



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 | v1 |
| This version publication date | 04 January 2019 |
| First version publication date | 04 January 2019 |

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