Clinical trial results:
Vorapaxar in the human endotoxemia model

Summary

EudraCT number	2016-000309-34
Trial protocol	AT
Global end of trial date	30 November 2016

Results information

Result version number	v2 (current)
This version publication date	03 September 2019
First version publication date	04 January 2019
Version creation reason	• Correction of full data set We have falsely described the statistical testing as testing for "equivalence", while it was done for "superiority". This will be corrected.

Trial information

Trial identification

Sponsor protocol code	7654321

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Spitalgasse 23, Vienna, Austria, 1090
Public contact	Dept. of Clinical Pharmacology, Medical University of Vienna, 0043 14040029810, klin-pharmakologie@meduniwien.ac.at
Scientific contact	Dept. of Clinical Pharmacology, Medical University of Vienna, 0043 14040029810, klin-pharmakologie@meduniwien.ac.at

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	30 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2016
Global end of trial reached?	Yes
Global end of trial date	30 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate whether vorapaxar reduces LPS induced coagulation activation assessed by prothrombin fragments F1+2

Protection of trial subjects:

"Willingness to comply with the trial's safety demands (to refrain from excessive sporting activities two weeks after Vorapaxar intake, i.e. full contact sports, climbing, mountain biking etc.)" was an inclusion criterion, which was applied to reduce the risk of bleeding.
Paracetamol was available to all subjects to alleviate flu-like symptoms associated with LPS-infusion.
The vorapaxar dose was titrated to a certain effect (based on whole blood aggregometry) to reduce the necessary dose.

Background therapy:

not applicable- healthy volunteers.

Evidence for comparator:

A placebo tablet was used as a comparator in this trial involving healthy volunteers. Since this was a model, no active treatment was necessary.

Actual start date of recruitment	01 June 2016
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	Austria: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

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)	16
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

16 healthy volunteers were included in this trial between July 25th 2016 and November 30th 2016. This was a single center study which was performed at the Medical University of Vienna, Austria.

Pre-assignment

Screening details:

Sixteen healthy volunteers were screened, which were all successfully included in the trial according to the applicable in- and exclusion criteria.

Period 1

Period 1 title	Main Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Blinding implementation details:

Placebos and Verum tablets were not distinguishable from each other by their physicochemical properties. An unblinded study nurse under supervision of an unblinded physician who had access to treatment allocation codes prepared study drugs. They were not otherwise involved in conducting the trial.

Arms

Are arms mutually exclusive?	No
Arm title	Vorapaxar

Arm description:

Verum arm

Arm type	Experimental
Investigational medicinal product name	Vorapaxar
Investigational medicinal product code	
Other name	Zontivity
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10mg per os were administered on day 1. On day 2 platelet aggregation (TRAP-induced) was measured and according to the results (80% inhibition compared to baseline were the target) additional 10mg vorapaxar could be added to the initial dose. This was necessary in 2 subjects, in whom platelet inhibition did not achieve the defined criteria.

Arm title	Placebo

Arm description:

Subjects received a placebo tablet as a control during experimental endotoxemia

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

Dosage and administration details:

Healthy volunteers received placebo tablets on day 1. If platelet aggregation did not achieve the predefined target (80% inhibition in TRAP induced whole blood aggregometry), another dose was given to subjects on day 2. This was necessary in all 16 subjects.

Number of subjects in period 1	Vorapaxar	Placebo
Started	15	16
Completed	15	16

Baseline characteristics

Reporting groups	
Reporting group title	Main Trial

Reporting group description:

16 healthy volunteers were included in this trial. This was designed as a crossover trial meaning that each subject completed both study periods. One subject did not participate in the second study period due to unforeseen unavailability. Thus only 15 subjects were included in the final analysis.

Reporting group values	Main Trial	Total	
Number of subjects	16	16	
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)	16	16	
From 65-84 years	0	0	
85 years and over	0	0	
Age group	0	0	
Age continuous Units: years			
median	31		
inter-quartile range (Q1-Q3)	27 to 34	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	15	15	
Weight Units: kg			
median	77		
inter-quartile range (Q1-Q3)	67 to 88	-	

Subject analysis sets	
Subject analysis set title	PP
Subject analysis set type	Per protocol

Subject analysis set description:

15 Subjects completed the trial per protocol. 1 Subject did not participate in the second study period and was therefore excluded from analysis.

Subject analysis set title	FA
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects that were included in the trial

Reporting group values	PP	FA	
Number of subjects	15	16	
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)	15	15	
From 65-84 years	0	0	
85 years and over	0	0	
Age group	0	0	
Age continuous Units: years			
median	30	31	
inter-quartile range (Q1-Q3)	26 to 34	27 to 34	
Gender categorical Units: Subjects			
Female	1	1	
Male	14	15	
Weight Units: kg			
median	73	77	
inter-quartile range (Q1-Q3)	67 to 87	67 to 88	

End points

End points reporting groups

Reporting group title	Vorapaxar
Reporting group description:	
Verum arm	
Reporting group title	Placebo
Reporting group description:	
Subjects received a placebo tablet as a control during experimental endotoxemia	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description:	
15 Subjects completed the trial per protocol. 1 Subject did not participate in the second study period and was therefore excluded from analysis.	
Subject analysis set title	FA
Subject analysis set type	Full analysis
Subject analysis set description:	
All subjects that were included in the trial	

Primary: Primary Endpoint Prothrombin Fragments F1.2

End point title	Primary Endpoint Prothrombin Fragments F1.2
End point description:	
individual maxima in each trial period (vorapaxar or placebo) were compared	
End point type	Primary
End point timeframe:	
0-24h	

End point values	Vorapaxar	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: pmol/L				
median (inter-quartile range (Q1-Q3))	1315 (835 to 1800)	2530 (1175 to 3895)		

Statistical analyses

Statistical analysis title	primary Analysis
Statistical analysis description:	
Wilcoxon signed rank test	
Comparison groups	Placebo v Vorapaxar

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	Wilcoxon (Mann-Whitney)

Secondary: Thrombin Antithrombin Complexes

End point title	Thrombin Antithrombin Complexes

End point description:

End point type	Secondary

End point timeframe:

0-24h, each period

End point values	Vorapaxar	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: µg/L				
median (inter-quartile range (Q1-Q3))	17.4 (8.06 to 25.10)	32.30 (3.9 to 55.2)		

Statistical analyses

Statistical analysis title	TAT

Statistical analysis description:

Wilcoxon Signed rank test, individual maxima in both study periods

Comparison groups	Vorapaxar v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Wilcoxon (Mann-Whitney)

Secondary: Plasmin Antiplasmin complexes

End point title	Plasmin Antiplasmin complexes

End point description:

End point type	Secondary

End point timeframe:

0-24h, both periods

End point values	Vorapaxar	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: µg/L				
median (inter-quartile range (Q1-Q3))	745 (625 to 1227)	1437 (764 to 1951)		

Statistical analyses

Statistical analysis title	PAP
Comparison groups	Vorapaxar v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	Wilcoxon (Mann-Whitney)

Secondary: von Willebrand Factor

End point title	von Willebrand Factor

End point description:

End point type	Secondary

End point timeframe:

0-24h, both study periods

End point values	Vorapaxar	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: %				
median (inter-quartile range (Q1-Q3))	162 (122 to 193)	234 (151 to 279)		

Statistical analyses

Statistical analysis title	vWF
Comparison groups	Vorapaxar v Placebo

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Wilcoxon (Mann-Whitney)

Secondary: E-Selectin

End point title	E-Selectin

End point description:

End point type	Secondary

End point timeframe:

24h, both study periods

End point values	Vorapaxar	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))	43.5 (39.85 to 89)	76.5 (48 to 92.5)		

Statistical analyses

Statistical analysis title	E-Sel
Comparison groups	Vorapaxar v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.031
Method	Wilcoxon (Mann-Whitney)

Secondary: Thrombomodulin

End point title	Thrombomodulin

End point description:

End point type	Secondary

End point timeframe:

0-24h, both trial periods

End point values	Vorapaxar	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: ng/mL				
median (inter-quartile range (Q1-Q3))	5.05 (4.46 to 5.77)	5.29 (4.58 to 5.49)		

Statistical analyses

Statistical analysis title	TM
Comparison groups	Vorapaxar v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	Wilcoxon (Mann-Whitney)

Secondary: soluble P-Selectin

End point title	soluble P-Selectin

End point description:

End point type	Secondary

End point timeframe:

24h, both periods

End point values	Vorapaxar	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: ng/mL				
median (inter-quartile range (Q1-Q3))	30.8 (21.6 to 33.9)	33.1 (22.4 to 37.9)		

Statistical analyses

Statistical analysis title	P-Sel
Comparison groups	Vorapaxar v Placebo

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	Wilcoxon (Mann-Whitney)

Secondary: Platelet Factor 4

End point title	Platelet Factor 4
End point description:	

End point type	Secondary
End point timeframe:	
24h, both periods	

End point values	Vorapaxar	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	53310 (36757 to 73273)	59803 (39446 to 138624)		

Statistical analyses

Statistical analysis title	PF4
Comparison groups	Vorapaxar v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.91
Method	Wilcoxon (Mann-Whitney)

Secondary: PAR-1 Receptor Expression

End point title	PAR-1 Receptor Expression
End point description:	
Maximum decrease in receptors compared to baseline	
End point type	Secondary
End point timeframe:	
24h, both periods	

End point values	Vorapaxar	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: Receptors on platelets	121	118		

Statistical analyses

Statistical analysis title	PAR-1
Comparison groups	Vorapaxar v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.19
Method	Wilcoxon (Mann-Whitney)

Secondary: Tumor necrosis Factor alpha

End point title	Tumor necrosis Factor alpha
End point description:	

End point type	Secondary
End point timeframe:	
24h, both periods	

End point values	Vorapaxar	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	27 (13 to 70)	75 (22 to 96)		

Statistical analyses

Statistical analysis title	TNFa
Comparison groups	Vorapaxar v Placebo

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005
Method	Wilcoxon (Mann-Whitney)

Secondary: Interleukin-6

End point title	Interleukin-6

End point description:

End point type	Secondary

End point timeframe:

24h, both periods.

End point values	Vorapaxar	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	82.03 (49.48 to 220.39)	227.7 (103.20 to 320.20)		

Statistical analyses

Statistical analysis title	IL6
Comparison groups	Vorapaxar v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.015
Method	Wilcoxon (Mann-Whitney)

Secondary: C-reactive Protein

End point title	C-reactive Protein

End point description:

End point type	Secondary

End point timeframe:

24h, both periods

End point values	Vorapaxar	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: mg/dL				
median (inter-quartile range (Q1-Q3))	1.53 (1.15 to 2.19)	2.44 (1.57 to 2.82)		

Statistical analyses

Statistical analysis title	CRP
Comparison groups	Vorapaxar v Placebo
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Screening until follow up. The whole study period lasted approximately 3 months for each subject,	
Assessment type	Systematic
Dictionary used	
Dictionary name	ICD
Dictionary version	10
Reporting groups	
Reporting group title	Vorapaxar
Reporting group description: Verum group	
Reporting group title	Placebo
Reporting group description: Placebo	

Serious adverse events	Vorapaxar	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 15 (0.00%)	0 / 16 (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: 1 %

Non-serious adverse events	Vorapaxar	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 15 (73.33%)	12 / 16 (75.00%)	
Nervous system disorders			
Headache	Additional description: commonly associated with endotoxemia		
subjects affected / exposed	8 / 15 (53.33%)	5 / 16 (31.25%)	
occurrences (all)	8	5	
Dizziness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Chills	Additional description: Chills are a regularly associated with endotoxemia		
subjects affected / exposed	4 / 15 (26.67%)	7 / 16 (43.75%)	
occurrences (all)	4	7	
Myalgia	Additional description: myalgia is commonly associated with endotoxemia		
subjects affected / exposed	2 / 15 (13.33%)	5 / 16 (31.25%)	
occurrences (all)	2	5	
malaise	Additional description: Commonly associated with endoxemia		
subjects affected / exposed	2 / 15 (13.33%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Exanthema			
subjects affected / exposed	0 / 15 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	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

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

short treatment with vorapaxar, very high variability in PF4 levels (sample handling?), timing of vorapaxar dosing (before LPS infusion)

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29864779