Clinical trial results:
A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Study the Safety and Efficacy of the Addition of Sitagliptin During Metformin Up-titration Compared with Metformin Up-titration Alone in Subjects with Type 2 Diabetes Mellitus

Summary

EudraCT number	2015-004224-59
Trial protocol	CZ
Global end of trial date	01 February 2018

Results information

Result version number	v1 (current)
This version publication date	14 February 2019
First version publication date	14 February 2019

Trial information

Trial identification

Sponsor protocol code	0431-848

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02791490
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Protocol Number: MK-0431-848

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	Senior Vice President, Global Clinical Development, 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	01 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This trial is designed to evaluate, in adult participants with Type 2 diabetes mellitus and inadequate glycemic control on sub-maximal metformin mono-therapy (1000 mg/day), the effect of up-titration of metformin plus the addition of sitagliptin compared to up-titration of metformin alone on glycemic control. The primary hypothesis of this study is that up-titration of metformin to 2000 mg/day (1000 mg, twice daily [b.i.d]) plus the addition of sitagliptin 100 mg/day provides greater reduction in hemoglobin A1C (A1C) compared to metformin up-titration alone. Another primary objective of this study is to evaluate the safety and tolerability of this 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:

Metformin is a well-established treatment for individuals with Type 2 diabetes mellitus which has been used in Europe for ~40 years and in the United States since 1995.

Sitagliptin is an orally active and highly-selective dipeptidyl peptidase intravenous (IV) (DPP-4) inhibitor indicated for the treatment of individuals with Type 2 diabetes mellitus.

Evidence for comparator: -

Actual start date of recruitment	16 June 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	Argentina: 53
Country: Number of subjects enrolled	Brazil: 59
Country: Number of subjects enrolled	Canada: 18
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	Guatemala: 73
Country: Number of subjects enrolled	Mexico: 85
Country: Number of subjects enrolled	Russian Federation: 80
Country: Number of subjects enrolled	United States: 79
Worldwide total number of subjects	458
EEA total number of subjects	11

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)	365
From 65 to 84 years	91
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This trial included male and female adult participants with Type 2 diabetes mellitus and inadequate glycemic control on sub-maximal metformin mono-therapy. Additional criteria applied.

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:

Participants received sitagliptin 100 mg once daily for 20 weeks. They also received immediate-release metformin (Met-IR), which was titrated from a baseline dose of 1000 mg/day (500 mg/twice a day [b.i.d]) up to 2000 mg/day (1000 mg/b.i.d.) by Day 15. Participants also received glycemic rescue therapy as needed.

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

Dosage and administration details:

Sitagliptin 100 mg once a day for 20 weeks.

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

Dosage and administration details:

Immediate-release metformin (Met-IR) titrated from a baseline dose of 1000 mg/day (500 mg/b.i.d.) up to 2000 mg/day (1000 mg/b.i.d.) by Day 15 and continued at that dose for remainder of treatment period.

Arm title	Placebo

Arm description:

Participants received placebo matching sitagliptin once daily for 20 weeks. They also received Met-IR, which was titrated from baseline dose of 1000 mg/day (500 mg/b.i.d.) up to 2000 mg/day (1000 mg/b.i.d.) by Day 15. Participants also received glycemic rescue therapy as needed.

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

Dosage and administration details:

Immediate-release metformin (Met-IR) titrated from a baseline dose of 1000 mg/day (500 mg/b.i.d.) up to 2000 mg/day (1000 mg/b.i.d.) by Day 15 and continued at that dose for remainder of treatment period.

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

Dosage and administration details:

Matching placebo to sitagliptin 100 mg once a day for 20 weeks.

Number of subjects in period 1	Sitagliptin	Placebo
Started	229	229
Completed	226	221
Not completed	3	8
Consent withdrawn by subject	2	6
Lost to follow-up	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Sitagliptin
Reporting group description:	
Participants received sitagliptin 100 mg once daily for 20 weeks. They also received immediate-release metformin (Met-IR), which was titrated from a baseline dose of 1000 mg/day (500 mg/twice a day [b.i.d]) up to 2000 mg/day (1000 mg/b.i.d.) by Day 15. Participants also received glycemic rescue therapy as needed.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matching sitagliptin once daily for 20 weeks. They also received Met-IR, which was titrated from baseline dose of 1000 mg/day (500 mg/b.i.d.) up to 2000 mg/day (1000 mg/b.i.d.) by Day 15. Participants also received glycemic rescue therapy as needed.	

Reporting group values	Sitagliptin	Placebo	Total
Number of subjects	229	229	458
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)	176	189	365
From 65-84 years	53	38	91
85 years and over	0	2	2
Age Continuous Units: years			
arithmetic mean	55.6	55.3	
standard deviation	± 10.5	± 10.4	-
Sex: Female, Male Units: Subjects			
Female	139	136	275
Male	90	93	183
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	23	27	50
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	8	7	15
White	167	155	322
More than one race	31	39	70
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	147	151	298

Not Hispanic or Latino	78	70	148
Unknown or Not Reported	4	8	12

Hemoglobin A1C (%)			
Units: Percentage of glycosylated hemoglobin			
arithmetic mean	8.6	8.7	
standard deviation	± 0.9	± 1.0	-
Fasting Plasma Glucose			
Units: mg/dL			
arithmetic mean	181.7	184.4	
standard deviation	± 41.6	± 44.7	-

End points

End points reporting groups

Reporting group title	Sitagliptin
Reporting group description:	
Participants received sitagliptin 100 mg once daily for 20 weeks. They also received immediate-release metformin (Met-IR), which was titrated from a baseline dose of 1000 mg/day (500 mg/twice a day [b.i.d]) up to 2000 mg/day (1000 mg/b.i.d.) by Day 15. Participants also received glycemic rescue therapy as needed.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matching sitagliptin once daily for 20 weeks. They also received Met-IR, which was titrated from baseline dose of 1000 mg/day (500 mg/b.i.d.) up to 2000 mg/day (1000 mg/b.i.d.) by Day 15. Participants also received glycemic rescue therapy as needed.	
Subject analysis set title	Sitagliptin
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received sitagliptin 100 mg once daily for 20 weeks. They also received Met-IR, which was titrated from a baseline dose of 1000 mg/day (500 mg/b.i.d.) up to 2000 mg/day (1000 mg/b.i.d.) by Day 15. Participants also received glycemic rescue therapy as needed.	
Subject analysis set title	Placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
Participants received placebo matching sitagliptin once daily for 20 weeks. They also received Met-IR, which was titrated from baseline dose of 1000 mg/day (500 mg/b.i.d.) up to 2000 mg/day (1000 mg/b.i.d.) by Day 15. Participants also received glycemic rescue therapy as needed.	

Primary: Change From Baseline in Hemoglobin A1C at Week 20

End point title	Change From Baseline in Hemoglobin A1C at Week 20
End point description:	
Hemoglobin A1C is a 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 change from baseline represents the Week 20 A1C value minus the Week 0 (baseline) A1C value. The population analyzed included all randomized participants who received at least 1 dose of study medication and had at least 1 observation for the analysis end point.	
End point type	Primary
End point timeframe:	
Baseline and Week 20	

End point values	Sitagliptin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	229	229		
Units: A1C (%)				
least squares mean (confidence interval 95%)	-1.10 (-1.28 to -0.93)	-0.69 (-0.88 to -0.51)		

Statistical analyses

Statistical analysis title	Change from Baseline in Hemoglobin A1C at Week 20
Comparison groups	Placebo v Sitagliptin
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Longitudinal Data Analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.59
upper limit	-0.23

Primary: Percentage of Participants Who Experienced at Least One Adverse Event (AE)

End point title	Percentage of Participants Who Experienced at Least One Adverse Event (AE)

End point description:

An adverse event (AE) is any untoward medical occurrence in a study participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. The population analyzed for this end point included all randomized participants who received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

Up to 22 weeks

End point values	Sitagliptin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	229	229		
Units: Percentage of participants				
number (not applicable)	44.1	45.9		

Statistical analyses

Statistical analysis title	Pct of part. who experienced at least one AE
Comparison groups	Sitagliptin v Placebo

Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	other
Method	Miettinen and Nurminen method
Parameter estimate	Difference in % vs Placebo
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	7.4

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

End point title	Percentage of Participants Who Discontinued Study Drug Due to an Adverse Event[1]

End point description:

An adverse event (AE) is any untoward medical occurrence in a study participant administered a pharmaceutical product that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product. The population analyzed for this end point included all randomized participants who received at least 1 dose of study medication.

End point type	Primary

End point timeframe:

Up to 20 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No between-group statistical comparison was provided for this primary end point because the statistical analysis plan called for between-group comparisons for only those safety endpoints reported by at least 4 participants in one or both treatment groups.

End point values	Sitagliptin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	229	229		
Units: Percentage of participants				
number (not applicable)	0.9	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Hemoglobin A1C <7% at Week 20

End point title	Percentage of Participants With Hemoglobin A1C <7% at Week 20

End point description:

Hemoglobin A1C is a 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 population analyzed included all randomized participants who received at least 1 dose of study medication and had

at least 1 observation for the analysis end point.

End point type	Secondary

End point timeframe:

Week 20

End point values	Sitagliptin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	229	229		
Units: Percentage of participants				
number (not applicable)	28.8	16.6		

Statistical analyses

Statistical analysis title	Pct of Participants with A1C<7% at Wk 20
Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Miettinen and Nurminen method
Parameter estimate	Relative Risk
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.2
upper limit	2.5

Secondary: Change from Baseline in Fasting Plasma Glucose (FPG) at Week 20

End point title	Change from Baseline in Fasting Plasma Glucose (FPG) at Week 20

End point description:

Plasma glucose was measured on a fasting basis and is expressed as mg/dL. Blood was drawn predose on Day 1 and after 20 weeks of treatment to determine change in FPG levels. The change from baseline represents the Week 20 FPG value minus the Week 0 (baseline) FPG value. The population analyzed included all randomized participants who received at least 1 dose of study medication and had at least 1 observation for the analysis end point.

End point type	Secondary

End point timeframe:

Baseline and Week 20

End point values	Sitagliptin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	229	229		
Units: mg/dL				
least squares mean (confidence interval 95%)	-29.3 (-37.5 to -21.1)	-16.9 (-25.2 to -8.6)		

Statistical analyses

Statistical analysis title	Chg from Baseline in FPG at Week 20
Comparison groups	Sitagliptin v Placebo
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Longitudinal Data Analysis
Parameter estimate	Difference in Least Squares Means
Point estimate	-12.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.2
upper limit	-4.6

Secondary: Percentage of Participants With Hemoglobin A1C ≥8.5% at Baseline That Attained A1C Goal of <7% at Week 20

End point title	Percentage of Participants With Hemoglobin A1C ≥8.5% at Baseline That Attained A1C Goal of <7% at Week 20

End point description:

Hemoglobin A1C is a 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 population analyzed included the subgroup of randomized participants who had a baseline hemoglobin A1C ≥8.5%, received at least 1 dose of study medication, and had at least 1 observation for the analysis endpoint.

End point type	Secondary

End point timeframe:

Baseline and Week 20

End point values	Sitagliptin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	122	122		
Units: Percentage of participants				
number (not applicable)	15.6	5.7		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Receiving Glycemic Rescue Therapy

End point title	Percentage of Participants Receiving Glycemic Rescue Therapy

End point description:

Participants who met pre-specified criteria for glycemic rescue received appropriate rescue therapy. The choice of anti-hyperglycemic rescue agent, dose, and regimen was directed by the investigator, as clinically appropriate. The population analyzed included all randomized participants who received at least 1 dose of study medication.

End point type	Secondary

End point timeframe:

Up to 20 weeks

End point values	Sitagliptin	Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	229	229		
Units: Percentage of participants				
number (not applicable)	1.3	3.1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 22 weeks

Adverse event reporting additional description:

All randomized participants who received at least 1 dose of study medication

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo matching sitagliptin once daily for 20 weeks. They also received Met-IR, which was titrated from baseline dose of 1000 mg/day (500 mg/b.i.d.) up to 2000 mg/day (1000 mg/b.i.d.) by Day 15. Participants also received glycemic rescue therapy as needed.

Reporting group title	Sitagliptin

Reporting group description:

Participants received sitagliptin 100 mg once daily for 20 weeks. They also received Met-IR, which was titrated from a baseline dose of 1000 mg/day (500 mg/b.i.d.) up to 2000 mg/day (1000 mg/b.i.d.) by Day 15. Participants also received glycemic rescue therapy as needed.

Serious adverse events	Placebo	Sitagliptin	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 229 (1.75%)	3 / 229 (1.31%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Stab wound			
subjects affected / exposed	1 / 229 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 229 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			

subjects affected / exposed	1 / 229 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Metrorrhagia			
subjects affected / exposed	1 / 229 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	0 / 229 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Fatty liver alcoholic			
subjects affected / exposed	0 / 229 (0.00%)	1 / 229 (0.44%)	
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	0 / 229 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 229 (0.44%)	0 / 229 (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	Placebo	Sitagliptin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 229 (4.80%)	18 / 229 (7.86%)	

Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	 11 / 229 (4.80%) 11	 18 / 229 (7.86%) 18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported