



Clinical trial results:

A Phase II single blind, randomized, placebo controlled trial to study the efficacy and safety of anti-von Willebrand factor Nanobody administered as adjunctive treatment to patients with acquired thrombotic thrombocytopenic purpura.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2010-019375-30 |
| Trial protocol | BE AT GB DE IT ES |
| Global end of trial date | 14 March 2014 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 24 March 2016 |
| First version publication date | 24 March 2016 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | ALX-0681-2.1/10 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01151423 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Ablynx |
| Sponsor organisation address | Technologiepark 21, Zwijnaarde, Belgium, B-9052 |
| Public contact | Medical Monitor, Ablynx, 32 9262 0000, clinicaltrials@ablynx.com |
| Scientific contact | Medical Monitor, Ablynx, 32 9262 0000, clinicaltrials@ablynx.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001157-PIP01-11 |
| 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 | 09 July 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 March 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 March 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to measure the reduction of time-to-response, defined by the achievement of laboratory blood marker response (platelets), confirmed at 48 hours after the initial reporting of this response (platelets $\geq 150,000/\mu\text{L}$ and lactate dehydrogenase [LDH] $\leq 2 \times \text{ULN}$).

Protection of trial subjects:

Only subjects who met all the study inclusion and none of the exclusion criteria were to be randomised to trial treatment. All subjects were free to withdraw from the clinical trial at any time for any reason. Close monitoring of all subjects was adhered to throughout the trial conduct.

An independent DSMB monitored accruing safety data during the study (SAEs on an ongoing basis and an 'early safety look', per protocol, when 16 subjects, 8 ALX-0081-treated and 8 placebo-treated, had completed treatment with study drug). Based on the 'early safety look', the DSMB recommended to the Sponsor that the study continue with no changes to the Protocol.

An interim analysis for safety with formal stopping rules was performed when 28 of the ALX-0081 treated subjects had been treated and assessed. Upon review of the interim safety analysis, the DSMB made the recommendation to continue the study with no changes to the protocol. The procedures and responsibilities for the collection, analysis, and review of the data by the DSMB as well as communication and documentation of their opinions and recommendations were defined in the DSMB charter.

Background therapy:

Subjects received the standard of care and treatment judged appropriate by the Investigator at each site and according to site guidelines for treatment of Thrombotic Thrombocytopenic Purpura (TTP). The principal treatment for acquired TTP was daily plasma exchange (PE). Discontinuation of daily PE depended on normalisation of platelet count, neurological status and other clinical and laboratory parameters. Though not recommended per this protocol, at the discretion of the investigator, the frequency of PE could be tapered rather than stopped completely at the time of platelet count normalisation.

Additional treatment was variable depending on local standard practice and could include adjunctive immunosuppressive treatment (e.g., corticosteroids, rituximab).

Evidence for comparator:

There are currently no specifically approved therapeutics for TTP. Therefore, no active comparator agents are available and a placebo controlled design was used. All subjects received standard care during the study.

| | |
|---|-----------------|
| Actual start date of recruitment | 07 January 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Switzerland: 3 |
| Country: Number of subjects enrolled | United States: 15 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | United Kingdom: 7 |
| Country: Number of subjects enrolled | Austria: 5 |
| Country: Number of subjects enrolled | Belgium: 9 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Germany: 9 |
| Country: Number of subjects enrolled | Italy: 15 |
| Country: Number of subjects enrolled | Australia: 1 |
| Worldwide total number of subjects | 75 |
| EEA total number of subjects | 53 |

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) | 73 |
| From 65 to 84 years | 2 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects with acquired thrombotic thrombocytopenic purpura (TTP) were recruited from 11 countries in Europe, Australia, and US. Only adults were recruited; no adolescent patients were enrolled, although planned. A total of 75 patients were included in the trial.

Pre-assignment

Screening details:

76 subjects were screened, 75 subjects were randomized (= ITT population): 36 in the ALX-0081 group, 39 in the placebo group. Three subjects did not receive study drug: 1 subject in the ALX-0081 group (due to participation in another study) and 2 subjects in the placebo group (1 due to protocol violation, 1 due to pregnancy).

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | Overall period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Single blind |
| Roles blinded | Subject |

Blinding implementation details:

A single-blinded study design was initiated because the dosing regimen was dependent on the results of the Ristocetin Cofactor (RICO) test following the initial dose. Therefore, a double-blind design was not feasible because the results of the RICO test effectively unblinded the Investigator. Single-blind design was maintained due to the objective nature of the primary endpoint.

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Caplacizumab |

Arm description:

Subjects received a first intravenous (i.v.) bolus of 10 mg caplacizumab via push injection within 6 h to 15 min prior to the initiation of PE on study. The first plasma exchange (PE) on study could either be the very first PE session for the current episode of acquired TTP (if the subject was randomised prior to the initiation of PE) or the second PE session (if the subject was randomised after a single PE session). The first PE on study was followed by subcutaneous (s.c.) administration of 10 mg study drug within 30 minutes after the end of the PE procedure.

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | caplacizumab |
| Investigational medicinal product code | |
| Other name | ALX-0081, anti-von Willebrand factor (vWF) nanobody |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous bolus use , Subcutaneous use |

Dosage and administration details:

The first administration of caplacizumab was a single i.v. bolus of 10 mg (filled at 5 mg/mL) caplacizumab, administered by a push injection, 6 hours to 15 minutes prior to the initiation of plasma exchange (PE) on study, followed by s.c. administration within 30 minutes after the end of the PE procedure. All subsequent study drug administrations were daily s.c. injections within 30 minutes after the end of the PE procedure (if applicable) or within 24 hours of the previous dose. Subjects received caplacizumab up to 30 days after the last daily plasma exchange session.

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

Arm description:

Subjects received a first intravenous (i.v.) bolus of placebo via push injection within 6 h to 15 min prior to the initiation of PE on study. The first plasma exchange (PE) on study could either be the very first PE session for the current episode of acquired TTP (if the subject was randomised prior to the initiation of PE) or the second PE session (if the subject was randomised after a single PE session). The first PE on study was followed by subcutaneous (s.c.) administration of placebo within 30 minutes after the end of the PE procedure.

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous bolus use , Subcutaneous use |

Dosage and administration details:

The first administration of placebo was a single i.v. bolus, administered by a push injection, 6 hours to 15 minutes prior to the initiation of plasma exchange (PE) on study, followed by s.c. administration within 30 minutes after the end of the PE procedure. All subsequent study drug administrations were daily s.c. injections within 30 minutes after the end of the PE procedure (if applicable) or within 24 hours of the previous dose. Subjects received placebo up to 30 days after the last daily plasma exchange session.

| Number of subjects in period 1 | Caplacizumab | Placebo |
|--|--------------|---------|
| Started | 36 | 39 |
| Completed | 20 | 21 |
| Not completed | 16 | 18 |
| Adverse event, serious fatal | - | 1 |
| Physician decision | 1 | 1 |
| Consent withdrawn by subject | 1 | 3 |
| Study terminated by sponsor for slow recruitment | 9 | 10 |
| Adverse event, non-fatal | 3 | - |
| Other | 1 | 1 |
| Pregnancy | - | 1 |
| Lost to follow-up | 1 | - |
| Protocol deviation | - | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Caplacizumab |
|-----------------------|--------------|

Reporting group description:

Subjects received a first intravenous (i.v.) bolus of 10 mg caplacizumab via push injection within 6 h to 15 min prior to the initiation of PE on study. The first plasma exchange (PE) on study could either be the very first PE session for the current episode of acquired TTP (if the subject was randomised prior to the initiation of PE) or the second PE session (if the subject was randomised after a single PE session). The first PE on study was followed by subcutaneous (s.c.) administration of 10 mg study drug within 30 minutes after the end of the PE procedure.

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

Reporting group description:

Subjects received a first intravenous (i.v.) bolus of placebo via push injection within 6 h to 15 min prior to the initiation of PE on study. The first plasma exchange (PE) on study could either be the very first PE session for the current episode of acquired TTP (if the subject was randomised prior to the initiation of PE) or the second PE session (if the subject was randomised after a single PE session). The first PE on study was followed by subcutaneous (s.c.) administration of placebo within 30 minutes after the end of the PE procedure.

| Reporting group values | Caplacizumab | Placebo | Total |
|---------------------------------------|--------------|---------|-------|
| Number of subjects | 36 | 39 | 75 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 35 | 38 | 73 |
| From 65-84 years | 1 | 1 | 2 |
| Age continuous Units: years | | | |
| arithmetic mean | 40.6 | 42.5 | |
| standard deviation | ± 12.7 | ± 13.2 | - |
| Gender categorical Units: Subjects | | | |
| Female | 24 | 20 | 44 |
| Male | 12 | 19 | 31 |
| Race Units: Subjects | | | |
| Caucasian | 32 | 34 | 66 |
| Black | 4 | 5 | 9 |

End points

End points reporting groups

| | |
|--|--------------|
| Reporting group title | Caplacizumab |
| Reporting group description: Subjects received a first intravenous (i.v.) bolus of 10 mg caplacizumab via push injection within 6 h to 15 min prior to the initiation of PE on study. The first plasma exchange (PE) on study could either be the very first PE session for the current episode of acquired TTP (if the subject was randomised prior to the initiation of PE) or the second PE session (if the subject was randomised after a single PE session). The first PE on study was followed by subcutaneous (s.c.) administration of 10 mg study drug within 30 minutes after the end of the PE procedure. | |
| Reporting group title | Placebo |
| Reporting group description: Subjects received a first intravenous (i.v.) bolus of placebo via push injection within 6 h to 15 min prior to the initiation of PE on study. The first plasma exchange (PE) on study could either be the very first PE session for the current episode of acquired TTP (if the subject was randomised prior to the initiation of PE) or the second PE session (if the subject was randomised after a single PE session). The first PE on study was followed by subcutaneous (s.c.) administration of placebo within 30 minutes after the end of the PE procedure. | |

Primary: 1. Time-to-response of treatment defined by a confirmed recovery of platelets $\geq 150,000/\mu\text{L}$

| | |
|--|--|
| End point title | 1. Time-to-response of treatment defined by a confirmed recovery of platelets $\geq 150,000/\mu\text{L}$ |
| End point description: Time-to-response, defined by the achievement of platelet count response, confirmed at 48 hours after the initial reporting of this response. Platelet response was defined as recovery of platelets $\geq 150,000/\mu\text{L}$. This response had to be confirmed at 48 hours after the initial reporting of platelet recovery $\geq 150,000/\mu\text{L}$ by a de novo measure of platelets $\geq 150,000/\mu\text{L}$ and LDH $\leq 2 \times \text{ULN}$ (i.e., 'confirmed platelet response'). | |
| End point type | Primary |
| End point timeframe: From the day of first study drug administration up to 30 days after first study drug administration. | |

| End point values | Caplacizumab | Placebo | | |
|---|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 ^[1] | 39 ^[2] | | |
| Units: day | | | | |
| median (confidence interval 95%) | | | | |
| YES - One PE Session Prior to Randomisation | 2.4 (1.9 to 3) | 4.3 (2.9 to 5.7) | | |
| NO - No PE Session Prior to Randomisation | 3 (2.7 to 3.9) | 4.9 (3.2 to 6.6) | | |

Notes:

[1] - Intent-to-treat population

[2] - Intent-to-treat population

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Stratified log-rank test; time-to-response |
| Statistical analysis description: | |
| The primary analysis consisted of a Kaplan-Meier analysis with time-to-response as endpoint and treatment group as the independent variable and stratified for absence/presence of one PE session prior to randomisation. Caplacizumab was compared to placebo using a one-sided log-rank test in order to assess superiority at 2.5% significance level. The HR was estimated from a Cox proportional Hazards regression model with presence(yes)/absence(no) of 1 PE session prior to randomisation as covariate | |
| Comparison groups | Caplacizumab v Placebo |
| Number of subjects included in analysis | 75 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.005 ^[3] |
| Method | Stratified log-rank test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.28 |
| upper limit | 3.78 |

Notes:

[3] - p-value from the stratified log-rank test is based on an analysis stratified for presence (YES) /absence (NO) of one plasma exchange (PE) session prior to randomisation.

Secondary: 2. Proportion of subjects with complete remission following initial daily PE

| | |
|---|--|
| End point title | 2. Proportion of subjects with complete remission following initial daily PE |
| End point description: | |
| Proportion of subjects with complete remission (defined as confirmed platelet response and absence of exacerbation) following initial daily plasma exchange | |
| End point type | Secondary |
| End point timeframe: | |
| From the start of the study up to 30 days after stop of the study drug treatment. | |

| | | | | |
|-----------------------------|-------------------|-------------------|--|--|
| End point values | Caplacizumab | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 ^[4] | 39 ^[5] | | |
| Units: Subjects | 29 | 18 | | |

Notes:

[4] - Intent-to-treat population

[5] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: 3. Proportion of subjects with exacerbations of TTP

| | |
|-----------------|---|
| End point title | 3. Proportion of subjects with exacerbations of TTP |
|-----------------|---|

End point description:

Proportion of subjects with exacerbations of TTP (defined as recurrent thrombocytopenia following a confirmed platelet response and requiring a re-initiation of daily PE treatment after ≥ 1 day but ≤ 30 days of no daily PE treatment).

Time to first exacerbation of TTP was also examined as part of this end point analysis; the median time to first exacerbation could not be determined because of the small number of events.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Within 30 days of last day of initial daily PE | |

| End point values | Caplacizumab | Placebo | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 ^[6] | 39 ^[7] | | |
| Units: Subjects | 3 | 11 | | |

Notes:

[6] - Intent-to-treat population

[7] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: 4. Proportion of subjects with relapse of TTP

| | |
|-----------------|---|
| End point title | 4. Proportion of subjects with relapse of TTP |
|-----------------|---|

End point description:

The proportion of subjects with relapse of TTP (defined as de novo TTP event that occurred later than 30 days after the last daily PE) was evaluated.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Later than 30 days after the last daily PE | |

| End point values | Caplacizumab | Placebo | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 ^[8] | 39 ^[9] | | |
| Units: Subjects | 11 | 3 | | |

Notes:

[8] - Intent-to-treat population

[9] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: 5a. Number of daily plasma exchange (PE) sessions during the initial daily plasma exchange period

| | |
|---|---|
| End point title | 5a. Number of daily plasma exchange (PE) sessions during the initial daily plasma exchange period |
| End point description: Number of daily plasma exchange sessions during the initial daily plasma exchange (PE) period which could include more than 1 PE per day was evaluated. | |
| End point type | Secondary |
| End point timeframe: During the initial daily plasma exchange (PE) period | |

| End point values | Caplacizumab | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 ^[10] | 37 ^[11] | | |
| Units: PE sessions | | | | |
| arithmetic mean (standard deviation) | 6.7 (± 3.69) | 8.4 (± 6.74) | | |

Notes:

[10] - Number of subjects from the Intent-to-treat population, with data available.

[11] - Number of subjects from the Intent-to-treat population, with data available.

Statistical analyses

No statistical analyses for this end point

Secondary: 5b. Total volume of plasma administered during the initial daily PE period

| | |
|---|--|
| End point title | 5b. Total volume of plasma administered during the initial daily PE period |
| End point description: The total volume of plasma administered during the initial daily PE period was measured | |
| End point type | Secondary |
| End point timeframe: During the initial daily PE period | |

| End point values | Caplacizumab | Placebo | | |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 34 ^[12] | 37 ^[13] | | |
| Units: mL | | | | |
| arithmetic mean (standard deviation) | 22481.8 (± 15914.85) | 28358.4 (± 21344.16) | | |

Notes:

[12] - Number of subjects from the intent-to-treat population, with data available.

[13] - Number of subjects from the intent-to-treat population, with data available.

Statistical analyses

No statistical analyses for this end point

Secondary: 5c. Number of days with at least one PE administration during the total

course of the study

| | |
|-----------------|---|
| End point title | 5c. Number of days with at least one PE administration during the total course of the study |
|-----------------|---|

End point description:

Number of days for plasma exchange was evaluated. This implies the number of days with at least one PE administration during the total course of the study.

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

End point timeframe:

During the total course of the study

| End point values | Caplacizumab | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 ^[14] | 37 ^[15] | | |
| Units: day | | | | |
| arithmetic mean (standard deviation) | 11.8 (± 7.43) | 12.6 (± 9.15) | | |

Notes:

[14] - Number of subjects from the intent-to-treat population, with data available.

[15] - Number of subjects from the intent-to-treat population, with data available.

Statistical analyses

No statistical analyses for this end point

Secondary: 5d. The maximum number of consecutive days per subject where there was no interruption of PE during the initial daily PE period

| | |
|-----------------|---|
| End point title | 5d. The maximum number of consecutive days per subject where there was no interruption of PE during the initial daily PE period |
|-----------------|---|

End point description:

The maximum number of consecutive days per subject of PE where there was no interruption of PE during the initial daily PE period.

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

End point timeframe:

During the initial daily PE period

| End point values | Caplacizumab | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 ^[16] | 37 ^[17] | | |
| Units: day | | | | |
| arithmetic mean (standard deviation) | 6.6 (± 3.35) | 8.1 (± 6.46) | | |

Notes:

[16] - Number of subjects from the intent-to-treat population, with data available.

[17] - Number of subjects from the intent-to-treat population, with data available.

Statistical analyses

No statistical analyses for this end point

Secondary: 6. Resolution of non-focal neurological symptoms

| | |
|-----------------|--|
| End point title | 6. Resolution of non-focal neurological symptoms |
|-----------------|--|

End point description:

Resolution of non-focal neurological symptoms as defined by neurocognitive function at complete remission, measured by a neurocognitive test battery (adults only).

The CNTB was completed by a low proportion of subjects with baseline data available only for 3 subjects in the caplacizumab and 4 subjects in the placebo group. Therefore, the results obtained are not considered representative of the overall study population and an analysis was not performed.

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

End point timeframe:

Not applicable

| End point values | Caplacizumab | Placebo | | |
|-----------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[18] | 0 ^[19] | | |
| Units: Subjects | | | | |

Notes:

[18] - Analysis was not performed, see also end point description

[19] - Analysis was not performed, see also end point description

Statistical analyses

No statistical analyses for this end point

Secondary: 7. Resolution of TTP-related signs or symptoms

| | |
|-----------------|--|
| End point title | 7. Resolution of TTP-related signs or symptoms |
|-----------------|--|

End point description:

Resolution or improvement (improvement of ≥ 1 grade in the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 scale) of TTP-related signs and symptoms as captured on physical examination and as adverse events. This endpoint was only evaluated for "resolution".

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

End point timeframe:

End of daily PE treatment period, end of study treatment period and at 1 month follow-up.

| End point values | Caplacizumab | Placebo | | |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 ^[20] | 39 ^[21] | | |
| Units: Subjects | | | | |
| End of daily PE treatment period | 29 | 29 | | |
| End of study treatment period | 30 | 33 | | |
| At 1 month follow-up | 31 | 27 | | |

Notes:

[20] - Intent-to-treat population.

[21] - Intent-to-treat population.

Statistical analyses

No statistical analyses for this end point

Secondary: 8. Mortality

| | |
|---|--------------|
| End point title | 8. Mortality |
| End point description: | |
| Total mortality up to 1 month follow-up | |
| End point type | Secondary |
| End point timeframe: | |
| From the start of the study up to 1 month follow-up | |

| End point values | Caplacizumab | Placebo | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 ^[22] | 39 ^[23] | | |
| Units: Deaths | 0 | 2 | | |

Notes:

[22] - Intent-to-treat population

[23] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: 9a. Number of plasma exchange (PE) related adverse events

| | |
|--|---|
| End point title | 9a. Number of plasma exchange (PE) related adverse events |
| End point description: | |
| Number of plasma exchange (PE) treatment-related adverse events (AE) | |
| End point type | Secondary |
| End point timeframe: | |
| From the start of the study up to 1 month follow-up | |

| End point values | Caplacizumab | Placebo | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 ^[24] | 39 ^[25] | | |
| Units: Adverse event | 72 | 44 | | |

Notes:

[24] - Intent-to-treat population

[25] - Intent-to-treat population.

Statistical analyses

No statistical analyses for this end point

Secondary: 9b. Number of subjects with plasma exchange related adverse events

| | |
|-----------------|--|
| End point title | 9b. Number of subjects with plasma exchange related adverse events |
|-----------------|--|

End point description:

Number of subjects with plasma exchange (PE) related adverse events (AE)

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

End point timeframe:

From the start of the study up to 1 month follow-up

| End point values | Caplacizumab | Placebo | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 ^[26] | 39 ^[27] | | |
| Units: Adverse events | 20 | 20 | | |

Notes:

[26] - Intent-to-treat population

[27] - Intent-to-treat population

Statistical analyses

No statistical analyses for this end point

Secondary: 10a. Number of treatment-emergent adverse events by severity

| | |
|-----------------|--|
| End point title | 10a. Number of treatment-emergent adverse events by severity |
|-----------------|--|

End point description:

Number and severity of treatment-emergent adverse events (AEs) were evaluated. The severity grades of AEs were defined as: mild, moderate, severe.

Note: the numbers listed do not include the treatment-emergent adverse events with missing severity

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

End point timeframe:

From the start of the study up to 1 month follow-up

| End point values | Caplacizumab | Placebo | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 ^[28] | 37 ^[29] | | |
| Units: Adverse event | | | | |
| Mild | 348 | 299 | | |
| Moderate | 154 | 173 | | |
| Severe | 37 | 23 | | |

Notes:

[28] - Safety population

[29] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: 10b. Number of subjects with treatment-emergent adverse events by severity

| | |
|-----------------|--|
| End point title | 10b. Number of subjects with treatment-emergent adverse events by severity |
|-----------------|--|

End point description:

Number of subjects with treatment-emergent adverse events (AEs) by severity. The severity grades of AEs were defined as: mild, moderate, severe.

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

End point timeframe:

From the start of the study up to 1 month follow-up

| End point values | Caplacizumab | Placebo | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 ^[30] | 37 ^[31] | | |
| Units: Subject | | | | |
| Mild | 31 | 36 | | |
| Moderate | 27 | 31 | | |
| Severe | 18 | 14 | | |

Notes:

[30] - Safety population

[31] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: 10c. Number of treatment-emergent adverse events and their relationship to study drug

| | |
|-----------------|---|
| End point title | 10c. Number of treatment-emergent adverse events and their relationship to study drug |
|-----------------|---|

End point description:

Number of treatment-emergent AEs and their relationship to study drug were evaluated.
Relationship of AEs to study drug was: related, possibly related, unlikely/not related.

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

End point timeframe:

From the start of the study up to 1 month follow-up

| End point values | Caplacizumab | Placebo | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 ^[32] | 37 ^[33] | | |
| Units: Adverse events | | | | |
| Related | 12 | 6 | | |
| Possibly related | 59 | 9 | | |
| Unlikely/Not related | 486 | 524 | | |

Notes:

[32] - Safety population

[33] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: 11. Immunogenicity

| | |
|-----------------|--------------------|
| End point title | 11. Immunogenicity |
|-----------------|--------------------|

End point description:

The development of anti-drug antibodies was monitored from the start of the study until last follow-up visit.

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

End point timeframe:

From the start of the study until last follow-up visit.

| End point values | Caplacizumab | Placebo | | |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 32 ^[34] | 30 ^[35] | | |
| Units: subjects | 3 | 0 | | |

Notes:

[34] - Number of subjects from the Safety population with data available

[35] - Number of subjects from the Safety population with data available

Statistical analyses

No statistical analyses for this end point

Secondary: 12a. Pharmacokinetics

| | |
|-----------------|-----------------------|
| End point title | 12a. Pharmacokinetics |
|-----------------|-----------------------|

End point description:

The concentration of caplacizumab in plasma was determined at different time points.

PK Population: The PK Population consisted of all subjects who received the study drug and for whom the primary PK data are considered to be sufficient and interpretable.

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

End point timeframe:

From the start of the study up to 1 month follow-up

| End point values | Caplacizumab | Placebo | | |
|--|--------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 ^[36] | 0 ^[37] | | |
| Units: ng/mL | | | | |
| arithmetic mean (standard error) | | | | |
| Baseline | 100 (± 0) | () | | |
| Day 1 of daily PE, 5 – 10 min postdose | 1765.9 (± 185.04) | () | | |
| Day 1 of daily PE, 3 - 6 hours postdose | 450.4 (± 36.15) | () | | |
| Day 1 of daily PE, 8 - 24 hours postdose | 562 (± 36.8) | () | | |
| Day 2 of daily PE, predose | 288 (± 24.05) | () | | |
| Day 2 of daily PE, 1 – 6 hrs postdose | 415.8 (± 24.75) | () | | |
| Day 2 of daily PE, 6 – 12 hrs postdose | 570.7 (± 52.22) | () | | |
| Day 2 of daily PE, 18 – 24 hrs postdose | 489.3 (± 32.54) | () | | |
| Last day of daily PE, predose | 348.4 (± 38.32) | () | | |
| Day 1 after daily PE | 521.9 (± 31.52) | () | | |
| Week 1 after daily PE | 490.6 (± 36.11) | () | | |
| Week 2 after daily PE | 524.9 (± 39.37) | () | | |
| Week 3 after daily PE | 499.6 (± 35.1) | () | | |
| Week 4 after daily PE | 503.4 (± 31.21) | () | | |
| Day 3 of follow-up period | 346.7 (± 25.43) | () | | |
| Day 7 of follow-up period | 162.3 (± 20.2) | () | | |
| 1 month follow-up | 100 (± 0) | () | | |

Notes:

[36] - PK population

[37] - No PK data were generated for the subjects in the placebo group

Statistical analyses

No statistical analyses for this end point

Secondary: 12b. Pharmacodynamics: Ristocetin cofactor (RICO) activity over time

| | |
|-----------------|--|
| End point title | 12b. Pharmacodynamics: Ristocetin cofactor (RICO) activity over time |
|-----------------|--|

| | |
|---|-----------|
| End point description: | |
| The change from baseline in ristocetin cofactor (RICO) activity was measured at different time points | |
| End point type | Secondary |
| End point timeframe: | |
| From the start of the study up to 1 month follow-up | |

| End point values | Caplacizumab | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 ^[38] | 37 ^[39] | | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 76.2 (± 4.95) | 82.1 (± 3.76) | | |
| Day 1 of daily PE, post dose | 16.2 (± 0.72) | 84.4 (± 6.09) | | |
| Day 2 of daily PE, post dose | 21.4 (± 3.64) | 94.4 (± 3.69) | | |
| Last day of daily PE, post dose | 15.4 (± 0.39) | 118.2 (± 1.78) | | |
| Day 1 after daily PE | 19.2 (± 3.94) | 105.2 (± 4.31) | | |
| Week 1 after daily PE | 15 (± 0) | 107.3 (± 3.05) | | |
| Week 2 after daily PE | 18.9 (± 2.87) | 109.2 (± 2.8) | | |
| Week 3 after daily PE | 17.4 (± 2.34) | 104 (± 3.46) | | |
| Week 4 after daily PE | 15.1 (± 0.07) | 105.5 (± 3.59) | | |
| Day 3 of follow-up period | 42.3 (± 6.33) | 99.1 (± 4.56) | | |
| Day 7 of follow-up period | 88.3 (± 4.99) | 99.7 (± 4.06) | | |
| 1 month follow-up | 94.6 (± 3.78) | 94.7 (± 5.35) | | |

Notes:

[38] - Safety population

[39] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: 12c. Pharmacodynamics: vWF:Ag over time

| | |
|---|---|
| End point title | 12c. Pharmacodynamics: vWF:Ag over time |
| End point description: | |
| The change from baseline in vWF:Ag concentration was measured at different time points. | |
| End point type | Secondary |
| End point timeframe: | |
| From the start of the study drug up to 1 month follow-up | |

| End point values | Caplacizumab | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 ^[40] | 37 ^[41] | | |
| Units: Percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 185.1 (± 15.09) | 204.4 (± 14.52) | | |

| | | | | |
|---------------------------------|-----------------|-----------------|--|--|
| Day 1 of daily PE, post dose | 120.6 (± 7.98) | 166.6 (± 9.24) | | |
| Day 2 of daily PE, post dose | 94.6 (± 4.83) | 140.2 (± 6.16) | | |
| Last day of daily PE, post dose | 93.6 (± 6.01) | 151.2 (± 14.25) | | |
| Day 1 after daily PE | 86.2 (± 6.15) | 166 (± 10.05) | | |
| Week 1 after daily PE | 93.4 (± 6.4) | 234.9 (± 20.91) | | |
| Week 2 after daily PE | 115.9 (± 12.42) | 242.6 (± 19.43) | | |
| Week 3 after daily PE | 102.4 (± 6.45) | 224.2 (± 18.62) | | |
| Week 4 after daily PE | 100.1 (± 5) | 204.3 (± 17.08) | | |
| Day 3 of follow-up period | 137.8 (± 9.32) | 184.1 (± 13.89) | | |
| Day 7 of follow-up period | 190.2 (± 12.9) | 190.3 (± 14.81) | | |
| 1 month follow-up | 176.3 (± 15.63) | 167.2 (± 15.46) | | |

Notes:

[40] - Safety population

[41] - Safety population

Statistical analyses

No statistical analyses for this end point

Secondary: 12d. Pharmacodynamics: Coagulation Factor VIII:C over time

| | |
|--|--|
| End point title | 12d. Pharmacodynamics: Coagulation Factor VIII:C over time |
| End point description: | |
| The change from baseline in Factor VIII clotting activity concentration was measured at different time points. | |
| End point type | Secondary |
| End point timeframe: | |
| From the start of the study up to 1 month follow-up | |

| End point values | Caplacizumab | Placebo | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 35 ^[42] | 37 ^[43] | | |
| Units: percentage | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 144.18 (± 11.14) | 156.8 (± 12.54) | | |
| Day 1 of daily PE, post dose | 104 (± 6.95) | 149 (± 9.16) | | |
| Day 2 of daily PE, post dose | 90.7 (± 5.49) | 152.9 (± 9.41) | | |
| Last day of daily PE, post dose | 102.4 (± 10.91) | 169.5 (± 17.79) | | |
| Day 1 after daily PE | 116.3 (± 13.33) | 234.2 (± 16.05) | | |
| Week 1 after daily PE | 116.4 (± 11.73) | 296.8 (± 26.07) | | |
| Week 2 after daily PE | 125.2 (± 16.88) | 291.1 (± 18.25) | | |

| | | | | |
|---------------------------|-----------------|-----------------|--|--|
| Week 3 after daily PE | 106.3 (± 9.7) | 273.1 (± 20.35) | | |
| Week 4 after daily PE | 95.8 (± 6.09) | 249.1 (± 18.27) | | |
| Day 3 of follow-up period | 146.3 (± 12.59) | 227.7 (± 17.32) | | |
| Day 7 of follow-up period | 208.6 (± 15.54) | 237.5 (± 15.65) | | |
| 1 month follow-up | 212.2 (± 17.33) | 200.1 (± 17.11) | | |

Notes:

[42] - Safety population

[43] - Safety population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For the entire study period and up to 12 months follow-up.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Caplacizumab (active drug) |
|-----------------------|----------------------------|

Reporting group description:

Subjects received a first intravenous (i.v.) bolus of 10 mg caplacizumab via push injection within 6 h to 15 min prior to the initiation of PE on study. The first plasma exchange (PE) on study could either be the very first PE session for the current episode of acquired TTP (if the subject was randomised prior to the initiation of PE) or the second PE session (if the subject was randomised after a single PE session).

The first PE on study was followed by subcutaneous (s.c.) administration of 10 mg study drug within 30 minutes after the end of the PE procedure.

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

Reporting group description:

Subjects received a first intravenous (i.v.) bolus of placebo via push injection within 6 h to 15 min prior to the initiation of PE on study. The first plasma exchange (PE) on study could either be the very first PE session for the current episode of acquired TTP (if the subject was randomised prior to the initiation of PE) or the second PE session (if the subject was randomised after a single PE session). The first PE on study was followed by subcutaneous (s.c.) administration of 10 mg study drug within 30 minutes after the end of the PE procedure.

| Serious adverse events | Caplacizumab (active drug) | Placebo | |
|---|----------------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 20 / 35 (57.14%) | 19 / 37 (51.35%) | |
| number of deaths (all causes) | 0 | 2 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Metrorrhagia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostatitis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Mental status changes | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Substance-induced psychotic disorder | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Autoantibody test | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transaminases increased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Traumatic fracture | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysarthria | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Facial paresis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Thrombotic thrombocytopenic purpura | | | |
| subjects affected / exposed | 13 / 35 (37.14%) | 13 / 37 (35.14%) | |
| occurrences causally related to treatment / all | 2 / 16 | 0 / 17 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Eye disorders | | | |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hypertransaminasaemia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis allergic | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bacterial infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle abscess | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 0 / 37 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 1 / 37 (2.70%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Caplacizumab (active drug) | Placebo | |
|---|-------------------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 33 / 35 (94.29%) | 37 / 37 (100.00%) | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 4 / 37 (10.81%) | |
| occurrences (all) | 4 | 4 | |
| Hypertension | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | 6 / 37 (16.22%) | |
| occurrences (all) | 6 | 7 | |
| Phlebitis | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 2 / 37 (5.41%) | |
| occurrences (all) | 3 | 2 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 2 / 37 (5.41%) | |
| occurrences (all) | 0 | 2 | |
| Hypotension | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 2 / 37 (5.41%) | |
| occurrences (all) | 4 | 2 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 6 / 37 (16.22%) | |
| occurrences (all) | 1 | 8 | |
| Catheter site pain | | | |

| | | | |
|--------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 35 (5.71%) | 1 / 37 (2.70%) | |
| occurrences (all) | 2 | 1 | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 2 / 37 (5.41%) | |
| occurrences (all) | 2 | 2 | |
| Fatigue | | | |
| subjects affected / exposed | 6 / 35 (17.14%) | 5 / 37 (13.51%) | |
| occurrences (all) | 10 | 6 | |
| Injection site bruising | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 2 / 37 (5.41%) | |
| occurrences (all) | 0 | 2 | |
| Injection site haemorrhage | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 1 / 37 (2.70%) | |
| occurrences (all) | 6 | 1 | |
| Local swelling | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 2 / 37 (5.41%) | |
| occurrences (all) | 0 | 2 | |
| Malaise | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 37 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 0 / 37 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 3 / 37 (8.11%) | |
| occurrences (all) | 3 | 5 | |
| Pain | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 1 / 37 (2.70%) | |
| occurrences (all) | 2 | 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 35 (17.14%) | 6 / 37 (16.22%) | |
| occurrences (all) | 7 | 6 | |
| Chills | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 3 / 37 (8.11%) | |
| occurrences (all) | 0 | 3 | |
| Reproductive system and breast | | | |

| | | | |
|---|------------------|-----------------|--|
| disorders | | | |
| Menorrhagia | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 37 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Metrorrhagia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 2 / 37 (5.41%) | |
| occurrences (all) | 1 | 2 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | 2 / 37 (5.41%) | |
| occurrences (all) | 6 | 2 | |
| Dyspnoea | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 4 / 37 (10.81%) | |
| occurrences (all) | 5 | 4 | |
| Epistaxis | | | |
| subjects affected / exposed | 11 / 35 (31.43%) | 4 / 37 (10.81%) | |
| occurrences (all) | 16 | 8 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 3 / 37 (8.11%) | |
| occurrences (all) | 3 | 3 | |
| Productive cough | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 1 / 37 (2.70%) | |
| occurrences (all) | 3 | 1 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 5 / 37 (13.51%) | |
| occurrences (all) | 3 | 5 | |
| Anxiety | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 5 / 37 (13.51%) | |
| occurrences (all) | 5 | 7 | |
| Depression | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 2 / 37 (5.41%) | |
| occurrences (all) | 1 | 2 | |
| Disorientation | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 1 / 37 (2.70%) | |
| occurrences (all) | 2 | 1 | |

| | | | |
|---|-----------------|-----------------|--|
| Insomnia | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | 5 / 37 (13.51%) | |
| occurrences (all) | 5 | 8 | |
| Restlessness | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 2 / 37 (5.41%) | |
| occurrences (all) | 0 | 2 | |
| Sleep disorder | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 2 / 37 (5.41%) | |
| occurrences (all) | 1 | 2 | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 35 (0.00%) | 2 / 37 (5.41%) | |
| occurrences (all) | 0 | 2 | |
| Investigations | | | |
| Activated partial thromboplastin time prolonged | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 37 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 2 / 37 (5.41%) | |
| occurrences (all) | 1 | 3 | |
| Blood lactate dehydrogenase increased | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 0 / 37 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Blood potassium decreased | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 3 / 37 (8.11%) | |
| occurrences (all) | 2 | 3 | |
| Brain natriuretic peptide increased | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 1 / 37 (2.70%) | |
| occurrences (all) | 2 | 2 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 37 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 37 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Haptoglobin decreased | | | |

| | | | |
|--|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | 1 / 37 (2.70%) 1 | |
| Neutrophil count increased subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | 0 / 37 (0.00%) 0 | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 3 | 3 / 37 (8.11%) 11 | |
| White blood cell count increased subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | 0 / 37 (0.00%) 0 | |
| AST increased subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 2 | 2 / 37 (5.41%) 3 | |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 4 / 35 (11.43%) 8 | 2 / 37 (5.41%) 2 | |
| Transfusion reaction subjects affected / exposed occurrences (all) | 4 / 35 (11.43%) 8 | 2 / 37 (5.41%) 3 | |
| Cardiac disorders | | | |
| Acute myocardial infarction subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 2 / 37 (5.41%) 2 | |
| Cardiac disorder subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 3 | 1 / 37 (2.70%) 1 | |
| Palpitations subjects affected / exposed occurrences (all) | 3 / 35 (8.57%) 3 | 2 / 37 (5.41%) 2 | |
| Tachycardia subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | 1 / 37 (2.70%) 1 | |
| Nervous system disorders | | | |

| | | | |
|--|------------------------|------------------------|--|
| Disturbance in attention subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | 0 / 37 (0.00%) 0 | |
| Dizziness subjects affected / exposed occurrences (all) | 6 / 35 (17.14%) 6 | 3 / 37 (8.11%) 3 | |
| Headache subjects affected / exposed occurrences (all) | 11 / 35 (31.43%) 19 | 10 / 37 (27.03%) 26 | |
| Migraine subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 4 | 0 / 37 (0.00%) 0 | |
| Paraesthesia subjects affected / exposed occurrences (all) | 7 / 35 (20.00%) 13 | 8 / 37 (21.62%) 14 | |
| Syncope subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | 2 / 37 (5.41%) 4 | |
| Transient ischaemic attack subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 3 | 1 / 37 (2.70%) 2 | |
| Tremor subjects affected / exposed occurrences (all) | 3 / 35 (8.57%) 3 | 0 / 37 (0.00%) 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | 8 / 37 (21.62%) 34 | |
| Leukocytosis subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 2 / 37 (5.41%) 2 | |
| Neutrophilia subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 2 / 37 (5.41%) 2 | |
| Eye disorders | | | |

| | | | |
|-----------------------------|------------------|------------------|--|
| Diplopia | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 2 / 37 (5.41%) | |
| occurrences (all) | 2 | 2 | |
| Vision blurred | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 1 / 37 (2.70%) | |
| occurrences (all) | 2 | 1 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 0 / 37 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 4 / 37 (10.81%) | |
| occurrences (all) | 3 | 27 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 3 / 37 (8.11%) | |
| occurrences (all) | 3 | 4 | |
| Constipation | | | |
| subjects affected / exposed | 7 / 35 (20.00%) | 10 / 37 (27.03%) | |
| occurrences (all) | 8 | 10 | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 35 (17.14%) | 3 / 37 (8.11%) | |
| occurrences (all) | 10 | 3 | |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 1 / 37 (2.70%) | |
| occurrences (all) | 4 | 1 | |
| Gingival bleeding | | | |
| subjects affected / exposed | 5 / 35 (14.29%) | 2 / 37 (5.41%) | |
| occurrences (all) | 6 | 2 | |
| Nausea | | | |
| subjects affected / exposed | 10 / 35 (28.57%) | 10 / 37 (27.03%) | |
| occurrences (all) | 20 | 12 | |
| Paraesthesia oral | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 1 / 37 (2.70%) | |
| occurrences (all) | 5 | 1 | |
| Vomiting | | | |

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|--|-----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 7 / 35 (20.00%) 11 | 7 / 37 (18.92%) 9 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 0 / 37 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Ecchymosis | | | |
| subjects affected / exposed | 1 / 35 (2.86%) | 2 / 37 (5.41%) | |
| occurrences (all) | 1 | 2 | |
| Erythema | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 1 / 37 (2.70%) | |
| occurrences (all) | 2 | 2 | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 2 / 35 (5.71%) | 1 / 37 (2.70%) | |
| occurrences (all) | 2 | 1 | |
| Petechiae | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 0 / 37 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Pruritus | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 3 / 37 (8.11%) | |
| occurrences (all) | 4 | 5 | |
| Rash | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 4 / 37 (10.81%) | |
| occurrences (all) | 6 | 4 | |
| Urticaria | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 3 / 37 (8.11%) | |
| occurrences (all) | 6 | 5 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 4 / 35 (11.43%) | 2 / 37 (5.41%) | |
| occurrences (all) | 6 | 2 | |
| Muscle spasms | | | |
| subjects affected / exposed | 3 / 35 (8.57%) | 5 / 37 (13.51%) | |
| occurrences (all) | 6 | 7 | |
| Musculoskeletal pain | | | |

| | | | |
|--|----------------------|-----------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 35 (8.57%) 3 | 2 / 37 (5.41%) 2 | |
| Myalgia subjects affected / exposed occurrences (all) | 7 / 35 (20.00%) 8 | 1 / 37 (2.70%) 2 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 5 / 35 (14.29%) 7 | 7 / 37 (18.92%) 11 | |
| Arthralgia subjects affected / exposed occurrences (all) | 3 / 35 (8.57%) 4 | 8 / 37 (21.62%) 11 | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 0 / 35 (0.00%) 0 | 2 / 37 (5.41%) 3 | |
| Influenza subjects affected / exposed occurrences (all) | 3 / 35 (8.57%) 3 | 2 / 37 (5.41%) 2 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 5 / 35 (14.29%) 6 | 0 / 37 (0.00%) 0 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 3 | 2 / 37 (5.41%) 2 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 2 | 2 / 37 (5.41%) 2 | |
| Fluid retention subjects affected / exposed occurrences (all) | 1 / 35 (2.86%) 1 | 2 / 37 (5.41%) 2 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 2 / 35 (5.71%) 3 | 5 / 37 (13.51%) 11 | |
| Hypocalcaemia | | | |

| | | | |
|-----------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 35 (2.86%) | 2 / 37 (5.41%) | |
| occurrences (all) | 6 | 2 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 9 / 35 (25.71%) | 8 / 37 (21.62%) | |
| occurrences (all) | 18 | 12 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 01 October 2010 | <p>Protocol Version 3.0 dated 01 Oct 2010 - main changes:</p> <ul style="list-style-type: none">• updating the primary endpoint (from 'reduction of time-to-recovery, defined by the achievement of laboratory blood marker response, confirmed at 48 hours after the initial reporting of this response' to 'time to response, based on the recovery of platelets $\geq 150,000/\mu\text{L}$ which must be confirmed at 48 hours after the initial reporting of platelet recovery $\geq 150,000/\mu\text{L}$ by a de novo measure of platelets $\geq 150,000/\mu\text{L}$ and $\text{LDH} \leq 2 \times \text{ULN}$'),• adding 2 exclusion criteria (known hypersensitivity to the active substance or to excipients of the study drug and severe liver impairment),• adjustment of time points for ECG measurements during the treatment phase• adding a paragraph on participation in concurrent clinical studies,• the use of an electronic diary was replaced by a nurse sheet and/or diary and additional time points for recuperating these documents were added. |
| 05 April 2011 | <p>Protocol Version 5.0 dated 05 Apr 2011 - main changes:</p> <ul style="list-style-type: none">• change the description of the patient population (from 'patients with a clinical diagnosis of TTP necessitating PE' to 'symptomatic patients with acute episodes of acquired TTP, requiring treatment with PE'),• to add a better description of how to interpret 'clinically relevant bleeding' (i.e., 'moderate to severe [including life-threatening] bleeding requiring urgent medical and/or surgical intervention') and• to rephrase actions to be taken in case of clinically relevant bleeding, to adjust the section on withdrawal of subjects from the study (to include pregnancy as reason for withdrawal and to note that subject withdrawal due to AEs were not to be replaced)• to add clarifications/specifications in several sections of the Study protocol (exclusion criteria, DSMB [summarize their function], study drug administration, management of overdose, allowed time windows for assessment, updated time points of lab assessments and dosing, AEs).• In case the FVIII:C assay was not available at the local laboratory, it could be replaced by an alternative method. |
| 21 October 2011 | <p>Protocol Version 8.0 dated 21-Oct-2011 - main changes:</p> <ul style="list-style-type: none">• clarify wording on endpoints (i.e., add the words 'confirmed platelet response' to the primary endpoint description and rewording of secondary/tertiary endpoints),• add an exclusion criterion to exclude severe chronic renal impairment,• change the dosing schedule (dose increase based on local RICO measurements is no longer included),• to delete local RICO measurements from the schedule of assessments,• to note possibility of PE tapering (which although not recommended is also not precluded and resulting in a redefinition of different time intervals during treatment phase [relative to end of daily PE instead of hospital discharge])• delete the PK/PD substudy (resulting in an adjustment of the PK/PD sampling schedule),• change the duration of hospitalisation,• to add clarifications/specifications in several sections (e.g., exclusion criteria [further clarification of liver impairment added], DSMB, handling of clinical relevant bleeding, the list of clinical outcome criteria for evaluation, PD criteria for evaluation, PE tapering, statistics). |

| | |
|-------------------|---|
| 25 September 2012 | <p>Protocol Version 10.0 dated 25-Sep-2012 - main changes:</p> <ul style="list-style-type: none"> • to add clarifications for the case of TTP exacerbation and TTP relapse (definitions of exacerbations and relapses in the endpoints and objectives were clarified to 'recurrent thrombocytopenia following a response and requiring a re-initiation of daily PE treatment after ≥ 1 day but ≤ 30 days after the last daily PE' and 'de novo event of TTP that occurs later than 30 days after the last daily PE', respectively, relating to daily PE instead of "no PE treatment") • clarifications on the timeframe of assessments in view of potential tapering of PE (which is not recommended per this protocol, but it is allowed if considered necessary by the Investigator) resulting in the fact that study drug administration is no longer coinciding with the 30 days post PE period for tapered subjects • to add more details on the planned statistical analysis • to add clarifications/specifications in several sections • the vWF multimers test was no longer to be performed |
| 25 September 2012 | <p>Protocol Version 11.0 dated 25 Sep 2012 reflects the changes in Protocol Version 10.0 and in addition:</p> <ul style="list-style-type: none"> • opening of the study to adolescents (12 to < 18 years), in line with the obligations and commitments outlined in EMA decision P/0060/2012, relating to PIP EMEA-001157-PIP01-11. Version 11.0 was created only in those centres where both the EC or IRB and the Investigator agreed to include adolescents. Affected sections include the synopsis, Introduction (e.g., safety/risk profile, rationale for dose selection), Trial design, Selection and Withdrawal of subjects, Study drug preparation and administration, Treatment, Study assessments and procedures, Statistical procedures, Patient information and consent/assent and Insurance/liability. |
| 24 June 2013 | <p>Protocol Version 12.0 dated 24 Jun 2013:</p> <ul style="list-style-type: none"> • revising the protocol to allow enrolment of subjects who have received one prior PE (within an acceptable time frame). <p>(Protocol Version 13.0 also dated 24-Jun-2013 is based on protocol Version 11.0 and in addition reflects the changes in Protocol Version 12.0)</p> |

Notes:

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.

Due to recruitment challenges, the study did not meet its enrollment target.

Notes: