Clinical trial results:
A Comparative Bioavailability Study of a Tablet versus an Investigational Oral Suspension of Vorapaxar

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	2014-004350-34
Trial protocol	Outside EU/EEA
Global end of trial date	12 December 2014

Results information

Result version number	v1 (current)
This version publication date	18 February 2016
First version publication date	18 February 2016

Trial information

Trial identification

Sponsor protocol code	P08074

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Merck Study Number: MK-5348-040

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, 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-000778-PIP02-12
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	12 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 December 2014
Global end of trial reached?	Yes
Global end of trial date	12 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to evaluate the comparative bioavailability between Vorapaxar (MK-5348) 0.2085 mg/mL 10 mL Oral Solution and Vorapaxar (MK-5348) 2.08 mg Tablets (Zontivity™) after a single dose in healthy participants under fasting 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	06 October 2014
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	Canada: 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:

This was an open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover study.

Pre-assignment

Screening details:

Healthy, non-smoking, male and female participants, from 18 to 55 years of age with body mass index (BMI) ≥19.0 and ≤30.0 kg/m^2 and weight ≥60 kg. Other inclusion and exclusion criteria applied.

Period 1

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

Arms

Arm title	All Enrolled

Arm description:

Participants received single oral dose of Vorapaxar 0.2085 mg/mL 10 mL Oral Solution and Vorapaxar 2.08 mg Tablets (Zontivity™) in a crossover fashion.

Arm type	Experimental
Investigational medicinal product name	Vorapaxar 0.2085 mg/mL 10 mL Oral Solution
Investigational medicinal product code	
Other name	MK-5348
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Single oral dose of Vorapaxar 0.2085 mg/mL 10 mL Oral Solution

Investigational medicinal product name	Vorapaxar 0.2085 mg tablet
Investigational medicinal product code	
Other name	MK-5348; Zontivity
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Single oral dose of Vorapaxar 0.2085 mg tablet

Number of subjects in period 1	All Enrolled
Started	24
Completed	24

Baseline characteristics

Reporting groups	
Reporting group title	All Enrolled
Reporting group description:	
Participants received single oral dose of Vorapaxar 0.2085 mg/mL 10 mL Oral Solution and Vorapaxar 2.08 mg Tablets (Zontivity™) in a crossover fashion.	

Reporting group values	All Enrolled	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	44		
standard deviation	± 8	-	
Gender Categorical Units: Subjects			
Female	14	14	
Male	10	10	

End points

End points reporting groups

Reporting group title	All Enrolled
Reporting group description:	
Participants received single oral dose of Vorapaxar 0.2085 mg/mL 10 mL Oral Solution and Vorapaxar 2.08 mg Tablets (Zontivity™) in a crossover fashion.	
Subject analysis set title	Vorapaxar-Oral Solution
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants who received single oral dose of vorapaxar oral solution regardless of sequence.	
Subject analysis set title	Vorapaxar-Tablet
Subject analysis set type	Full analysis
Subject analysis set description:	
All participants who received single oral dose of vorapaxar tablet regardless of sequence.	

Primary: Area Under the Concentration-time Curve From Time 0 to the LastMeasurable Sample (AUC0-last)

End point title	Area Under the Concentration-time Curve From Time 0 to the LastMeasurable Sample (AUC0-last)
End point description:	
Blood samples taken at pre-dose (0-hour) and 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 48, and 72 hours after drug administration to determine the AUC0-last. Results were natural log-transformed and analyzed with a linear mixed effects model with fixed effects terms for treatment and period.	
End point type	Primary
End point timeframe:	
Predose (0hour) and 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 48, and 72 hours after drug administration	

End point values	Vorapaxar-Oral Solution	Vorapaxar-Tablet		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	24		
Units: nM•hr				
geometric mean (confidence interval 95%)	634 (571 to 704)	629 (570 to 695)		

Statistical analyses

Statistical analysis title	Bioequivalence
Statistical analysis description:	
Geometric mean ratio (GMR) determined by dividing the GM for Oral solution by GM for tablet. The two forms were considered bioequivalent if the 90% confidence interval for the GMR was within 80.00-125.00%	
Comparison groups	Vorapaxar-Oral Solution v Vorapaxar-Tablet

Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	GMR
Point estimate	100.72
Confidence interval	
level	90 %
sides	2-sided
lower limit	97.86
upper limit	103.66

Primary: Maximum measured analyte concentration over the sampling period (Cmax)

End point title	Maximum measured analyte concentration over the sampling period (Cmax)

End point description:

Blood samples taken at pre-dose (0-hour) and 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 48, and 72 hours after drug administration to determine the Cmax. Results were natural log-transformed and analyzed with a linear mixed effects model with fixed effects terms for treatment and period.

End point type	Primary

End point timeframe:

Predose (0hour) and 0.5, 1, 1.5, 2, 3, 4, 6, 12, 24, 48, and 72 hours after drug administration

End point values	Vorapaxar-Oral Solution	Vorapaxar-Tablet		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	24		
Units: nM				
geometric mean (confidence interval 95%)	54.1 (50 to 58.4)	48.7 (44.4 to 53.5)		

Statistical analyses

Statistical analysis title	Geometric mean ratio (GMR)

Statistical analysis description:

GMR determined by dividing the GM for Oral solution by GM for tablet. The two forms were considered bioequivalent if the 90% confidence interval for the GMR was within 80.00-125.00%.

Comparison groups	Vorapaxar-Oral Solution v Vorapaxar-Tablet
Number of subjects included in analysis	48
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Geometric mean ratio (GMR)
Point estimate	110.94

Confidence interval	
level	90 %
sides	2-sided
lower limit	101.52
upper limit	121.24

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to 14 days after last dose of study drug for each period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Vorapaxar-Oral Solution
Reporting group description: All participants who received single oral dose of vorapaxar oral solution regardless of sequence	
Reporting group title	Vorapaxar-Tablet
Reporting group description: All participants who received single oral dose of vorapaxar tablet regardless of sequence	

Serious adverse events	Vorapaxar-Oral Solution	Vorapaxar-Tablet	
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: 5 %

Non-serious adverse events	Vorapaxar-Oral Solution	Vorapaxar-Tablet	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 24 (8.33%)	1 / 24 (4.17%)	
Nervous system disorders			
Somnolence			
subjects affected / exposed	2 / 24 (8.33%)	1 / 24 (4.17%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported