Clinical trial results:
A Study to Evaluate the Comparative Bioavailability of the Investigational Oral Pediatric Minitablet Formulation of MK-1439 Compared to the Adult Formulation of MK-1439 in Healthy Adult Subjects

Summary

EudraCT number	2016-004728-48
Trial protocol	Outside EU/EEA
Global end of trial date	27 June 2015

Results information

Result version number	v1 (current)
This version publication date	08 February 2017
First version publication date	08 February 2017

Trial information

Trial identification

Sponsor protocol code	1439-043

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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)	EMEA-001676-PIP01-14, EMEA-001695-PIP01-14
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	27 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 June 2015
Global end of trial reached?	Yes
Global end of trial date	27 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to evaluate the comparative bioavailability of a single-dose of the investigational oral pediatric mini-tablet formulation of MK-1439 (doravirine), 0.8 mg (100 mg total dose) compared to the adult formulation of doravirine tablets,100 mg in healthy adult males and females under fasted conditions.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 24
Worldwide total number of subjects	24
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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Healthy, non-tobacco using, adult male and females, 18-55 years of age were enrolled in this trial.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Arm title	All Randomized Participants

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Adult Doravirine 100 mg x 1
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Following an overnight fast of at least 10 hours, a single doravirine adult formulation 100 mg tablet was administered orally.

Investigational medicinal product name	Pediatric Doravirine 0.8 mg x 125
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Following an overnight fast of at least 10 hours, 125 doravirine oral pediatric formulation mini-tablets (equivalent to
100 mg) was administered orally.

Number of subjects in period 1	All Randomized Participants
Started	24
Completed	24

Baseline characteristics

Reporting groups

Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	24	24	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	24	24	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	34.6		
standard deviation	± 9.4	-	
Gender Categorical Units: Subjects			
Female	7	7	
Male	17	17	

Subject analysis sets

Subject analysis set title	Adult Doravirine 100 mg x 1
Subject analysis set type	Safety analysis

Subject analysis set description:

Following an overnight fast of at least 10 hours, a single doravirine adult formulation 100 mg tablet was administered orally.

Subject analysis set title	Pediatric Doravirine 0.8 mg x 125
Subject analysis set type	Safety analysis

Subject analysis set description:

Following an overnight fast of at least 10 hours, 125 doravirine oral pediatric formulation 0.8 mg mini-tablets (equivalent to 100 mg) was administered orally.

Reporting group values	Adult Doravirine 100 mg x 1	Pediatric Doravirine 0.8 mg x 125	
Number of subjects	24	24	
Age Categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	

Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	24	24	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	34.6	34.6	
standard deviation	± 9.4	± 9.4	
Gender Categorical			
Units: Subjects			
Female	7	7	
Male	17	17	

End points

End points reporting groups

Reporting group title	All Randomized Participants
Reporting group description: -	
Subject analysis set title	Adult Doravirine 100 mg x 1
Subject analysis set type	Safety analysis
Subject analysis set description:	
Following an overnight fast of at least 10 hours, a single doravirine adult formulation 100 mg tablet was administered orally.	
Subject analysis set title	Pediatric Doravirine 0.8 mg x 125
Subject analysis set type	Safety analysis
Subject analysis set description:	
Following an overnight fast of at least 10 hours, 125 doravirine oral pediatric formulation 0.8 mg mini-tablets (equivalent to 100 mg) was administered orally.	

Primary: Area under the concentration versus time curve from time 0-infinity (AUC0-∞) of doravirine

End point title	Area under the concentration versus time curve from time 0-infinity (AUC0-∞) of doravirine
End point description:	
Blood samples were collected at pre-dose and at intervals up to 72 hours after dosing in each period, and the plasma concentrations of doravirine were determined. Values were natural log-transformed before analysis and analyzed with a linear mixed effects model with fixed effects terms for treatment and period. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between different treatment measurements within the same subject. The populations analyzed was all participants as treated during each treatment period.	
End point type	Primary
End point timeframe:	
Pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 12, 24, 48, and 72 hours post-dose	

End point values	Adult Doravirine 100 mg x 1	Pediatric Doravirine 0.8 mg x 125		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	24		
Units: µM.hr				
geometric mean (confidence interval 95%)	38.3 (32.3 to 45.3)	28.1 (23.4 to 33.9)		

Statistical analyses

Statistical analysis title	Ratio Pediatric/Adult tablet
Statistical analysis description:	
Geometric Mean Ratio (GMR)	
Comparison groups	Adult Doravirine 100 mg x 1 v Pediatric Doravirine 0.8 mg x 125

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	GMR
Point estimate	0.73
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.68
upper limit	0.8

Notes:

[1] - The number of participants in this analysis was not 48. As this was a crossover study, the 48 observations were from 24 participants.

Primary: Maximum concentration (Cmax) of doravirine

End point title	Maximum concentration (Cmax) of doravirine

End point description:

Blood samples were collected at pre-dose and at intervals up to 72 hours after dosing in each period, and the plasma concentrations of doravirine were determined. Values were natural log-transformed before analysis and analyzed with a linear mixed effects model with fixed effects terms for treatment and period. An unstructured covariance matrix was used to allow for unequal treatment variances and to model the correlation between different treatment measurements within the same subject. The populations analyzed was all participants as treated during each treatment period.

End point type	Primary

End point timeframe:

Pre-dose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 12, 24, 48, and 72 hours post-dose

End point values	Adult Doravirine 100 mg x 1	Pediatric Doravirine 0.8 mg x 125		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	23[2]		
Units: nM				
geometric mean (confidence interval 95%)	2170 (1820 to 2580)	1150 (992 to 1320)		

Notes:

[2] - One participant with a missing concentration value was not included in the analysis

Statistical analyses

Statistical analysis title	Ratio Pediatric/Adult tablet

Statistical analysis description:

GMR

Comparison groups	Adult Doravirine 100 mg x 1 v Pediatric Doravirine 0.8 mg x 125

Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	GMR
Point estimate	0.53
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.47
upper limit	0.59

Notes:

[3] - The number of participants in this analysis was not 47. As this was a crossover study, the 47 observations were from 24 participants.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of treatment on Day 1 up to Day 4 of each treatment period

Adverse event reporting additional description:

All participants as treated during each treatment period by the treatment received at the time of the event. As this was a crossover study, and each participant received more than one treatment, participants could be counted more than once.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Doravirine 100 mg x 1

Reporting group description:

Following an overnight fast of at least 10 hours, a single doravirine adult formulation 100 mg tablet was administered orally.

Reporting group title	Doravirine 0.8 mg x 125

Reporting group description:

Following an overnight fast of at least 10 hours, 125 doravirine oral pediatric formulation 0.8 mg mini-tablets (equivalent to 100 mg) was administered orally.

Serious adverse events	Doravirine 100 mg x 1	Doravirine 0.8 mg x 125	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 24 (0.00%)	0 / 24 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Doravirine 100 mg x 1	Doravirine 0.8 mg x 125	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 24 (16.67%)	2 / 24 (8.33%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 24 (4.17%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Blood glucose increased			
subjects affected / exposed	2 / 24 (8.33%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
White blood cell count increased			
subjects affected / exposed	1 / 24 (4.17%)	1 / 24 (4.17%)	
occurrences (all)	1	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 May 2015	Amendment 1: Included description of the size and the number of mini-tablets to be administered with dosing

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported