Clinical trial results:
A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial to Study the Safety and Efficacy of the Addition of MK-3102 to Subjects With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Combination Therapy with Glimepiride and Metformin

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2012-002612-10
Trial protocol	PL
Global end of trial date	23 December 2014

Results information

Result version number	v1 (current)
This version publication date	23 December 2016
First version publication date	23 December 2016

Trial information

Trial identification

Sponsor protocol code	3102-022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01704261
WHO universal trial number (UTN)	-
Other trial identifiers	Protocol number: MK-3102-022

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	23 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 December 2014
Global end of trial reached?	Yes
Global end of trial date	23 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

After 24 weeks, to assess the effect of the addition of treatment with omarigliptin (MK-3102) compared with the addition of placebo on hemoglobin A1C.

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:

Participants should remain on a stable dose of metformin (≥1500 mg/day) throughout the trial.

Participants should remain on a stable dose of glimepiride (≥4 mg/day) throughout the trial. In the event of hypoglycemia, the glimepiride dose can be down-titrated to a minimum dose of 1 mg/day.

Evidence for comparator: -

Actual start date of recruitment	19 October 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 20
Country: Number of subjects enrolled	Romania: 130
Country: Number of subjects enrolled	Russian Federation: 13
Country: Number of subjects enrolled	South Africa: 40
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 35
Country: Number of subjects enrolled	United States: 69
Worldwide total number of subjects	307
EEA total number of subjects	150

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)	238
From 65 to 84 years	69
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Fifty-one sites received IEC/IRB approval and were shipped clinical supplies.

Pre-assignment

Screening details:

In total, 583 participants were screened and 276 participants were excluded during screening. The most common reason for participants not being randomized was screen failure. The most common reasons for screen failure were not meeting the metformin and glimepiride dose requirements inclusion criterion or meeting exclusionary laboratory values.

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	Omarigliptin

Arm description:

Omarigliptin 25 mg capsule administered orally once a week for 24 weeks. Participants continue pre-study concomitant therapy of open-label glimepiride tablet(s) orally once daily (total daily dose >=4 mg per day) and metformin tablet(s) orally once or twice daily (total daily dose >=1500 mg per day).

Arm type	Experimental
Investigational medicinal product name	Omarigliptin 25 mg
Investigational medicinal product code	
Other name	MK-3102
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Omarigliptin 25 mg capsule administered orally once a week for 24 weeks. Participants continue pre-study concomitant therapy of open-label glimepiride tablet(s) orally once daily (total daily dose >=4 mg per day) and metformin tablet(s) orally once or twice daily (total daily dose >=1500 mg per day).

Arm title	Placebo

Arm description:

Matching placebo to omarigliptin capsule administered orally once a week for 24 weeks. Participants continue pre-study concomitant therapy of open-label glimepiride tablet(s) orally once daily (total daily dose >=4 mg per day) and metformin tablet(s) orally once or twice daily (total daily dose >=1500 mg per day).

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

Dosage and administration details:

Matching placebo to omarigliptin capsule administered orally once a week for 24 weeks. Participants continue pre-study concomitant therapy of open-label glimepiride tablet(s) orally once daily (total daily dose >=4 mg per day) and metformin tablet(s) orally once or twice daily (total daily dose >=1500 mg per day).

Number of subjects in period 1	Omarigliptin	Placebo
Started	154	153
Completed	141	138
Not completed	13	15
Consent withdrawn by subject	12	15
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Omarigliptin
Reporting group description:	
Omarigliptin 25 mg capsule administered orally once a week for 24 weeks. Participants continue pre-study concomitant therapy of open-label glimepiride tablet(s) orally once daily (total daily dose >=4 mg per day) and metformin tablet(s) orally once or twice daily (total daily dose >=1500 mg per day).	
Reporting group title	Placebo
Reporting group description:	
Matching placebo to omarigliptin capsule administered orally once a week for 24 weeks. Participants continue pre-study concomitant therapy of open-label glimepiride tablet(s) orally once daily (total daily dose >=4 mg per day) and metformin tablet(s) orally once or twice daily (total daily dose >=1500 mg per day).	

Reporting group values	Omarigliptin	Placebo	Total
Number of subjects	154	153	307
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)	126	112	238
From 65-84 years	28	41	69
85 years and over	0	0	0
Age Continuous | Units: Years			
arithmetic mean	57.2	58.4	
standard deviation	± 8.4	± 9.4	-
Gender, Male/Female Units: Participants			
Female	81	79	160
Male	73	74	147

End points

End points reporting groups

Reporting group title	Omarigliptin
Reporting group description:	
Omarigliptin 25 mg capsule administered orally once a week for 24 weeks. Participants continue pre-study concomitant therapy of open-label glimepiride tablet(s) orally once daily (total daily dose >=4 mg per day) and metformin tablet(s) orally once or twice daily (total daily dose >=1500 mg per day).	
Reporting group title	Placebo
Reporting group description:	
Matching placebo to omarigliptin capsule administered orally once a week for 24 weeks. Participants continue pre-study concomitant therapy of open-label glimepiride tablet(s) orally once daily (total daily dose >=4 mg per day) and metformin tablet(s) orally once or twice daily (total daily dose >=1500 mg per day).	

Primary: Change from baseline in hemoglobin A1c (A1C) at Week 24

End point title	Change from baseline in hemoglobin A1c (A1C) at Week 24
End point description:	
A1C is blood marker used to report average blood glucose levels over a prolonged periods of time and is reported as a percentage (%). Thus, this change from baseline reflects the Week 24 A1C minus the Week 0 A1C. The Full Analysis Set (FAS) population consisted of all randomized participants who received at least 1 dose of study medication and had a baseline measurement or a measurement for the analysis endpoint after receiving study medication. One participant was in 2 clinical trials in parallel and was excluded from all efficacy and safety analysis.	
End point type	Primary
End point timeframe:	
Baseline and Week 24	

End point values	Omarigliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: %A1C				
least squares mean (confidence interval 95%)	-0.67 (-0.84 to -0.5)	-0.06 (-0.23 to 0.12)		

Statistical analyses

Statistical analysis title	Difference in the least squares means
Statistical analysis description:	
Based on a constrained longitudinal data analysis (cLDA) method with a restriction of the same baseline mean across treatment groups.	
Comparison groups	Omarigliptin v Placebo

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Difference in the least squares means
Parameter estimate	Mean difference (final values)
Point estimate	-0.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.85
upper limit	-0.38

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 AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure. All Subjects as Treated (ASaT) population, defined as all randomized participants who received at least 1 dose of study medication. Participants were included in the treatment group corresponding to the study treatment they actually received. One participant was in 2 clinical trials and was excluded from all efficacy and safety analysis.

End point type	Primary

End point timeframe:

Up to Week 27

End point values	Omarigliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: Percentage of participants				
number (not applicable)	57.5	47.7		

Statistical analyses

Statistical analysis title	Difference in % Omarigliptin vs Placebo
Comparison groups	Omarigliptin v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in % Omarigliptin vs Placebo
Point estimate	9.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	20.8

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

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

End point description:

An AE is defined as any unfavorable and unintended sign including an abnormal laboratory finding, symptom or disease associated with the use of a medical treatment or procedure, regardless of whether it is considered related to the medical treatment or procedure. The ASaT Population was defined as all randomized participants who received at least 1 dose of study medication. Participants were included in the treatment group corresponding to the study treatment they actually received. One participant was in 2 clinical trials and was excluded from all efficacy and safety analysis.

End point type	Primary

End point timeframe:

Up to Week 24

End point values	Omarigliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: Percentage of participants				
number (not applicable)	2.6	2.6		

Statistical analyses

Statistical analysis title	Difference in % Omarigliptin vs Placebo
Comparison groups	Omarigliptin v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in % Omarigliptin vs Placebo
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	4.3

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. FPG is expressed as mg/dL. 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 baseline). The FAS population consisted of all randomized participants who received at least 1 dose of study medication and had a baseline measurement or a measurement for the analysis endpoint after receiving study medication. One participant was in 2 clinical trials in parallel and was excluded from all efficacy and safety analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 24

End point values	Omarigliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: mg/dL				
least squares mean (confidence interval 95%)	-19.6 (-26.7 to -12.5)	-3 (-10.2 to 4.1)		

Statistical analyses

Statistical analysis title	Difference in the least squares means

Statistical analysis description:

Based on a constrained longitudinal data analysis (cLDA) method with a restriction of the same baseline mean across treatment groups.

Comparison groups	Omarigliptin v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Difference in the least squares means
Parameter estimate	Mean difference (final values)
Point estimate	-16.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.5
upper limit	-7.8

Secondary: Percentage of participants attaining A1C glycemic goals of <7% and <6.5% at Week 24

End point title	Percentage of participants attaining A1C glycemic goals of <7% and <6.5% at Week 24

End point description:

The percentage of participants who achieved A1C values <6.5% (48 mmol/mol) or <7.0% (53 mmol/mol) in the FAS population at Week 24. The FAS Population consisted of all randomized participants who received at least 1 dose of study medication and had a baseline measurement or a

measurement for the analysis endpoint after receiving study medication. One participant was in 2 clinical trials in parallel and was excluded from all efficacy and safety analysis.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Omarigliptin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	153	153		
Units: Percentage of participants				
number (confidence interval 95%)				
<7.0%	23.8 (17.5 to 31.5)	4.4 (2.1 to 9.3)		
<6.5%	10.1 (6.1 to 16.4)	2.1 (0.7 to 6)		

Statistical analyses

Statistical analysis title	Between-group Rate Difference

Statistical analysis description:

Between-group confidence intervals and p-value (%) A1C <7.0%; estimated using standard multiple imputation techniques. Miettinen & Nurminen method.

Comparison groups	Omarigliptin v Placebo
Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.005
Method	Miettinen & Nurminen method
Parameter estimate	Between-group Rate Difference (%)
Point estimate	8
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.7
upper limit	14.5

Statistical analysis title	Between-group Rate Difference

Statistical analysis description:

Between-group confidence intervals and p-value (%) A1C <7.0%; estimated using standard multiple imputation techniques. Miettinen & Nurminen method.

Comparison groups	Omarigliptin v Placebo

Number of subjects included in analysis	306
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Miettinen & Nurminen method
Parameter estimate	Between-group Rate Difference (%)
Point estimate	19.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	11.7
upper limit	27.6

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 27

Adverse event reporting additional description:

The ASaT Population was all randomized participants who received at least one study drug. Participants were included in the treatment group corresponding to the study treatment they actually received. One participant was in 2 clinical trials and was excluded from all efficacy and safety analysis.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Matching placebo to omarigliptin capsule administered orally once a week for 24 weeks. Participants continue pre-study concomitant therapy of open-label glimepiride tablet(s) orally once daily (total daily dose >=4 mg per day) and metformin tablet(s) orally once or twice daily (total daily dose >=1500 mg per day).

Reporting group title	Omarigliptin

Reporting group description:

Omarigliptin 25 mg capsule administered orally once a week for 24 weeks. Participants continue pre-study concomitant therapy of open-label glimepiride tablet(s) orally once daily (total daily dose >=4 mg per day) and metformin tablet(s) orally once or twice daily (total daily dose >=1500 mg per day).

Serious adverse events	Placebo	Omarigliptin	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 153 (3.27%)	3 / 153 (1.96%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Road traffic accident			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular disorder			

subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal ulcer haemorrhage			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 153 (0.65%)	0 / 153 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 153 (0.00%)	1 / 153 (0.65%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Omarigliptin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 153 (15.03%)	29 / 153 (18.95%)	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	9 / 153 (5.88%)	4 / 153 (2.61%)	
occurrences (all)	11	4	
Urinary tract infection			
subjects affected / exposed	3 / 153 (1.96%)	9 / 153 (5.88%)	
occurrences (all)	4	9	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	13 / 153 (8.50%)	18 / 153 (11.76%)	
occurrences (all)	44	65	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 January 2013	AM1 - Modification of inclusion criteria regarding contraception
26 April 2013	AM4 - Addition of amylase and lipase to the chemistry panel

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported