



## 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
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#### 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:

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**Results analysis stage**

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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:

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**General information about the trial**

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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/ $\mu$ L and lactate dehydrogenase [LDH]  $\leq$  2 x 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:

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**Population of trial subjects**

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**Subjects enrolled per country**

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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:

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**Subjects enrolled per age group**

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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
<b>Arm title</b>	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.

<b>Arm title</b>	Placebo
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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.

<b>Number of subjects in period 1</b>	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
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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
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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
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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
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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 $\geq 150,000/\mu\text{L}$
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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
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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 <sup>[1]</sup>	39 <sup>[2]</sup>		
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

<b>Statistical analysis title</b>	Stratified log-rank test; time-to-response
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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
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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
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End point timeframe:

From the start of the study up to 30 days after stop of the study drug treatment.

<b>End point values</b>	Caplacizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36 <sup>[4]</sup>	39 <sup>[5]</sup>		
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
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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  $\geq 1$  day but  $\leq 30$  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
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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 <sup>[6]</sup>	39 <sup>[7]</sup>		
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
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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
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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 <sup>[8]</sup>	39 <sup>[9]</sup>		
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 <sup>[10]</sup>	37 <sup>[11]</sup>		
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 <sup>[12]</sup>	37 <sup>[13]</sup>		
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
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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
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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 <sup>[14]</sup>	37 <sup>[15]</sup>		
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
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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
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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 <sup>[16]</sup>	37 <sup>[17]</sup>		
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 <sup>[18]</sup>	0 <sup>[19]</sup>		
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  $\geq 1$  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 <sup>[20]</sup>	39 <sup>[21]</sup>		
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 <sup>[22]</sup>	39 <sup>[23]</sup>		
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 <sup>[24]</sup>	39 <sup>[25]</sup>		
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
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End point description:

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

End point type	Secondary
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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 <sup>[26]</sup>	39 <sup>[27]</sup>		
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
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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
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End point timeframe:

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

<b>End point values</b>	Caplacizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35 <sup>[28]</sup>	37 <sup>[29]</sup>		
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
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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
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End point timeframe:

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

<b>End point values</b>	Caplacizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35 <sup>[30]</sup>	37 <sup>[31]</sup>		
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
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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 <sup>[32]</sup>	37 <sup>[33]</sup>		
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 <sup>[34]</sup>	30 <sup>[35]</sup>		
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 <sup>[36]</sup>	0 <sup>[37]</sup>		
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 <sup>[38]</sup>	37 <sup>[39]</sup>		
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 <sup>[40]</sup>	37 <sup>[41]</sup>		
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
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End point description:

The change from baseline in Factor VIII clotting activity concentration was measured at different time points.

End point type	Secondary
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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 <sup>[42]</sup>	37 <sup>[43]</sup>		
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

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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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	16.1
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### Reporting groups

Reporting group title	Caplacizumab (active drug)
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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
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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.

<b>Serious adverse events</b>	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	
<b>Respiratory, thoracic and mediastinal disorders</b>			
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	
<b>Psychiatric disorders</b>			
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	
<b>Investigations</b>			
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	
<b>Transaminases increased</b>			
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	
<b>Liver function test abnormal</b>			
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	
<b>Injury, poisoning and procedural complications</b>			
<b>Traumatic fracture</b>			
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	
<b>Cardiac disorders</b>			
<b>Atrial fibrillation</b>			
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	
<b>Atrial flutter</b>			
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	
<b>Nervous system disorders</b>			
<b>Dizziness</b>			
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	
<b>Headache</b>			
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	
<b>Blood and lymphatic system disorders</b>			
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	
<b>Hyperhidrosis</b>			
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	
<b>Renal and urinary disorders</b>			
<b>Haematuria</b>			
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	
<b>Musculoskeletal and connective tissue disorders</b>			
<b>Muscle spasms</b>			
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	
<b>Pain in extremity</b>			
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	
<b>Infections and infestations</b>			
<b>Bacterial infection</b>			
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	
<b>Muscle abscess</b>			
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	
<b>Sepsis</b>			
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 %

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

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	
<b>Gastrointestinal disorders</b>			
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			

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

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	
<b>Infections and infestations</b>			
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	
<b>Metabolism and nutrition disorders</b>			
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"><li>• 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 <math>\geq 150,000/\mu\text{L}</math> which must be confirmed at 48 hours after the initial reporting of platelet recovery <math>\geq 150,000/\mu\text{L}</math> by a de novo measure of platelets <math>\geq 150,000/\mu\text{L}</math> and <math>\text{LDH} \leq 2 \times \text{ULN}</math>'),</li><li>• adding 2 exclusion criteria (known hypersensitivity to the active substance or to excipients of the study drug and severe liver impairment),</li><li>• adjustment of time points for ECG measurements during the treatment phase</li><li>• adding a paragraph on participation in concurrent clinical studies,</li><li>• 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.</li></ul>
05 April 2011	<p>Protocol Version 5.0 dated 05 Apr 2011 - main changes:</p> <ul style="list-style-type: none"><li>• 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'),</li><li>• 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</li><li>• 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)</li><li>• 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).</li><li>• In case the FVIII:C assay was not available at the local laboratory, it could be replaced by an alternative method.</li></ul>
21 October 2011	<p>Protocol Version 8.0 dated 21-Oct-2011 - main changes:</p> <ul style="list-style-type: none"><li>• clarify wording on endpoints (i.e., add the words 'confirmed platelet response' to the primary endpoint description and rewording of secondary/tertiary endpoints),</li><li>• add an exclusion criterion to exclude severe chronic renal impairment,</li><li>• change the dosing schedule (dose increase based on local RICO measurements is no longer included),</li><li>• to delete local RICO measurements from the schedule of assessments,</li><li>• 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])</li><li>• delete the PK/PD substudy (resulting in an adjustment of the PK/PD sampling schedule),</li><li>• change the duration of hospitalisation,</li><li>• 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).</li></ul>

25 September 2012	<p>Protocol Version 10.0 dated 25-Sep-2012 - main changes:</p> <ul style="list-style-type: none"> <li>• 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 <math>\geq 1</math> day but <math>\leq 30</math> 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')</li> <li>• 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</li> <li>• to add more details on the planned statistical analysis</li> <li>• to add clarifications/specifications in several sections</li> <li>• the vWF multimers test was no longer to be performed</li> </ul>
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"> <li>• opening of the study to adolescents (12 to &lt; 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.</li> </ul>
24 June 2013	<p>Protocol Version 12.0 dated 24 Jun 2013:</p> <ul style="list-style-type: none"> <li>• revising the protocol to allow enrolment of subjects who have received one prior PE (within an acceptable time frame).</li> </ul> <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: