Clinical trial results:
A Phase III double-blind, randomized, parallel group, multicenter placebo-controlled trial to study the efficacy and safety of caplacizumab in patients with acquired thrombotic thrombocytopenic purpura.

Summary

EudraCT number	2015-001098-42
Trial protocol	BE CZ ES AT DE HU NL Outside EU/EEA IT
Global end of trial date	16 August 2017

Results information

Result version number	v1 (current)
This version publication date	30 August 2018
First version publication date	20 July 2018

Trial information

Trial identification

Sponsor protocol code	ALX0681-C301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02553317
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ablynx
Sponsor organisation address	Technologiepark 21, Zwijnaarde, Belgium, 9052
Public contact	Medical Monitor, Ablynx, 32 (0)9 262 00 00 , clinicaltrials@ablynx.com
Scientific contact	Medical Monitor, Ablynx, 32 (0)9 262 00 00 , clinicaltrials@ablynx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-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	20 September 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 August 2017
Global end of trial reached?	Yes
Global end of trial date	16 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy of caplacizumab in more rapidly restoring normal platelet counts as measure of prevention of further microvascular thrombosis.

Protection of trial subjects:

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

Background therapy:

- Plasma exchange (PE) with plasma (e.g., fresh frozen plasma, solvent detergent/viral-inactivated plasma, cryosupernatant) at 1 to 1.5x estimated plasma volume daily. Once the platelet count was ≥ 150,000/µL, daily PE had to continue for at least 2 days. Tapering of PE after platelet count normalization, defined as reducing its frequency to less than once per day, was strongly discouraged and, if considered, had to be discussed with the Medical Monitor.
- Corticosteroid treatment was to be given at a dose of at least 1 mg/kg/day during daily PE and continued for the first week after the end of daily PE. Afterwards, corticosteroids could be tapered at the discretion of the Investigator, with the aim of being corticosteroid-free by Day 30 after stop of daily PE as clinically indicated. Other immunosuppressive treatment (e.g. rituximab) was permitted, per standard site practice.

Evidence for comparator:

not applicable

Actual start date of recruitment	19 November 2015
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	Netherlands: 1
Country: Number of subjects enrolled	Spain: 14
Country: Number of subjects enrolled	United Kingdom: 21
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Canada: 13

Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	United States: 32
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Italy: 10
Worldwide total number of subjects	145
EEA total number of subjects	81

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)	133
From 65 to 84 years	12
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 145 subjects was randomized at 55 sites located in Europe (34 sites; 91 subjects), Asia (4 sites, 6 subjects), Australia (3 sites, 3 subjects), and North America (14 sites; 45 subjects). Consent was obtained from the first subject on 19 Nov 2015; the last subject completed the final visit on 16 Aug 2017.

Pre-assignment

Screening details:

Of the 149 subjects screened, 4 were screen failures and 145 were randomly assigned to treatment (Intent-to-treat [ITT] population). All, except for 1 subject, received study drug and were included in the safety population and in the modified ITT (mITT) population.

Period 1

Period 1 title	Overall Study Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Study drug treatment allocation was double-blind (DB). In case of a recurrence (i.e., defined as recurrent thrombocytopenia after initial recovery of platelet count requiring re-initiation of daily PE, occurring during the post-daily PE treatment period), subjects received open-label (OL) caplacizumab together with daily PE, irrespective of the initial treatment allocation. The blind for the initial treatment allocation was not broken.

Arms

Are arms mutually exclusive?	Yes
Arm title	Caplacizumab

Arm description:

Caplacizumab 10 mg once daily

Arm type	Experimental
Investigational medicinal product name	Caplacizumab
Investigational medicinal product code	ALX-0081
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

- First day of treatment: 10 mg intravenous injection prior to plasma exchange followed by a 10 mg subcutaneous injection (in the abdominal region) after completion of plasma exchange on that day.
- Subsequent days of treatment during plasma exchange: daily 10 mg subcutaneous injection (in the abdominal region) following plasma exchange
- Treatment after plasma exchange period: daily 10 mg subcutaneous injections for 30 days. If the underlying immunological disease was not resolved, treatment could be extended for a maximum of 4 additional 1-week periods (i.e., 28 days) and was to be accompanied by optimization of immunosuppression.

Arm title	Placebo

Arm description:

Placebo once daily

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use, Subcutaneous use

Dosage and administration details:

- First day of treatment: intravenous injection prior to plasma exchange followed by a subcutaneous injection after completion of plasma exchange on that day.
- Subsequent days of treatment during plasma exchange: daily subcutaneous injection following plasma exchange
- Treatment after plasma exchange period: daily subcutaneous injections for 30 days. If the underlying immunological disease was not resolved, treatment could be extended for a maximum of 4 additional 1-week periods (i.e., 28 days) and was to be accompanied by optimization of immunosuppression.

Number of subjects in period 1	Caplacizumab	Placebo
Started	72	73
Completed	58	50
Not completed	14	23
Adverse event, serious fatal	1	3
Consent withdrawn by subject	4	5
Physician decision	2	4
Adverse event, non-fatal	6	5
Consent withdrawn by legal representative	-	1
Other	1	3
Non-compliance with study drug	-	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Caplacizumab
Reporting group description: Caplacizumab 10 mg once daily	
Reporting group title	Placebo
Reporting group description: Placebo once daily	

Reporting group values	Caplacizumab	Placebo	Total
Number of subjects	72	73	145
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	68	65	133
From 65-84 years	4	8	12
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	44.9	47.3	
standard deviation	± 13.46	± 14.07	-
Gender categorical Units: Subjects			
Female	49	51	100
Male	23	22	45

End points

End points reporting groups

Reporting group title	Caplacizumab
Reporting group description: Caplacizumab 10 mg once daily	
Reporting group title	Placebo
Reporting group description: Placebo once daily	

Primary: Time to platelet count response

End point title	Time to platelet count response

End point description:

Platelet count response was defined as initial platelet count ≥ 150,000/µL with subsequent stop of daily PE within 5 days. It refers to the first time both conditions, platelet count ≥ 150,000/µL and the stop of daily PE within 5 days, were met.
There was a statistically significant reduction in time to confirmed platelet response in the DB caplacizumab group, compared to the DB placebo group based on the Kaplan-Meier (KM) analysis and a stratified log-rank test (p = 0.0099). This was confirmed by a hazard, or platelet count normalization rate, ratio (95% CI) for the DB caplacizumab group versus the DB placebo group of 1.55 (1.095; 2.195) based on a Cox proportional hazards model. This means that at any given time point, subjects treated with caplacizumab were 1.55 times more likely to achieve platelet count response compared to subjects treated with placebo.

End point type	Primary

End point timeframe:

Only data from the double blind daily PE period up to the cut-off point were used. The cut-off point was defined by, whichever occurred first:
- 45 days of daily PE after the start of study drug
- the stop of daily PE
- the stop of study drug treatment

End point values	Caplacizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[1]	73[2]		
Units: day				
median (confidence interval 95%)	2.69 (1.89 to 2.83)	2.88 (2.68 to 3.56)		

Notes:

[1] - Intent-to-treat population (for the respective study period)

[2] - Intent-to-treat population (for the respective study period)

Attachments (see zip file)	Time to platelet count response figures/Figures primary

Statistical analyses

Statistical analysis title	stratified log-rank test

Statistical analysis description:

Time to platelet count response in the caplacizumab arm and placebo arm was compared by conducting a two-sided stratified log-rank test based on a KM analysis, with severity of neurological involvement

(according to the Glasgow coma scale [GCS] category, stratification factor used in randomization: ≤12 / 13-15) as stratification factor. The resulting p-value was compared with a significance level of 5%.

Comparison groups	Caplacizumab v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0099
Method	Logrank

Statistical analysis title	Cox proportional hazard model

Statistical analysis description:

Time to platelet count response was analyzed using a Cox proportional hazards regression model with time to platelet count response as dependent variable, and treatment group and GCS category as independent variables. The hazard (or platelet count normalization rate) ratio from the Cox model was reported along with 95% CI.

Comparison groups	Caplacizumab v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.095
upper limit	2.195

Secondary: Proportion of subjects with TTP-Related Death, Recurrence of TTP, or a Major Thromboembolic Event During the Study Drug Treatment Period

End point title	Proportion of subjects with TTP-Related Death, Recurrence of TTP, or a Major Thromboembolic Event During the Study Drug Treatment Period

End point description:

The proportion of subjects with TTP-related death, a recurrence of TTP, or at least one treatment-emergent major thromboembolic event in the ITT population (i.e., the first key secondary endpoint).

End point type	Secondary

End point timeframe:

The study drug treatment period. For both treatment groups, only events that occurred prior to a switch to open-label caplacizumab were evaluated for this analysis.

End point values	Caplacizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[3]	73[4]		
Units: percent	13	49		

Notes:

[3] - Intent-to-treat population (for the respective study period)

[4] - Intent-to-treat population (for the respective study period)

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel (CMH) test

Statistical analysis description:

A Cochran-Mantel-Haenszel (CMH) test was conducted with adjustment for GCS category (stratification factor used in randomization).

Comparison groups	Caplacizumab v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel

Secondary: Proportion of subjects with a recurrence of TTP in the Overall Study Period

End point title	Proportion of subjects with a recurrence of TTP in the Overall Study Period

End point description:

The proportion of subjects with a recurrence of TTP during the overall study period (i.e., including follow-up [FU]) (i.e., the second key secondary endpoint).

End point type	Secondary

End point timeframe:

The overall study period (covers both the overall treatment period and the follow-up period)

End point values	Caplacizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[5]	73[6]		
Units: percent	13	38		

Notes:

[5] - Intent-to-treat population (for the respective study period)

[6] - Intent-to-treat population (for the respective study period)

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel (CMH) test

Statistical analysis description:

A CMH test was conducted with adjustment for GCS category (stratification factor used in randomization).

Comparison groups	Caplacizumab v Placebo

Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	Cochran-Mantel-Haenszel

Secondary: The proportion of subjects with refractory disease

End point title	The proportion of subjects with refractory disease

End point description:

Proportion of subjects with refractory TTP, defined as absence of platelet count doubling after 4 days of standard treatment, and lactate dehydrogenase (LDH) > upper limit of normal (ULN) (i.e., the third key secondary endpoint).

End point type	Secondary

End point timeframe:

The study drug treatment period

End point values	Caplacizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[7]	73[8]		
Units: percent	0	4		

Notes:

[7] - Intent-to-treat population (for the respective study period)

[8] - Intent-to-treat population (for the respective study period)

Statistical analyses

Statistical analysis title	Cochran-Mantel-Haenszel (CMH) test

Statistical analysis description:

A CMH test was conducted with adjustment for GCS category (stratification factor used in randomization).

Comparison groups	Caplacizumab v Placebo
Number of subjects included in analysis	144
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0572
Method	Cochran-Mantel-Haenszel

Secondary: Time to normalization of organ damage marker levels

End point title	Time to normalization of organ damage marker levels

End point description:

Time to first normalization of LDH, cardiac troponin I (cTnI) and serum creatinine was defined as: first time of LDH ≤ ULN and cTnI ≤ ULN and serum creatinine ≤ ULN - time of first i.v. loading dose of study drug after randomization + 1 minute. Subjects in either initial treatment group who switched to open-label caplacizumab before having reached the endpoint were censored at time of switch.
Of note, the key secondary endpoints were hierarchically ordered to allow statistical testing for these endpoints at the same nominal significance level of 5% without adjustment, as long as the tests

occurred in the pre-defined sequential order, and given that all null hypotheses tested for endpoints with a higher rank (including the primary endpoint) were rejected. No confirmatory testing was done for this fourth key secondary endpoint, as the statistical test was not significant for the proportion of subjects with refractory disease (i.e., the third key secondary endpoint).

End point type	Secondary

End point timeframe:

Overall study period (excluding the open-label period)

End point values	Caplacizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[9]	66[10]		
Units: day				
median (confidence interval 95%)	2.86 (1.93 to 3.86)	3.36 (1.88 to 7.71)		

Notes:

[9] - Intent-to-treat population (for the respective study period) with biomarker level data available

[10] - Intent-to-treat population (for the respective study period) with biomarker level data available

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of days of plasma exchange

End point title	Number of days of plasma exchange

End point description:

The number of days of plasma exchange (PE) during the overall study drug treatment period, including the number of days of PE during the open-label study drug treatment period. Data were analyzed according to the initial treatment allocation (both before and after switch to open-label caplacizumab).

End point type	Other pre-specified

End point timeframe:

Overall study drug treatment period

End point values	Caplacizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[11]	73[12]		
Units: day				
arithmetic mean (standard error)	5.8 (± 0.51)	9.4 (± 0.81)		

Notes:

[11] - Intent-to-treat population (for the respective study period)

[12] - Intent-to-treat population (for the respective study period)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Total volume of plasma exchange

End point title	Total volume of plasma exchange

End point description:

The total volume of plasma exchange (PE) during the overall study drug treatment Period, including the total volume of PE during the open-label study drug treatment period. Data were analyzed according to the initial treatment allocation (both before and after switch to open-label caplacizumab).

End point type	Other pre-specified

End point timeframe:

Overall study drug treatment period

End point values	Caplacizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[13]	73[14]		
Units: litre(s)				
arithmetic mean (standard error)	21.33 (± 1.619)	35.93 (± 4.169)		

Notes:

[13] - Intent-to-treat population (for the respective study period)

[14] - Intent-to-treat population (for the respective study period)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of days in intensive care unit

End point title	Number of days in intensive care unit

End point description:

The number of days in intensive care unit (ICU) during the overall study drug treatment period, including the number of days in ICU during the open-label study drug treatment period. Data were analyzed according to the initial treatment allocation (both before and after switch to open-label caplacizumab).

End point type	Other pre-specified

End point timeframe:

Overall study drug treatment period

End point values	Caplacizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[15]	73[16]		
Units: day				
arithmetic mean (standard error)	3.4 (± 0.40)	9.7 (± 2.12)		

Notes:

[15] - Intent-to-treat population (for the respective study period)

[16] - Intent-to-treat population (for the respective study period)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Number of days in hospital

End point title	Number of days in hospital

End point description:

The number of days in hospital during the overall study drug treatment period, including the number of days in hospital during the open-label study drug treatment period. Data were analyzed according to the initial treatment allocation (both before and after switch to open-label caplacizumab).

End point type	Other pre-specified

End point timeframe:

Overall study drug treatment period

End point values	Caplacizumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71[17]	73[18]		
Units: day				
arithmetic mean (standard error)	9.9 (± 0.70)	14.4 (± 1.22)		

Notes:

[17] - Intent-to-treat population (for the respective study period)

[18] - Intent-to-treat population (for the respective study period)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From time of first study drug administration until the subject's study completion/discontinuation date.

Adverse event reporting additional description:

Double Blind Caplacizumab/Double Blind placebo groups (subjects randomized to capacizumab/placebo, respectively): AEs starting in the DB or FU Periods for subjects with no OL Period. Only AEs starting in the DB Period for subjects with an OL Period
OL Caplacizumab group (all subjects with OL Period): AEs starting in the OL or FU Periods

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Double-blind Caplacizumab

Reporting group description:

Caplacizumab 10 mg once daily

Reporting group title	Double-blind Placebo

Reporting group description:

Placebo once daily

Reporting group title	Open-label Caplacizumab

Reporting group description:

In case of recurrence: open-label caplacizumab 10 mg once daily

Serious adverse events	Double-blind Caplacizumab	Double-blind Placebo	Open-label Caplacizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 71 (39.44%)	39 / 73 (53.42%)	7 / 28 (25.00%)
number of deaths (all causes)	1	3	0
number of deaths resulting from adverse events	1	3	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jugular vein thrombosis			
subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Serum sickness			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic ovarian cyst			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	4 / 71 (5.63%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia	Additional description: Verbatim term of SAE with fatal outcome : Hypoxia with bleeding into the lung		
subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory failure			

subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 71 (0.00%)	0 / 73 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic transfusion reaction			
subjects affected / exposed	0 / 71 (0.00%)	3 / 73 (4.11%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Myocardial infarction			

subjects affected / exposed	1 / 71 (1.41%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriospasm coronary			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 71 (2.82%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia	Additional description: verbatim term of SAE with fatal outcome: cerebral ischemia		
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic transformation stroke	Additional description: Verbatim term of SAE with fatal outcome: worsened massive ischemic stroke with hemorrhagic transformation		

subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 71 (0.00%)	0 / 73 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Thrombotic thrombocytopenic purpura	Additional description: Verbatim term of SAE with fatal outcome: worsening thrombotic thrombocytopenic purpura (TTP) with coma and death		
subjects affected / exposed	9 / 71 (12.68%)	29 / 73 (39.73%)	4 / 28 (14.29%)
occurrences causally related to treatment / all	0 / 9	2 / 29	0 / 4
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Thrombotic microangiopathy			
subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gingival bleeding			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal necrosis			
subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal ischaemia			
subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder necrosis			

subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash erythematous			
subjects affected / exposed	0 / 71 (0.00%)	0 / 73 (0.00%)	1 / 28 (3.57%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthropathy			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Septic shock	Additional description: verbatim term of SAE with fatal outcome: septic shock		
subjects affected / exposed	0 / 71 (0.00%)	2 / 73 (2.74%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Bacteraemia			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related sepsis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Double-blind Caplacizumab	Double-blind Placebo	Open-label Caplacizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	67 / 71 (94.37%)	65 / 73 (89.04%)	25 / 28 (89.29%)
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 71 (5.63%)	8 / 73 (10.96%)	1 / 28 (3.57%)
occurrences (all)	4	8	1
Haematoma			
subjects affected / exposed	3 / 71 (4.23%)	2 / 73 (2.74%)	2 / 28 (7.14%)
occurrences (all)	7	2	2
Hypotension			
subjects affected / exposed	4 / 71 (5.63%)	2 / 73 (2.74%)	1 / 28 (3.57%)
occurrences (all)	4	3	1
Hot flush			
subjects affected / exposed	0 / 71 (0.00%)	0 / 73 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
General disorders and administration site conditions			
Catheter site haemorrhage			
subjects affected / exposed	5 / 71 (7.04%)	5 / 73 (6.85%)	8 / 28 (28.57%)
occurrences (all)	6	5	10
Fatigue			
subjects affected / exposed	10 / 71 (14.08%)	6 / 73 (8.22%)	2 / 28 (7.14%)
occurrences (all)	10	6	2
Pyrexia			
subjects affected / exposed	10 / 71 (14.08%)	6 / 73 (8.22%)	1 / 28 (3.57%)
occurrences (all)	12	6	1
Oedema peripheral			
subjects affected / exposed	4 / 71 (5.63%)	7 / 73 (9.59%)	1 / 28 (3.57%)
occurrences (all)	4	8	2
Asthenia			

subjects affected / exposed	2 / 71 (2.82%)	4 / 73 (5.48%)	2 / 28 (7.14%)
occurrences (all)	3	4	3
Chest pain			
subjects affected / exposed	1 / 71 (1.41%)	5 / 73 (6.85%)	1 / 28 (3.57%)
occurrences (all)	1	6	1
Catheter site pain			
subjects affected / exposed	1 / 71 (1.41%)	5 / 73 (6.85%)	0 / 28 (0.00%)
occurrences (all)	1	5	0
Injection site pain			
subjects affected / exposed	1 / 71 (1.41%)	4 / 73 (5.48%)	1 / 28 (3.57%)
occurrences (all)	1	4	1
Pain			
subjects affected / exposed	4 / 71 (5.63%)	1 / 73 (1.37%)	0 / 28 (0.00%)
occurrences (all)	7	1	0
Injection site haematoma			
subjects affected / exposed	1 / 71 (1.41%)	3 / 73 (4.11%)	2 / 28 (7.14%)
occurrences (all)	1	4	2
Injection site erythema			
subjects affected / exposed	1 / 71 (1.41%)	1 / 73 (1.37%)	2 / 28 (7.14%)
occurrences (all)	1	1	4
Injection site pruritus			
subjects affected / exposed	2 / 71 (2.82%)	0 / 73 (0.00%)	2 / 28 (7.14%)
occurrences (all)	2	0	2
Injection site reaction			
subjects affected / exposed	1 / 71 (1.41%)	0 / 73 (0.00%)	2 / 28 (7.14%)
occurrences (all)	1	0	2
Face oedema			
subjects affected / exposed	0 / 71 (0.00%)	0 / 73 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	4 / 71 (5.63%)	2 / 73 (2.74%)	1 / 28 (3.57%)
occurrences (all)	5	2	1
Respiratory, thoracic and mediastinal disorders			

Epistaxis			
subjects affected / exposed	21 / 71 (29.58%)	2 / 73 (2.74%)	5 / 28 (17.86%)
occurrences (all)	32	2	5
Dyspnoea			
subjects affected / exposed	7 / 71 (9.86%)	2 / 73 (2.74%)	2 / 28 (7.14%)
occurrences (all)	10	2	2
Psychiatric disorders			
Insomnia			
subjects affected / exposed	6 / 71 (8.45%)	8 / 73 (10.96%)	0 / 28 (0.00%)
occurrences (all)	7	8	0
Anxiety			
subjects affected / exposed	4 / 71 (5.63%)	6 / 73 (8.22%)	1 / 28 (3.57%)
occurrences (all)	4	6	1
Agitation			
subjects affected / exposed	5 / 71 (7.04%)	4 / 73 (5.48%)	0 / 28 (0.00%)
occurrences (all)	6	4	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 71 (0.00%)	1 / 73 (1.37%)	2 / 28 (7.14%)
occurrences (all)	0	1	2
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	5 / 71 (7.04%)	10 / 73 (13.70%)	2 / 28 (7.14%)
occurrences (all)	7	24	10
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	4 / 71 (5.63%)	3 / 73 (4.11%)	1 / 28 (3.57%)
occurrences (all)	4	5	4
Tachycardia			
subjects affected / exposed	2 / 71 (2.82%)	4 / 73 (5.48%)	1 / 28 (3.57%)
occurrences (all)	2	4	1
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 71 (19.72%)	6 / 73 (8.22%)	6 / 28 (21.43%)
occurrences (all)	18	10	6
Dizziness			

subjects affected / exposed	7 / 71 (9.86%)	8 / 73 (10.96%)	2 / 28 (7.14%)
occurrences (all)	8	8	3
Paraesthesia			
subjects affected / exposed	8 / 71 (11.27%)	6 / 73 (8.22%)	0 / 28 (0.00%)
occurrences (all)	9	6	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 71 (5.63%)	6 / 73 (8.22%)	4 / 28 (14.29%)
occurrences (all)	4	9	8
Eye disorders			
Vision blurred			
subjects affected / exposed	5 / 71 (7.04%)	5 / 73 (6.85%)	0 / 28 (0.00%)
occurrences (all)	6	5	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	10 / 71 (14.08%)	7 / 73 (9.59%)	2 / 28 (7.14%)
occurrences (all)	12	8	2
Gingival bleeding			
subjects affected / exposed	12 / 71 (16.90%)	1 / 73 (1.37%)	4 / 28 (14.29%)
occurrences (all)	13	1	5
Constipation			
subjects affected / exposed	7 / 71 (9.86%)	5 / 73 (6.85%)	4 / 28 (14.29%)
occurrences (all)	7	6	6
Diarrhoea			
subjects affected / exposed	7 / 71 (9.86%)	5 / 73 (6.85%)	4 / 28 (14.29%)
occurrences (all)	7	5	7
Abdominal pain			
subjects affected / exposed	5 / 71 (7.04%)	4 / 73 (5.48%)	2 / 28 (7.14%)
occurrences (all)	5	4	4
Vomiting			
subjects affected / exposed	3 / 71 (4.23%)	4 / 73 (5.48%)	2 / 28 (7.14%)
occurrences (all)	3	5	2
Abdominal pain upper			
subjects affected / exposed	1 / 71 (1.41%)	1 / 73 (1.37%)	4 / 28 (14.29%)
occurrences (all)	1	1	8
Dyspepsia			

subjects affected / exposed	2 / 71 (2.82%)	1 / 73 (1.37%)	2 / 28 (7.14%)
occurrences (all)	2	1	2
Haematochezia			
subjects affected / exposed	2 / 71 (2.82%)	0 / 73 (0.00%)	2 / 28 (7.14%)
occurrences (all)	5	0	2
Lip haemorrhage			
subjects affected / exposed	0 / 71 (0.00%)	0 / 73 (0.00%)	2 / 28 (7.14%)
occurrences (all)	0	0	2
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	12 / 71 (16.90%)	5 / 73 (6.85%)	1 / 28 (3.57%)
occurrences (all)	14	8	1
Rash			
subjects affected / exposed	5 / 71 (7.04%)	9 / 73 (12.33%)	4 / 28 (14.29%)
occurrences (all)	6	11	4
Pruritus			
subjects affected / exposed	5 / 71 (7.04%)	6 / 73 (8.22%)	2 / 28 (7.14%)
occurrences (all)	6	6	4
Petechiae			
subjects affected / exposed	4 / 71 (5.63%)	5 / 73 (6.85%)	3 / 28 (10.71%)
occurrences (all)	4	5	5
Ecchymosis			
subjects affected / exposed	2 / 71 (2.82%)	4 / 73 (5.48%)	3 / 28 (10.71%)
occurrences (all)	2	4	3
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	5 / 71 (7.04%)	2 / 73 (2.74%)	2 / 28 (7.14%)
occurrences (all)	7	2	2
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	4 / 71 (5.63%)	6 / 73 (8.22%)	0 / 28 (0.00%)
occurrences (all)	5	7	0
Arthralgia			
subjects affected / exposed	4 / 71 (5.63%)	3 / 73 (4.11%)	3 / 28 (10.71%)
occurrences (all)	4	3	4
Back pain			

subjects affected / exposed	5 / 71 (7.04%)	3 / 73 (4.11%)	1 / 28 (3.57%)
occurrences (all)	5	3	1
Muscular weakness			
subjects affected / exposed	4 / 71 (5.63%)	2 / 73 (2.74%)	0 / 28 (0.00%)
occurrences (all)	5	2	0
Myalgia			
subjects affected / exposed	2 / 71 (2.82%)	1 / 73 (1.37%)	2 / 28 (7.14%)
occurrences (all)	2	1	3
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 71 (5.63%)	4 / 73 (5.48%)	0 / 28 (0.00%)
occurrences (all)	4	4	0
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 71 (5.63%)	0 / 73 (0.00%)	0 / 28 (0.00%)
occurrences (all)	4	0	0
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	6 / 71 (8.45%)	14 / 73 (19.18%)	2 / 28 (7.14%)
occurrences (all)	6	15	2
Hyperglycaemia			
subjects affected / exposed	4 / 71 (5.63%)	4 / 73 (5.48%)	1 / 28 (3.57%)
occurrences (all)	5	4	2
Hypocalcaemia			
subjects affected / exposed	1 / 71 (1.41%)	5 / 73 (6.85%)	2 / 28 (7.14%)
occurrences (all)	1	8	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 April 2016	The main reason for the first protocol amendment was rewording and reordering of key and other secondary endpoints in view of hierarchical statistical testing for the key secondary endpoints. In addition, the interim analysis of efficacy was removed and the description of analysis of key secondary endpoints was updated to reflect the hierarchical testing. The secondary objectives were reworded to correspond to the rewording of the secondary endpoints.
20 July 2016	The main reason for the second protocol amendment was to increase the planned sample size. The number of subjects planned to be included in the study was increased from 92 to 132 to account for a change in the assumed treatment difference for the primary endpoint in the sample size calculation, to account for drop-outs, and to increase the statistical power of the key secondary endpoint analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported