

**Clinical trial results:
A Single-Dose Study to Assess the Pharmacokinetics, Safety, and
Tolerability of Sitagliptin in Adolescents
Summary**

EudraCT number	2014-004993-40
Trial protocol	Outside EU/EEA
Global end of trial date	14 February 2011

Results information

Result version number	v1 (current)
This version publication date	05 April 2016
First version publication date	30 July 2015

Trial information**Trial identification**

Sponsor protocol code	0431-081
-----------------------	----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00730275
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)	Yes
EMA paediatric investigation plan number(s)	EMA-000470-PIP01-08, EMA-000471-PIP01-08, EMA-000472-PIP01-08
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 February 2011
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 February 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study will assess the safety, tolerability and pharmacokinetics of sitagliptin in 10 to 17 year old participants with type 2 diabetes.

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: the initiation of administering sitagliptin 200 mg was dependent on the review of safety and pharmacokinetic (PK) data from sitagliptin 50 mg and 100 mg.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 July 2008
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	United States: 35
Worldwide total number of subjects	35
EEA total number of subjects	0

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)	3
Adolescents (12-17 years)	32
Adults (18-64 years)	0

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligibility criteria included male and female participants who were between 10 to 17 years of age with a history of type 2 diabetes.

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 50 mg

Arm description:

Participants who received a single oral dose of sitagliptin 50 mg.

Arm type	Experimental
Investigational medicinal product name	Sitagliptin phosphate
Investigational medicinal product code	
Other name	Januvia, MK-0431
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were to fast 8 hours prior to dosing. All doses were to be given with 240 ml of water. Sitagliptin 50 mg and/or 100 mg tablet was to be administered as a single dose of 50 mg, 100 mg, or 200 mg.

Arm title	Sitagliptin 100 mg
------------------	--------------------

Arm description:

Participants who received a single oral dose of sitagliptin 100 mg.

Arm type	Experimental
Investigational medicinal product name	Sitagliptin phosphate
Investigational medicinal product code	
Other name	Januvia, MK-0431
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were to fast 8 hours prior to dosing. All doses were to be given with 240 ml of water. Sitagliptin 50 mg and/or 100 mg tablet was to be administered as a single dose of 50 mg, 100 mg, or 200 mg.

Arm title	Sitagliptin 200 mg
------------------	--------------------

Arm description:

Participants who received a single oral dose of sitagliptin 200 mg.

Arm type	Experimental
----------	--------------

Investigational medicinal product name	Sitagliptin phosphate
Investigational medicinal product code	
Other name	Januvia, MK-0431
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Participants were to fast 8 hours prior to dosing. All doses were to be given with 240 ml of water. Sitagliptin 50 mg and/or 100 mg tablet was to be administered as a single dose of 50 mg, 100 mg, or 200 mg.

Arm title	Placebo
------------------	---------

Arm description:

Participants who received a single oral dose of matching placebo to sitagliptin 50 mg, 100 mg or 200 mg.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo to sitagliptin 50 mg and/or 100 mg administered as a single dose

Number of subjects in period 1	Sitagliptin 50 mg	Sitagliptin 100 mg	Sitagliptin 200 mg
Started	9	9	8
Completed	9	9	8
Not completed	0	0	0
Consent withdrawn by subject	-	-	-

Number of subjects in period 1	Placebo
Started	9
Completed	8
Not completed	1
Consent withdrawn by subject	1

Baseline characteristics

Reporting groups

Reporting group title	Sitagliptin 50 mg
Reporting group description: Participants who received a single oral dose of sitagliptin 50 mg.	
Reporting group title	Sitagliptin 100 mg
Reporting group description: Participants who received a single oral dose of sitagliptin 100 mg.	
Reporting group title	Sitagliptin 200 mg
Reporting group description: Participants who received a single oral dose of sitagliptin 200 mg.	
Reporting group title	Placebo
Reporting group description: Participants who received a single oral dose of matching placebo to sitagliptin 50 mg, 100 mg or 200 mg.	

Reporting group values	Sitagliptin 50 mg	Sitagliptin 100 mg	Sitagliptin 200 mg
Number of subjects	9	9	8
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	13.9 ± 2.52	14.3 ± 1.41	14.8 ± 1.75
Gender categorical Units: Subjects			
Female	6	5	5
Male	3	4	3

Reporting group values	Placebo	Total	
Number of subjects	9	35	
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	14.1 ± 2.26	-	
Gender categorical Units: Subjects			
Female	8	24	
Male	1	11	

End points

End points reporting groups

Reporting group title	Sitagliptin 50 mg
Reporting group description:	Participants who received a single oral dose of sitagliptin 50 mg.
Reporting group title	Sitagliptin 100 mg
Reporting group description:	Participants who received a single oral dose of sitagliptin 100 mg.
Reporting group title	Sitagliptin 200 mg
Reporting group description:	Participants who received a single oral dose of sitagliptin 200 mg.
Reporting group title	Placebo
Reporting group description:	Participants who received a single oral dose of matching placebo to sitagliptin 50 mg, 100 mg or 200 mg.

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

End point title	Number of participants who experienced at least one adverse event ^[1]
End point description:	An 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. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the Sponsor's product, is also an adverse event. Population for analysis included all enrolled participants.
End point type	Primary
End point timeframe:	Up to 14 days following administration of study drug
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: There was no plan to perform a between group statistical comparison for this endpoint.

End point values	Sitagliptin 50 mg	Sitagliptin 100 mg	Sitagliptin 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	8	9
Units: Participants	3	1	1	2

Statistical analyses

No statistical analyses for this end point

Primary: Area under the concentration time curve (AUC) from time 0 to infinity following a single dose of sitagliptin

End point title	Area under the concentration time curve (AUC) from time 0 to infinity following a single dose of sitagliptin ^[2]
-----------------	---

End point description:

Serum samples were used to determine the AUC from time 0 to infinity for sitagliptin. The placebo group is not included in the table below; this endpoint only evaluated the sitagliptin groups. Analysis population includes all participants who received a single dose of sitagliptin 50 mg, 100 mg, or 200 mg.

End point type Primary

End point timeframe:

Pre-dose through 72 hours post-dose

Notes:

[2] - 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 endpoint only reported values for participants from arms treated with sitagliptin, since no pharmacokinetic parameters were available for participants treated with placebo.

End point values	Sitagliptin 50 mg	Sitagliptin 100 mg	Sitagliptin 200 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	8	
Units: nM*hour				
geometric mean (confidence interval 95%)	3438 (2881 to 4103)	5869 (4918 to 7003)	12965 (10749 to 15638)	

Statistical analyses

Statistical analysis title Dose-adjusted (to 100 mg) AUC: Pooled across Doses

Statistical analysis description:

Geometric Mean across all dose strengths. Back-transformed mean and confidence interval from univariate analysis performed on natural log-transformed values.

Comparison groups	Sitagliptin 100 mg v Sitagliptin 50 mg v Sitagliptin 200 mg
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric mean
Point estimate	6392
Confidence interval	
level	95 %
sides	2-sided
lower limit	5766
upper limit	7086

Secondary: Maximum concentration (Cmax) following a single dose of sitagliptin

End point title Maximum concentration (Cmax) following a single dose of sitagliptin^[3]

End point description:

Serum samples were used to determine the Cmax for sitagliptin. The placebo group is not included in the table below; this endpoint only evaluated the sitagliptin groups. Analysis population includes all participants who received a single dose of sitagliptin 50 mg, 100 mg, or 200 mg.

End point type Secondary

End point timeframe:

Pre-dose through 72 hours post-dose

Notes:

[3] - 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 endpoint only reported values for participants from arms treated with sitagliptin, since no pharmacokinetic parameters were available for participants treated with placebo.

End point values	Sitagliptin 50 mg	Sitagliptin 100 mg	Sitagliptin 200 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	8	
Units: nM				
geometric mean (confidence interval 95%)	366 (288 to 464)	666 (526 to 845)	1876 (1458 to 2413)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time of occurrence of maximum concentration (Tmax) following a single dose of sitagliptin

End point title	Time of occurrence of maximum concentration (Tmax) following a single dose of sitagliptin ^[4]
-----------------	--

End point description:

Serum samples were used to determine the Tmax for sitagliptin. The placebo group is not included in the table below; this endpoint only evaluated the sitagliptin groups. Analysis population includes all participants who received a single dose of sitagliptin 50 mg, 100 mg, or 200 mg.

End point type	Secondary
----------------	-----------

End point timeframe:

Pre-dose through 72 hours post-dose

Notes:

[4] - 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 endpoint only reported values for participants from arms treated with sitagliptin, since no pharmacokinetic parameters were available for participants treated with placebo.

End point values	Sitagliptin 50 mg	Sitagliptin 100 mg	Sitagliptin 200 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	8	
Units: Hours				
median (full range (min-max))	3 (1.5 to 5)	3 (2 to 4.5)	2.5 (1 to 3.1)	

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent terminal half-life (apparent t1/2) following a single dose of sitagliptin

End point title	Apparent terminal half-life (apparent t1/2) following a single dose of sitagliptin ^[5]
-----------------	---

End point description:

Serum samples were used to determine the apparent t1/2 for sitagliptin. The placebo group is not included in the table below; this endpoint only evaluated the sitagliptin groups. Analysis population includes all participants who received a single dose of sitagliptin 50 mg, 100 mg, or 200 mg. Summary statistics presented are the harmonic mean and Jackknife-standard deviation.

End point type Secondary

End point timeframe:

Pre-dose through 72 hours post-dose

Notes:

[5] - 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 endpoint only reported values for participants from arms treated with sitagliptin, since no pharmacokinetic parameters were available for participants treated with placebo.

End point values	Sitagliptin 50 mg	Sitagliptin 100 mg	Sitagliptin 200 mg	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	9	9	8	
Units: Hours				
arithmetic mean (standard deviation)	12.1 (± 1.7)	11.2 (± 2.1)	11.7 (± 1.8)	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Dipeptidyl Peptidase-4 (DPP-4) activity following a single dose of sitagliptin or placebo

End point title Plasma Dipeptidyl Peptidase-4 (DPP-4) activity following a single dose of sitagliptin or placebo

End point description:

Plasma DPP-4 activity was analyzed using the 24-hour weighted average inhibition (WAI) and percent inhibition at 24 hours post-dose. WAI was defined as the AUC of inhibition divided by the length of the post-dose time interval. Positive values of WAI represent a decrease in DPP-4 activity. Analysis population includes all participants who received a single dose of sitagliptin or placebo.

End point type Secondary

End point timeframe:

Pre-dose through 24 hours post-dose

End point values	Sitagliptin 50 mg	Sitagliptin 100 mg	Sitagliptin 200 mg	Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	9	9	8	8
Units: Percent inhibition				
least squares mean (confidence interval 95%)				
24-hour WAI of DPP-4 activity	73.98 (70.59 to 76.99)	80.53 (77.98 to 82.78)	87.96 (86.29 to 89.43)	6.76 (-6.21 to 18.14)
DPP-4 activity at 24 hours post-dose	53.98 (46.74 to 60.24)	62.78 (56.92 to 67.84)	75.76 (71.7 to 79.24)	3.57 (-12.6 to 17.43)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 14 days after study drug administration

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	14.0
--------------------	------

Reporting groups

Reporting group title	Sitagliptin 50 mg
-----------------------	-------------------

Reporting group description:

Participants who received a single oral dose of sitagliptin 50 mg.

Reporting group title	Sitagliptin 100 mg
-----------------------	--------------------

Reporting group description:

Participants who received a single oral dose of sitagliptin 100 mg.

Reporting group title	Sitagliptin 200 mg
-----------------------	--------------------

Reporting group description:

Participants who received a single oral dose of sitagliptin 200 mg.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Participants who received a single oral dose of matching placebo to sitagliptin 50 mg, 100 mg or 200 mg.

Serious adverse events	Sitagliptin 50 mg	Sitagliptin 100 mg	Sitagliptin 200 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	0 / 9 (0.00%)	0 / 8 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

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

Non-serious adverse events	Sitagliptin 50 mg	Sitagliptin 100 mg	Sitagliptin 200 mg
Total subjects affected by non-serious adverse events subjects affected / exposed	3 / 9 (33.33%)	1 / 9 (11.11%)	1 / 8 (12.50%)
Vascular disorders Phlebitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	1 / 9 (11.11%) 1	0 / 8 (0.00%) 0
Nervous system disorders Headache subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
General disorders and administration site conditions Infusion site pain subjects affected / exposed occurrences (all) Infusion site swelling subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1	0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting	1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 2	0 / 9 (0.00%) 0 0 / 9 (0.00%) 0 0 / 9 (0.00%) 0	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0 0 / 8 (0.00%) 0

subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0	0 / 9 (0.00%) 0	1 / 8 (12.50%) 1
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Nasal congestion subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0 0 / 9 (0.00%) 0	0 / 9 (0.00%) 0 0 / 9 (0.00%) 0	0 / 8 (0.00%) 0 0 / 8 (0.00%) 0
Metabolism and nutrition disorders Hypoglycaemia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1	0 / 9 (0.00%) 0	0 / 8 (0.00%) 0

Non-serious adverse events	Placebo		
Total subjects affected by non-serious adverse events subjects affected / exposed	2 / 9 (22.22%)		
Vascular disorders Phlebitis subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
General disorders and administration site conditions Infusion site pain subjects affected / exposed occurrences (all)	0 / 9 (0.00%) 0		

<p>Infusion site swelling subjects affected / exposed occurrences (all)</p>	<p>0 / 9 (0.00%) 0</p>		
<p>Pyrexia subjects affected / exposed occurrences (all)</p>	<p>0 / 9 (0.00%) 0</p>		
<p>Gastrointestinal disorders</p> <p>Abdominal pain subjects affected / exposed occurrences (all)</p> <p>Abdominal pain upper subjects affected / exposed occurrences (all)</p> <p>Diarrhoea subjects affected / exposed occurrences (all)</p> <p>Vomiting subjects affected / exposed occurrences (all)</p>	<p>0 / 9 (0.00%) 0</p> <p>0 / 9 (0.00%) 0</p> <p>0 / 9 (0.00%) 0</p> <p>0 / 9 (0.00%) 0</p>		
<p>Reproductive system and breast disorders</p> <p>Dysmenorrhoea subjects affected / exposed occurrences (all)</p>	<p>0 / 9 (0.00%) 0</p>		
<p>Respiratory, thoracic and mediastinal disorders</p> <p>Nasal congestion subjects affected / exposed occurrences (all)</p> <p>Oropharyngeal pain subjects affected / exposed occurrences (all)</p>	<p>1 / 9 (11.11%) 1</p> <p>1 / 9 (11.11%) 1</p>		
<p>Metabolism and nutrition disorders</p> <p>Hypoglycaemia subjects affected / exposed occurrences (all)</p>	<p>0 / 9 (0.00%) 0</p>		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2008	Amendment 1: The primary reason for this amendment was to add that Panel C will be conducted regardless of whether the pre-specified drug exposures are achieved in Panels A or B.
19 March 2009	Amendment 2: The primary reason for this amendment was to permit enrollment of participants with a history of thyroid disease that has been clinically stable for at least 3 months prior to randomization at the discretion of the investigator, and with the concurrence of the Merck clinical monitor. Concomitant therapy with thyroid hormone was to be permitted if the participant had been taking a stable dose for at least 3 months prior to administration of study drug, and is euthyroid as documented by thyroid stimulating hormone testing at prestudy.
21 April 2009	Amendment 3: The primary reason for this amendment was to increase the total number of participants with type 2 diabetes mellitus in the study from 24 to at least 36 (12 subjects per panel).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported