDA model including terms for treatment, time, background AHA, the interaction of time and background AHA, and the interaction of time by treatment with the constraint that the mean baseline is the same for all treatment groups. The analysis population included all randomized and treated participants who had at least one observation for the analysis endpoint, at baseline or subsequent to at least one dose of study treatment.	
End point type	Secondary
End point timeframe:	
Week 24	

End point values	Sitagliptin	Dapagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	306		
Units: Percentage of Participants				
number (not applicable)	42.6	27.0		

Statistical analyses

Statistical analysis title	Difference in % (Sitagliptin - Dapagliflozin)

Statistical analysis description:

Miettinen and Nurminen (M&N) method with multiple imputation from a LDA Model. The percentage of participants was estimated using standard multiple imputation techniques from LDA model including terms for treatment, time, background AHA, the interaction of time and background AHA, and the interaction of time by treatment.

Comparison groups	Sitagliptin v Dapagliflozin
Number of subjects included in analysis	613
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in % (Sit. - Dap.)
Point estimate	15.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.7
upper limit	23.2

Secondary: Change from Baseline in Fasting Plasma Glucose (FPG) at Week 24

End point title	Change from Baseline in Fasting Plasma Glucose (FPG) at Week 24

End point description:

Blood glucose was measured on a fasting basis. Blood was drawn at predose on Day 1 and after 24 weeks of treatment to determine change in plasma glucose levels (i.e., FPG at Week 24 minus FPG at Week 0). The analysis population included all randomized and treated participants who had at least one observation for the analysis endpoint, at baseline or subsequent to at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Sitagliptin	Dapagliflozin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	306		
Units: mg/dL				
least squares mean (confidence interval 95%)	-16.5 (-20.6 to -12.5)	-20.1 (-24.3 to -15.9)		

Statistical analyses

Statistical analysis title	Difference in the LSM CFB at Week 24
Statistical analysis description:	
Difference in LSM (Sitagliptin - Dapagliflozin) change from Baseline at Week 24 are compared. Based on a LDA model including terms for treatment, time, background AHA, the interaction of time and background AHA, and the interaction of time by treatment.	
Comparison groups	Sitagliptin v Dapagliflozin
Number of subjects included in analysis	613
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Difference in the LSM (Sit. - Dap.)
Point estimate	3.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	8.3

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 26 weeks	
Adverse event reporting additional description:	
The population analyzed included all randomized and treated participants.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	Dapagliflozin
Reporting group description: -	
Reporting group title	Sitagliptin
Reporting group description: -	

Serious adverse events	Dapagliflozin	Sitagliptin	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 306 (4.25%)	10 / 307 (3.26%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (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			
Epiphyseal fracture			
subjects affected / exposed	0 / 306 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			

subjects affected / exposed	1 / 306 (0.33%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint injury			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	0 / 306 (0.00%)	1 / 307 (0.33%)	
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	0 / 306 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (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	0 / 306 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	0 / 306 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral ischaemia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 306 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancreatitis acute			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reflux gastritis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	0 / 306 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Haemarthrosis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Atypical pneumonia			
subjects affected / exposed	0 / 306 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 306 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dapagliflozin	Sitagliptin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 306 (6.86%)	22 / 307 (7.17%)	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	21 / 306 (6.86%)	22 / 307 (7.17%)	
occurrences (all)	64	51	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 March 2016	Amendment 02: The primary reason for amendment was to increase participant enrollment by expansion of background AHAs to include patients on either metformin monotherapy or metformin in dual combination with a sulfonylurea agent and the A1C upper limit to 9.5%.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported