Clinical trial results:
A Phase III, Randomized, Double-Blind, Clinical Trial to Study the Efficacy and Safety of MK-0431D (a fixed-dose combination [FDC] of sitagliptin and simvastatin) for the Treatment of Patients With Type 2 Diabetes Mellitus (T2DM) with Inadequate Glycemic Control on Metformin Monotherapy

Summary

EudraCT number	2012-001868-29
Trial protocol	LT LV HU CZ PL IT
Global end of trial date	01 November 2013

Results information

Result version number	v1
This version publication date	27 April 2016
First version publication date	18 March 2015

Trial information

Trial identification

Sponsor protocol code	MK-0431D-266

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01678820
WHO universal trial number (UTN)	-

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	01 November 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 November 2013
Global end of trial reached?	Yes
Global end of trial date	01 November 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

1. To assess the effect of MK-0431D compared to sitagliptin alone on hemoglobin A1c (A1C). 2. To assess the safety and tolerability of MK-0431D.

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.
The following additional measure defined for this individual study was in place for the protection of trial subjects: participants not meeting specific glycemic goals received rescue therapy initiated with glimepiride (open-label, supplied locally).

Background therapy:

Participants will continue on their stable, pre-screening metformin daily dose of >= 1500 mg for at least 12 weeks prior to randomization and during the study.

Evidence for comparator: -

Actual start date of recruitment	10 October 2012
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	Poland: 6
Country: Number of subjects enrolled	Czech Republic: 11
Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Latvia: 1
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Macedonia, the former Yugoslav Republic of: 3
Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Puerto Rico: 5
Country: Number of subjects enrolled	Romania: 11
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Croatia: 2
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	South Africa: 17
Country: Number of subjects enrolled	United States: 218
Worldwide total number of subjects	299
EEA total number of subjects	51

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)	251
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

All participants randomized population.

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/Simvastatin FDC

Arm description:

Sitagliptin 100 mg/simvastatin 40 mg fixed dose combination (FDC) plus placebo to sitagliptin plus placebo to simvastatin administered orally once daily in the evening for 16 weeks. Participants will continue on their stable pre-screening metformin dose and dosing regimen of >=1500 mg daily for the duration of the study. Participants may receive glimepiride 1 mg once daily or 2 mg once daily (may be uptitrated to 6 mg once daily) as rescue therapy.

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

Dosage and administration details:

Sitagliptin 100 mg/Simvastatin 40 mg fixed-dose combination tablet administered once daily in the evening.

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

Dosage and administration details:

Placebo to simvastatin administered once daily in the evening.

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 administered once daily in the evening.

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

Dosage and administration details:

Participants will continue on their stable, pre-screening metformin daily dose of >= 1500 mg for at least 12 weeks prior to randomization and during the study.

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

Dosage and administration details:

Following randomization, participants requiring glycemic rescue may receive open-label glimepiride initiated at a dose of 1 mg/day or 2 mg/day which may be up-titrated to 6 mg/day taken once daily with breakfast or the first main meal of the day.

Arm title	Sitagliptin

Arm description:

Sitagliptin 100 mg plus placebo to simvastatin plus placebo to sitagliptin/simvastatin FDC administered orally once daily in the evening for 16 weeks.
Participants will continue on their stable pre-screening metformin dose and dosing regimen of >=1500 mg daily for the duration of the study. Participants may receive glimepiride 1 mg once daily or 2 mg once daily (may be up-titrated to 6 mg once daily) as rescue therapy.

Arm type	Active comparator
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 oral tablet administered once daily in the evening.

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

Dosage and administration details:

Placebo to simvastatin administered once daily in the evening.

Investigational medicinal product name	Placebo to sitagliptin/simvastatin FDC
Investigational medicinal product code	
Other name	MK-0431D
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo to sitagliptin/simvastatin FDC tablet administered once daily in the evening.

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

Dosage and administration details:

Participants will continue on their stable, pre-screening metformin daily dose of >= 1500 mg for at least 12 weeks prior to randomization and during the study.

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

Dosage and administration details:

Following randomization, participants requiring glycemic rescue may receive open-label glimepiride initiated at a dose of 1 mg/day or 2 mg/day which may be up-titrated to 6 mg/day taken once daily with breakfast or the first main meal of the day.

Arm title	Simvastatin

Arm description:

Simvastatin 40 mg plus placebo to sitagliptin plus placebo to sitagliptin/simvastatin FDC administered orally once daily in the evening for 16 weeks.
Participants will continue on their stable pre-screening metformin dose and dosing regimen of >=1500 mg daily for the duration of the study. Participants may receive glimepiride 1 mg once daily or 2 mg once daily (may be up-titrated to 6 mg once daily) as rescue therapy.

Arm type	Active comparator
Investigational medicinal product name	Simvastatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Simvastatin 40 mg tablet administered orally once daily in the evening.

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 administered once daily in the evening.

Investigational medicinal product name	Placebo to sitagliptin/simvastatin FDC
Investigational medicinal product code	
Other name	MK-0431D
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo to sitagliptin/simvastatin FDC tablet administered once daily in the evening.

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

Dosage and administration details:

Participants will continue on their stable, pre-screening metformin daily dose of >= 1500 mg for at least 12 weeks prior to randomization and during the study.

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

Dosage and administration details:

Following randomization, participants requiring glycemic rescue may receive open-label glimepiride initiated at a dose of 1 mg/day or 2 mg/day which may be up-titrated to 6 mg/day taken once daily with breakfast or the first main meal of the day.

Number of subjects in period 1	Sitagliptin/Simvastat in FDC	Sitagliptin	Simvastatin
Started	100	99	100
Treated with double-blind study drug	100	97	98
Completed	38	36	43
Not completed	62	63	57
Consent withdrawn by subject	2	5	2
Physician decision	-	-	1
Not treated with double-blind study drug	-	2	2
Adverse event	2	2	2
Non-compliance with study drug	-	1	-
Protocol Specified Criteria	2	3	1
Lost to follow-up	7	2	2
Studty Terminated by Sponsor	45	43	43
Protocol deviation	4	5	4

Baseline characteristics

Reporting groups	
Reporting group title	Sitagliptin/Simvastatin FDC
Reporting group description:	
Sitagliptin 100 mg/simvastatin 40 mg fixed dose combination (FDC) plus placebo to sitagliptin plus placebo to simvastatin administered orally once daily in the evening for 16 weeks. Participants will continue on their stable pre-screening metformin dose and dosing regimen of >=1500 mg daily for the duration of the study. Participants may receive glimepiride 1 mg once daily or 2 mg once daily (may be uptitrated to 6 mg once daily) as rescue therapy.	
Reporting group title	Sitagliptin
Reporting group description:	
Sitagliptin 100 mg plus placebo to simvastatin plus placebo to sitagliptin/simvastatin FDC administered orally once daily in the evening for 16 weeks. Participants will continue on their stable pre-screening metformin dose and dosing regimen of >=1500 mg daily for the duration of the study. Participants may receive glimepiride 1 mg once daily or 2 mg once daily (may be up-titrated to 6 mg once daily) as rescue therapy.	
Reporting group title	Simvastatin
Reporting group description:	
Simvastatin 40 mg plus placebo to sitagliptin plus placebo to sitagliptin/simvastatin FDC administered orally once daily in the evening for 16 weeks. Participants will continue on their stable pre-screening metformin dose and dosing regimen of >=1500 mg daily for the duration of the study. Participants may receive glimepiride 1 mg once daily or 2 mg once daily (may be up-titrated to 6 mg once daily) as rescue therapy.	

Reporting group values	Sitagliptin/Simvastatin FDC	Sitagliptin	Simvastatin
Number of subjects	100	99	100
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	54.9	54.2	54.9
standard deviation	± 10.2	± 10.3	± 10
Gender categorical			
Units: Subjects			
Female	45	52	49
Male	55	47	51
Hemoglobin A1c (A1C)			
Units: percent			
arithmetic mean	8.16	8.15	8.22
standard deviation	± 0.94	± 1.09	± 1.19
Fasting plasma glucose (FPG)			
Units: mg/dL			
arithmetic mean	169.9	175.9	175.7
standard deviation	± 42.3	± 48.6	± 49.3
Low-density lipoprotein cholesterol (LDL-C)			
Units: mg/dL			
arithmetic mean	106.5	103.9	100.9
standard deviation	± 26.7	± 24.2	± 22
Total cholesterol (TC)			

Units: mg/dL			
arithmetic mean	189.3	187.7	183.5
standard deviation	± 30.9	± 29.6	± 28.4
Apolipoprotein B (Apo B)			
Population includes all randomized participants with data. Sitagliptin, n=95.			
Units: mg/dL			
arithmetic mean	97.8	95.4	94.1
standard deviation	± 19	± 19	± 17.2
Non high-density lipoprotein cholesterol (non-HDL-C)			
Population includes all randomized participants with data. Sitagliptin, n=97.			
Units: mg/dL			
arithmetic mean	141.7	139.5	136.5
standard deviation	± 30.9	± 29.9	± 27.1
Triglycerides (TG)			
Units: mg/dL			
arithmetic mean	177.4	180.8	184.2
standard deviation	± 101.2	± 119.1	± 118.6
High-density lipoprotein cholesterol (HDL-C)			
Units: mg/dL			
arithmetic mean	47.6	48.2	47
standard deviation	± 11.3	± 12.1	± 11.2
Very low-density lipoprotein cholesterol (VLDL-C)			
Population includes all randomized participants with data. Sitagliptin, n=97.			
Units: mg/dL			
arithmetic mean	35.4	35.8	35.7
standard deviation	± 18.8	± 20.4	± 18.8

Reporting group values	Total		
Number of subjects	299		
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	146		
Male	153		
Hemoglobin A1c (A1C)			
Units: percent			
arithmetic mean			
standard deviation	-		
Fasting plasma glucose (FPG)			
Units: mg/dL			
arithmetic mean			
standard deviation	-		
Low-density lipoprotein cholesterol (LDL-C)			

Units: mg/dL arithmetic mean standard deviation	- -		
Total cholesterol (TC) Units: mg/dL arithmetic mean standard deviation	- -		
Apolipoprotein B (Apo B)			
Population includes all randomized participants with data. Sitagliptin, n=95.			
Units: mg/dL arithmetic mean standard deviation	- -		
Non high-density lipoprotein cholesterol (non-HDL-C)			
Population includes all randomized participants with data. Sitagliptin, n=97.			
Units: mg/dL arithmetic mean standard deviation	- -		
Triglycerides (TG) Units: mg/dL arithmetic mean standard deviation	- -		
High-density lipoprotein cholesterol (HDL-C) Units: mg/dL arithmetic mean standard deviation	- -		
Very low-density lipoprotein cholesterol (VLDL-C)			
Population includes all randomized participants with data. Sitagliptin, n=97.			
Units: mg/dL arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Sitagliptin/Simvastatin FDC

Reporting group description:

Sitagliptin 100 mg/simvastatin 40 mg fixed dose combination (FDC) plus placebo to sitagliptin plus placebo to simvastatin administered orally once daily in the evening for 16 weeks. Participants will continue on their stable pre-screening metformin dose and dosing regimen of >=1500 mg daily for the duration of the study. Participants may receive glimepiride 1 mg once daily or 2 mg once daily (may be uptitrated to 6 mg once daily) as rescue therapy.

Reporting group title	Sitagliptin

Reporting group description:

Sitagliptin 100 mg plus placebo to simvastatin plus placebo to sitagliptin/simvastatin FDC administered orally once daily in the evening for 16 weeks.
Participants will continue on their stable pre-screening metformin dose and dosing regimen of >=1500 mg daily for the duration of the study. Participants may receive glimepiride 1 mg once daily or 2 mg once daily (may be up-titrated to 6 mg once daily) as rescue therapy.

Reporting group title	Simvastatin

Reporting group description:

Simvastatin 40 mg plus placebo to sitagliptin plus placebo to sitagliptin/simvastatin FDC administered orally once daily in the evening for 16 weeks.
Participants will continue on their stable pre-screening metformin dose and dosing regimen of >=1500 mg daily for the duration of the study. Participants may receive glimepiride 1 mg once daily or 2 mg once daily (may be up-titrated to 6 mg once daily) as rescue therapy.

Primary: Change from baseline in A1C at Week 16 (sitagliptin/simvastatin FDC vs. sitagliptin)

End point title	Change from baseline in A1C at Week 16 (sitagliptin/simvastatin FDC vs. sitagliptin)[1]

End point description:

A1C is measured as percent. Thus, this change from baseline reflects the Week 16 A1C percent minus the Week 0 A1C percent. This primary endpoint only includes results for sitagliptin/simvastatin FDC vs. sitagliptin. Results for simvastatin are presented below under secondary endpoints.
Full analysis set (FAS) population defined as all randomized participants who took at least one dose of study drug and had at least one measurement for the analysis of this outcome measure (baseline or subsequent to the first dose of study drug).

End point type	Primary

End point timeframe:

Baseline and Week 16

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This primary endpoint only includes results for sitagliptin/simvastatin FDC vs. sitagliptin. Results for simvastatin are presented under secondary endpoints.

End point values	Sitagliptin/Simvastatin FDC	Sitagliptin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	97		
Units: percent				
least squares mean (confidence interval 95%)	-0.41 (-0.64 to -0.17)	-0.59 (-0.83 to -0.36)		

Statistical analyses

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Sitagliptin
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.267 [3]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	0.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.14
upper limit	0.52

Notes:

[2] - Due to inadequate sample size, the primary hypothesis of non-inferiority was not tested. Nominal p-value is provided.
[3] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Primary: Number of participants who experienced at least one adverse event (AE)

End point title	Number of participants who experienced at least one adverse event (AE)

End point description:

Excludes data after rescue therapy. Adverse event is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the Sponsor's product, whether or not considered related to the use of the product.
All participants as treated population defined as all randomized participants who received at least one dose of study drug.

End point type	Primary

End point timeframe:

Up to 16 weeks for non-serious AEs; up to 18 weeks for serious AEs

End point values	Sitagliptin/Simvastatin FDC	Sitagliptin	Simvastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	97	98	
Units: Participants	13	13	17	

Statistical analyses

Statistical analysis title	Difference in percents
Comparison groups	Sitagliptin/Simvastatin FDC v Sitagliptin
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	other[4]
Parameter estimate	Difference in percents
Point estimate	-0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	9.3

Notes:

[4] - Based on Miettinen & Nurminen method

Statistical analysis title	Difference in percents
Comparison groups	Sitagliptin/Simvastatin FDC v Simvastatin
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[5]
Parameter estimate	Difference in percents
Point estimate	-4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.7
upper limit	5.8

Notes:

[5] - Based on Miettinen & Nurminen method

Primary: Number of participants who discontinued study drug due to an adverse event

End point title	Number of participants who discontinued study drug due to an adverse event[6]

End point description:

Excludes data after rescue therapy. Adverse event is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the Sponsor's product, whether or not considered related to the use of the product.
All participants as treated population defined as all randomized participants who received at least one dose of study drug.

End point type	Primary

End point timeframe:

Up to 16 weeks

Notes:

[6] - 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: As pre-specified in the protocol, 95% confidence intervals were only provided for events with an incidence of at least 4 participants in at least one of the treatment arms.

End point values	Sitagliptin/Simvastatin FDC	Sitagliptin	Simvastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	97	98	
Units: Participants	2	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in A1C at Week 16 (sitagliptin/simvastatin FDC vs. simvastatin)

End point title	Change from baseline in A1C at Week 16 (sitagliptin/simvastatin FDC vs. simvastatin)[7]

End point description:

A1C is measured as percent. Thus, this change from baseline reflects the Week 16 A1C percent minus the Week 0 A1C percent. This primary outcome measure only includes results for sitagliptin/simvastatin FDC vs. simvastatin. Results for sitagliptin are presented above under primary outcome measures.
FAS population defined as all randomized participants who took at least one dose of study drug and had at least one measurement for the analysis of this outcome measure (baseline or subsequent to the first dose of study drug).

End point type	Secondary

End point timeframe:

Baseline and Week 16

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This secondary endpoint only includes results for sitagliptin/simvastatin FDC vs. simvastatin. Results for sitagliptin are presented under primary endpoints.

End point values	Sitagliptin/Simvastatin FDC	Simvastatin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	98		
Units: percent				
least squares mean (confidence interval 95%)	-0.41 (-0.64 to -0.17)	0.21 (-0.02 to 0.45)		

Statistical analyses

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Simvastatin
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	< 0.001 [9]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	-0.62

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.95
upper limit	-0.28

Notes:

[8] - Due to inadequate sample size, the secondary hypothesis was not tested. Nominal p-value is provided.
[9] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Secondary: Change from baseline in FPG at Week 16

End point title	Change from baseline in FPG at Week 16

End point description:

Change from baseline reflects the Week 16 value minus the Week 0 value.
FAS population defined as all randomized participants who took at least one dose of study drug and who had at least one measurement for the analysis of this outcome measure (baseline or subsequent to the first dose of study drug).

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Sitagliptin/Simvastatin FDC	Sitagliptin	Simvastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	97	98	
Units: mg/dL				
least squares mean (confidence interval 95%)	-7.9 (-21 to 5.2)	-9.6 (-23.4 to 4.1)	21.3 (7.9 to 34.7)	

Statistical analyses

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Sitagliptin
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.856 [11]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.1
upper limit	20.6

Notes:

[10] - There is no hypothesis comparing Sitagliptin/Simvastatin vs. Sitagliptin for FPG. Nominal p-value is provided.
[11] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Simvastatin
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.002 [13]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	-29.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-47.9
upper limit	-10.6

Notes:

[12] - There is no hypothesis comparing Sitagliptin/Simvastatin vs. Simvastatin for FPG. Nominal p-value is provided.
[13] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Secondary: Percent change from baseline in LDL-C at Week 16

End point title	Percent change from baseline in LDL-C at Week 16

End point description:

Percent change from baseline was calculated as the Week 16 value minus the Week 0 value, divided by the Week 0 value ×100%.
FAS population defined as all randomized participants who took at least one dose of study drug and had at least one measurement for the analysis of this outcome measure (baseline or subsequent to the first dose of study drug).

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Sitagliptin/Simvastatin FDC	Sitagliptin	Simvastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	97	98	
Units: Percent change				
least squares mean (confidence interval 95%)	-21.6 (-32.3 to -10.8)	4 (-6.9 to 14.9)	-26.9 (-37.5 to -16.3)	

Statistical analyses

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Sitagliptin
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	< 0.001 [15]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	-25.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.6
upper limit	-15.6

Notes:

[14] - Due to inadequate sample size, the secondary hypothesis was not tested. Nominal p-value is provided.
[15] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Simvastatin
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.286 [17]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	15.2

Notes:

[16] - There is no hypothesis comparing Sitagliptin/Simvastatin vs. Simvastatin for LDL-C-lowering. Nominal p-value is provided.
[17] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Secondary: Percent change from baseline in TC at Week 16

End point title	Percent change from baseline in TC at Week 16

End point description:

Percent change from baseline was calculated as the Week 16 value minus the Week 0 value, divided by the Week 0 value ×100%.
FAS population defined as all randomized participants who took at least one dose of study drug and had at least one measurement for the analysis of this outcome measure (baseline or subsequent to the first dose of study drug).

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Sitagliptin/Simvastatin FDC	Sitagliptin	Simvastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	97	98	
Units: Percent change				
least squares mean (confidence interval 95%)	-18.4 (-26.6 to -10.2)	-0.4 (-8.6 to 7.9)	-18.4 (-26.4 to -10.4)	

Statistical analyses

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Sitagliptin
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	< 0.001 [19]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	-18.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.2
upper limit	-12

Notes:

[18] - There is no hypothesis comparing Sitagliptin/Simvastatin FDC vs. Sitagliptin for TC-lowering. Nominal p-value is provided.
[19] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Simvastatin
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.99 [21]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	6

Notes:

[20] - There is no hypothesis comparing Sitagliptin/Simvastatin FDC vs. Simvastatin for TC-lowering. Nominal p-value is provided.
[21] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Secondary: Percent change from baseline in Apo B at Week 16

End point title	Percent change from baseline in Apo B at Week 16

End point description:

Percent change from baseline was calculated as the Week 16 value minus the Week 0 value, divided by the Week 0 value ×100%. FAS population defined as all randomized participants who took at least one dose of study drug and had at least one measurement for the analysis of this outcome measure (baseline or subsequent to the first dose of study drug).

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Sitagliptin/Simvastatin FDC	Sitagliptin	Simvastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	94	98	
Units: Percent change				
least squares mean (confidence interval 95%)	-16.9 (-27 to -6.8)	3.3 (-7.1 to 13.7)	-19.8 (-30 to -9.6)	

Statistical analyses

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Sitagliptin
Number of subjects included in analysis	194
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	< 0.001 [23]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	-20.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-28.3
upper limit	-12.2

Notes:

[22] - There is no hypothesis comparing Sitagliptin/Simvastatin FDC vs. Sitagliptin for Apo B-lowering. Nominal p-value is provided.
[23] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Simvastatin

Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	= 0.469 [25]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	10.7

Notes:

[24] - There is no hypothesis comparing Sitagliptin/Simvastatin FDC vs. Simvastatin for Apo B-lowering. Nominal p-value is provided.
[25] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Secondary: Percent change from baseline in non-HDL-C at Week 16

End point title	Percent change from baseline in non-HDL-C at Week 16

End point description:

Percent change from baseline was calculated as the Week 16 value minus the Week 0 value, divided by the Week 0 value ×100%.
FAS population defined as all randomized participants who took at least one dose of study drug and had at least one measurement for the analysis of this outcome measure (baseline or subsequent to the first dose of study drug).

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Sitagliptin/Simvastatin FDC	Sitagliptin	Simvastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	96	98	
Units: Percent change				
least squares mean (confidence interval 95%)	-23.9 (-33.9 to -13.9)	0.6 (-9.5 to 10.7)	-24.2 (-34 to -14.4)	

Statistical analyses

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Sitagliptin
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other[26]
P-value	< 0.001 [27]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	-24.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.6
upper limit	-16.3

Notes:

[26] - There is no hypothesis comparing Sitagliptin/Simvastatin FDC vs. Sitagliptin for non-HDL-C-lowering. Nominal p-value is provided.
[27] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Simvastatin
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[28]
P-value	= 0.937 [29]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.7
upper limit	8.3

Notes:

[28] - There is no hypothesis comparing Sitagliptin/Simvastatin FDC vs. Simvastatin for non-HDL-C-lowering. Nominal p-value is provided.
[29] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Secondary: Percent change from baseline in TG at Week 16

End point title	Percent change from baseline in TG at Week 16

End point description:

Percent change from baseline was calculated as the Week 16 value minus the Week 0 value, divided by the Week 0 value ×100%.
FAS population defined as all randomized participants who took at least one dose of study drug and had at least one measurement for the analysis of this outcome measure (baseline or subsequent to the first dose of study drug).

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Sitagliptin/Simvastatin FDC	Sitagliptin	Simvastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	97	98	
Units: Percent change				
least squares mean (confidence interval 95%)	-20.4 (-51.9 to 11.1)	-4.9 (-39.5 to 29.7)	-10.1 (-52.1 to 31.9)	

Statistical analyses

Statistical analysis title	Difference in estimated means
Comparison groups	Sitagliptin/Simvastatin FDC v Sitagliptin
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	= 0.068 [31]
Method	Robust Regression
Parameter estimate	Difference in estimated means
Point estimate	-15.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.2
upper limit	1.2

Notes:

[30] - There is no hypothesis comparing Sitagliptin/Simvastatin FDC vs. Sitagliptin for TG-lowering. Nominal p-value is provided.
[31] - Based on a robust regression using M-estimation with treatment, region, and a covariate for baseline triglycerides (mg/dL). Missing data were imputed by multiple imputations.

Statistical analysis title	Difference in estimated means
Comparison groups	Sitagliptin/Simvastatin FDC v Simvastatin
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	= 0.365 [33]
Method	Robust Regression
Parameter estimate	Difference in estimated means
Point estimate	-10.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.6
upper limit	13

Notes:

[32] - There is no hypothesis comparing Sitagliptin/Simvastatin FDC vs. Simvastatin for TG-lowering. Nominal p-value is provided.
[33] - Based on a robust regression using M-estimation with treatment, region, and a covariate for baseline triglycerides (mg/dL). Missing data were imputed by multiple imputations.

Secondary: Percent change from baseline in HDL-C at Week 16

End point title	Percent change from baseline in HDL-C at Week 16

End point description:

Percent change from baseline was calculated as the Week 16 value minus the Week 0 value, divided by the Week 0 value ×100%.
FAS population defined as all randomized participants who took at least one dose of study drug and had

at least one measurement for the analysis of this outcome measure (baseline or subsequent to the first dose of study drug).

End point type	Secondary
End point timeframe:	
Baseline and Week 16	

End point values	Sitagliptin/Simvastatin FDC	Sitagliptin	Simvastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	97	98	
Units: Percent change				
least squares mean (confidence interval 95%)	2.5 (-2.7 to 7.8)	2 (-3.3 to 7.4)	2.1 (-3 to 7.3)	

Statistical analyses

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Sitagliptin
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	= 0.857 [35]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	5.8

Notes:

[34] - There is no hypothesis comparing Sitagliptin/Simvastatin FDC vs. Sitagliptin for HDL-C-lowering. Nominal p-value is provided.

[35] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Simvastatin
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[36]
P-value	= 0.879 [37]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	0.4

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	5.6

Notes:

[36] - There is no hypothesis comparing Sitagliptin/Simvastatin FDC vs. Simvastatin for HDL-C-lowering. Nominal p-value is provided.
[37] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Secondary: Percent change from baseline in VLDL-C at Week 16

End point title	Percent change from baseline in VLDL-C at Week 16

End point description:

Percent change from baseline was calculated as the Week 16 value minus the Week 0 value, divided by the Week 0 value ×100%.
FAS population defined as all randomized participants who took at least one dose of study drug and had at least one measurement for the analysis of this outcome measure (baseline or subsequent to the first dose of study drug).

End point type	Secondary

End point timeframe:

Baseline and Week 16

End point values	Sitagliptin/Simvastatin FDC	Sitagliptin	Simvastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	96	98	
Units: Percent change				
least squares mean (confidence interval 95%)	-17.5 (-33.8 to -1.2)	12.9 (-4.2 to 29.9)	-2.2 (-18.9 to 14.5)	

Statistical analyses

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Sitagliptin
Number of subjects included in analysis	196
Analysis specification	Pre-specified
Analysis type	other[38]
P-value	= 0.004 [39]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	-30.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-51
upper limit	-9.7

Notes:

[38] - There is no hypothesis comparing Sitagliptin/Simvastatin FDC vs. Sitagliptin for VLDL-C-lowering. Nominal p-value is provided.
[39] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Statistical analysis title	Difference in least squares means
Comparison groups	Sitagliptin/Simvastatin FDC v Simvastatin
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[40]
P-value	= 0.141 [41]
Method	Longitudinal Data Analysis Model
Parameter estimate	Difference in least squares means
Point estimate	-15.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-35.8
upper limit	5.1

Notes:

[40] - There is no hypothesis comparing Sitagliptin/Simvastatin FDC vs. Simvastatin for VLDL-C-lowering. Nominal p-value is provided.
[41] - Based on a longitudinal data analysis model including terms for region, treatment, time, and the interaction of time by treatment with the restriction of common mean across treatment groups at baseline.

Secondary: Percentage of participants with A1C level <7% at Week 16

End point title	Percentage of participants with A1C level <7% at Week 16

End point description:

Percentage of participants achieving glycemic goal (A1C <7%) after 16 weeks of treatment. Data as observed. FAS population defined as all randomized participants who took at least one dose of study drug and had at least one measurement for the analysis of this outcome measure (baseline or subsequent to the first dose of study drug).

End point type	Secondary

End point timeframe:

Week 16

End point values	Sitagliptin/Simvastatin FDC	Sitagliptin	Simvastatin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	100	97	98	
Units: Percentage of participants				
number (not applicable)	29.9	29.6	17.6	

Statistical analyses

Statistical analysis title	Difference in percents
Comparison groups	Sitagliptin/Simvastatin FDC v Sitagliptin

Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	other[42]
Parameter estimate	Difference in percents
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.2
upper limit	12.9

Notes:

[42] - Based on Miettinen & Nurminen method. Missing data were imputed by multiple imputations.

Statistical analysis title	Difference in percents
Comparison groups	Sitagliptin/Simvastatin FDC v Simvastatin
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	other[43]
Parameter estimate	Difference in percents
Point estimate	12.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	24

Notes:

[43] - Based on Miettinen & Nurminen method. Missing data were imputed by multiple imputations.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Up to 18 weeks

Adverse event reporting additional description:

All participants as treated population defined as all randomized participants who received at least one dose of study drug. Serious adverse events include data after rescue therapy and non-serious adverse events exclude data after rescue therapy

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Sitagliptin/Simvastatin FDC

Reporting group description:

Sitagliptin 100 mg/simvastatin 40 mg fixed dose combination (FDC) plus placebo to sitagliptin plus placebo to simvastatin administered orally once daily in the evening. Participants will continue on their stable pre-screening metformin dose and dosing regimen of >=1500 mg daily for the duration of the study. Participants may receive glimepiride 1 mg once daily or 2 mg once daily (may be uptitrated to 6 mg once daily) as rescue therapy.

Reporting group title	Sitagliptin

Reporting group description:

Sitagliptin 100 mg plus placebo to simvastatin plus placebo to sitagliptin/simvastatin FDC administered orally once daily in the evening for 16 weeks.
Participants will continue on their stable pre-screening metformin dose and dosing regimen of >=1500 mg daily for the duration of the study. Participants may receive glimepiride 1 mg once daily or 2 mg once daily (may be up-titrated to 6 mg once daily) as rescue therapy.

Reporting group title	Simvastatin

Reporting group description:

Simvastatin 40 mg plus placebo to sitagliptin plus placebo to sitagliptin/simvastatin FDC administered orally once daily in the evening for 16 weeks.
Participants will continue on their stable pre-screening metformin dose and dosing regimen of >=1500 mg daily for the duration of the study. Participants may receive glimepiride 1 mg once daily or 2 mg once daily (may be up-titrated to 6 mg once daily) as rescue therapy.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No non-serious adverse event exceeded the 5% threshold for any reporting group.

Serious adverse events	Sitagliptin/Simvastatin FDC	Sitagliptin	Simvastatin
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 100 (1.00%)	0 / 97 (0.00%)	1 / 98 (1.02%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 100 (1.00%)	0 / 97 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			

subjects affected / exposed	1 / 100 (1.00%)	0 / 97 (0.00%)	0 / 98 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 100 (0.00%)	0 / 97 (0.00%)	1 / 98 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Sitagliptin/Simvastat in FDC	Sitagliptin	Simvastatin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 100 (0.00%)	0 / 97 (0.00%)	0 / 98 (0.00%)

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? Yes

Date	Interruption	Restart date
12 September 2013	The trial was terminated for business reasons.	-

Notes:

Limitations and caveats

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

The early termination of this study resulted in a smaller number of participants analyzed.

Notes: