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# **STATISTICAL ANALYSIS PLAN**

## **ALX0681-C301**

**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.**

**Version: Final 1.1**

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**Protocol:**

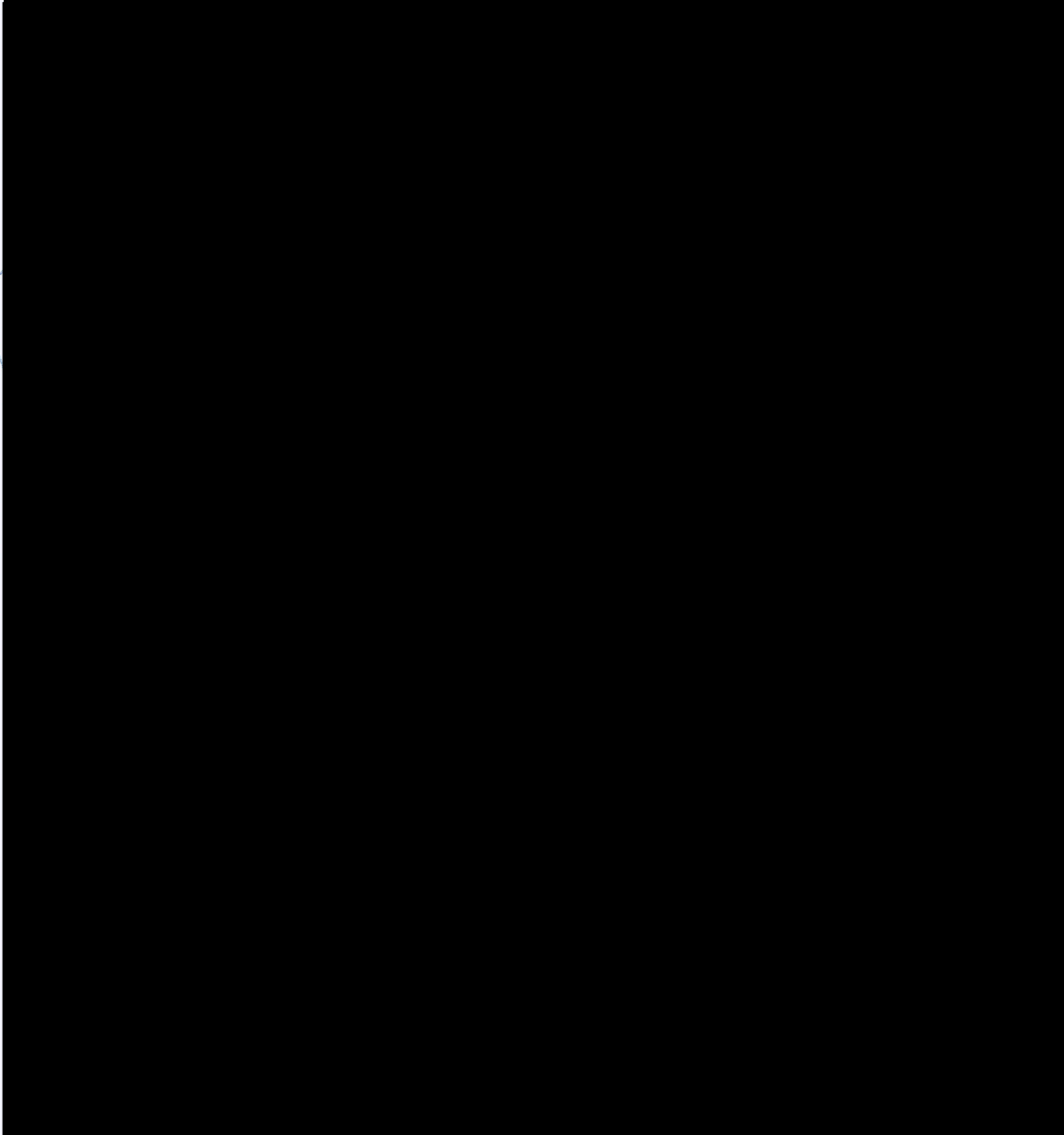
**ALX0681-C301 Final version 3.0 – Pediatric v 1.0 31 AUG 2016**



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**SIGNATURE PAGE**

The undersigned agree to the content outlined in this Statistical Analysis Plan.





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## LIST OF ABBREVIATIONS

Ab	Antibody
ADA	Anti-drug antibody
ADaM	Analysis data model
ADAMTS13	A disintegrin-like and metalloprotease with thrombospondin repeats 13
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical classification system
AUC	Area under the curve
BQL	Below quantification limit
BMI	Body mass index
BUN	Blood urea nitrogen
CDR	Complementarity-determining region
CI	Confidence interval
cm	centimeter
CRF	Case report form
CRP	C-reactive protein
CSP	Clinical study protocol
CTCAE	Common terminology criteria for adverse events
cTnl	Cardiac troponin I
CV	Coefficient of variation
DB	Double-blind
DBP	Diastolic blood pressure
dPE	Daily Plasma Exchange
DSMB	Data safety monitoring board
DVT	Deep venous thrombosis
DY	Day
E	Number of subjects exposed
ECG	Electrocardiogram
FVIII	Coagulation factor VIII
FVIII:C	FVIII clotting activity
GCS	Glasgow coma scale
GI	Gastrointestinal
H	High
HIV	Human immune deficiency virus
ICF	Informed consent form
ICU	Intensive care unit
INF	Infinity



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INR	International normalized ratio
ITT	Intent-to-treat
i.v.	Intravenous(ly)
kg	kilogram
L	Low
LDA	Low disease activity
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
m	meter
mADA	Modified anti-drug antibody
MCMC	Markov Chain Monte Carlo
MedDRA	Medical dictionary for regulatory activities
mg	milligram
MI	Multiple Imputation
mL	milliliter
MRD	Minimal required dilution
N	Normal / No
NAb	Neutralizing antibody
NC	Not calculated
NR	No result
OL	Open-label
PD	Pharmacodynamics
PE	Plasma exchange
PK	Pharmacokinetics
PP	Per protocol
RICO	Ristocetin cofactor
SAE	Serious adverse event
SBP	Systolic blood pressure
s.c.	Subcutaneous(ly)
SD	Standard deviation
SDTM	Standard data tabulation method
SE	Standard error
SI	Standard international
SMMSE	Standardized mini mental state examination
SMQ	Standardized MedDRA query
SOP	Standard operating procedure
TB	Tuberculosis
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
TTP	Thrombotic thrombocytopenic purpura
ULN	Upper limit of normal range
ULvWF	Ultra large von Willebrand factor
vWF	von Willebrand factor



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Y	Yes
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## CHANGES COMPARED TO PREVIOUS VERSION

<b>Version 1.1 (dated 14 September 2017) compared to Version 1.0 (dated 07 August 2017).</b>	
The statistical analysis plan version number and date were updated throughout the document (including headers and footers). The List of Figures and List of Tables were updated. The section titled : "Changes Compared to Previous Version (s)" was completed.	
Section(s) affected by updates	Change/Rationale
Section 7.1.2	The following wording was added as a clarification to table on TEAE leading to drug withdrawal and drug interruption: "TEAEs leading to study drug withdrawal and TEAEs leading to study drug interruption will be summarized separately and combined for each treatment group".
Section 9.1.2	The following sentence was added as a clarification for figures: "These positive samples (for which no titration could be done) should be plotted as log(MRD) equal to 0.36 in the figure."
Table 14.2.1.1.1, 14.2.1.1.3, 14.2.1.1.7, 14.2.1.1.9	The hazard ratio (including CI) of the corresponding Cox proportional hazards model has been included in the table.
Table 14.2.1.8.4	Population of table updated
Figure 14.2.1.1.4	New figure added: -Platelet count - Sensitivity: Time to platelet count response (ITT - Constrained response definition)
Others	Typographical errors were fixed in a few places in the document.



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## 1 INTRODUCTION

This statistical analysis plan (SAP) contains a more technical and detailed elaboration of the principal features of the analysis described in the clinical study protocol (CSP) for the ALX0681-C301 study, also referred to as the HERCULES study, and includes detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

Caplacizumab is being developed for treatment of acquired thrombotic thrombocytopenic purpura (TTP). TTP is a rare and potentially life-threatening thrombotic microangiopathy, in which accumulation of ULvWF multimers leads to an increased risk of thrombus formation in small blood vessels due to excessive platelet aggregation. Plasma exchange (PE) and immunosuppressive therapy is the standard of care treatment for acquired TTP.

A phase II trial provided evidence for the clinical efficacy of caplacizumab as potential treatment for patients with acquired TTP who were receiving standard of care therapy, with respect to reducing the time-to-response (based on confirmed recovery in platelet counts). In addition, a reduction of the incidence of exacerbations during treatment was observed. A post-hoc analysis to assess the impact of treatment with caplacizumab on the incidence of major thromboembolic events during the study drug treatment period and the incidence of TTP-related mortality during this study indicated that fewer caplacizumab-treated subjects experienced one or more major thromboembolic events or died during the study drug treatment period (11.4% *versus* 43.2% for placebo). These findings are expected to be predictive of tangible clinical benefits in terms of reduced mortality/morbidity. ALX0681-C301 is a phase III study designed to generate confirmatory evidence on the phase II findings. The higher incidence of relapse shortly after discontinuation of caplacizumab treatment was associated with persistent low ADAMTS13 activity (<10%), suggesting unresolved underlying auto-immune activity. The current study will also evaluate whether such patients would benefit from continuing treatment with caplacizumab for a longer period after discontinuation of PE.

While acquired TTP is much less common in the pediatric population than in adults, the clinical features of the disease and its management are similar. Thus, the potential benefit of treatment with caplacizumab is believed to be similar in both populations. The ALX0681-C301 study is open for recruitment of pediatric subjects.

## 2 STUDY OBJECTIVES

### 2.1 Primary objective

The primary objective of the study in adults, as defined in the protocol, is to evaluate efficacy of caplacizumab in more rapidly restoring normal platelet counts as measure of prevention of further microvascular thrombosis.



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## 2.2 Secondary objectives

The secondary objectives of the study in adults, as defined in the protocol, are to evaluate:

- the effect of study drug on a composite endpoint consisting of TTP-related mortality, recurrence of TTP and major thromboembolic events during study drug treatment
- the effect of study drug on prevention of recurrence of TTP over the entire study period
- the effect of study drug on refractoriness to treatment
- the effect of study drug on biomarkers of organ damage: lactate dehydrogenase (LDH), cardiac troponin I (cTnI), and serum creatinine
- the effect of study drug on PE parameters (days of PE and volume), days in intensive care unit (ICU), days in hospital
- adverse events (AEs)
- pharmacodynamic (PD) parameters: von Willebrand factor antigen (vWF:Ag), coagulation factor VIII clotting (FVIII:C) activity, ristocetin cofactor (RICO) activity
- pharmacokinetic (PK) parameters
- immunogenicity (anti-drug antibodies [ADA])

For pediatric subjects, the objective is to report the efficacy, safety, PK and PD properties and immunogenicity of caplacizumab in pediatric subjects experiencing an acute episode of acquired TTP.

## 3 STUDY DESIGN

### 3.1 Overall study design

This is a phase III, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of caplacizumab treatment when administered in addition to standard of care treatment (daily PE + corticosteroids) in subjects with an acute episode of acquired TTP. The study will evaluate the efficacy of caplacizumab in more rapidly restoring normal platelet counts and the effect of treatment with caplacizumab on a composite endpoint of TTP-related mortality, prevention of recurrence of the presenting TTP episode and prevention of major thromboembolic events during study drug treatment.

After confirmation of eligibility to study participation and after the start of PE treatment, 132 adults will be randomized in a ratio of 1:1 to either receive caplacizumab or placebo in addition to standard of care therapy. Randomization will be stratified by severity of neurological involvement (Glasgow coma scale [GCS]  $\leq 12$  vs. GCS=13-15). Stratification is foreseen to ensure balanced treatment arms for the key secondary endpoints related to neurological involvement and not for the primary endpoint for which the stratification parameter is not known to be relevant.

In addition, in specific centers that approved inclusion of these subjects, the study is open for recruitment of children (aged  $\geq 2$  to  $< 12$  years) and adolescents (aged  $\geq 12$  to  $< 18$  years) with

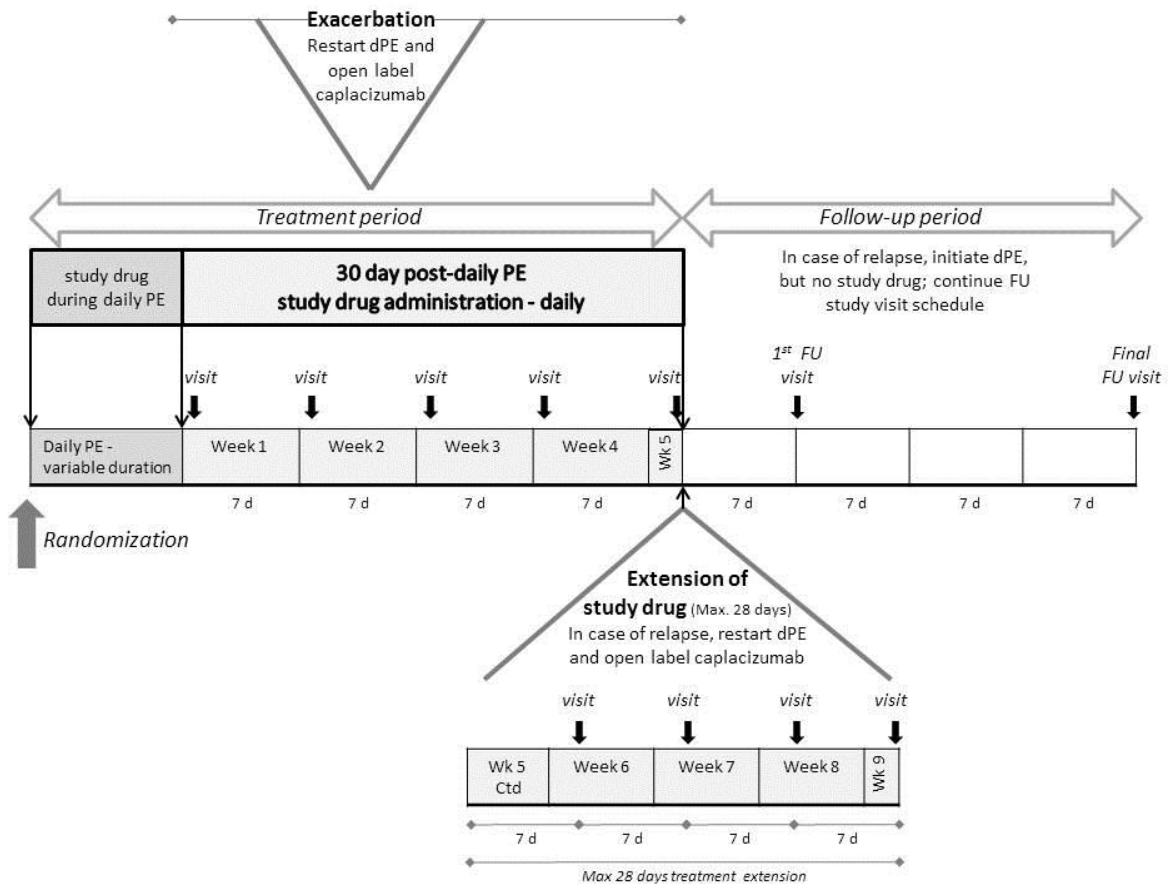


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acquired TTP, requiring treatment with PE. Potential enrollment of pediatric subjects will be stopped once the enrollment objective for adult subjects has been met.

After confirmation of eligibility to study participation and after the start of PE treatment, pediatric subjects will be allocated to open-label treatment with caplacizumab.

An overview of the study design is as follows (see also CSP Section 3.1.1 for more details):



Note: Randomization is not applicable for children and adolescents as they will be allocated to open-label treatment with caplacizumab.

The anticipated study duration per subject is approximately 2 months in case of no treatment extensions and no exacerbations, and up to approximately 6 months in case of treatment extension and exacerbation during the 30-days post-daily PE period or relapse during treatment extension. The end of the study is defined as the last visit of the last subject participating in the study.

The Schedule of Assessments can be found in [Appendix A: Schedule of Assessments](#).

### 3.2 Determination of sample size

The primary hypothesis of interest in this study is to test the superiority of caplacizumab compared to placebo with respect to the time to platelet count response (initial platelet count  $\geq 150 \times 10^9/L$  with subsequent stop of daily PE within 5 days). The required sample size is



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calculated to obtain a power of at least 80% to detect a significant reduction in time to platelet count response using a two-sided Log-rank test, at a significance level of 5%. The accrual period is taken to be 2.5 years and the time-to-event period is set at 45 days. An estimated reduction of time to platelet count response for subjects in the caplacizumab arm of 40% is assumed. With a median time to response in the placebo arm assumed to be 7 days, this would correspond with a median time to response in the caplacizumab arm of 4.2 days. In addition, an expected drop-out rate of 10% in the first 10 days after first administration of study drug is taken into account in the calculations. Based on these assumptions a total sample size of 132 subjects (121 events) will provide a power of 80%.

A total sample size of 132 subjects will also provide approximately 83% power to detect a 20% reduction in the first key secondary endpoint, using a two-sided chi-squared test with a large sample approximation and a 5% significance level. This assumes incidence rates of 30% and 10% in the placebo and caplacizumab arms, respectively.

### **3.3 Study endpoints**

This section mainly describes the endpoints defined for adult subjects.

The objective for the pediatric substudy is to report the efficacy, safety, PK and PD properties and immunogenicity of caplacizumab in pediatric subjects experiencing an acute episode of acquired TTP. In this sense the endpoints are partly similar to those of the adult population but the feasibility of any specific analysis will, to a large extent, depend upon the amount of available data (i.e., the number of pediatric patients included). In case the total number of patients in the pediatric group is smaller than 3, only listings but no summary tables will be created. Results for the pediatric substudy will be reported separately.

#### **3.3.1 Primary endpoint**

The primary endpoint of the study is: time to platelet count response. Platelet count response is defined as initial platelet count  $\geq 150 \times 10^9/L$  with subsequent stop of daily PE within 5 days.

#### **3.3.2 Secondary endpoints**

##### **3.3.2.1 Key secondary endpoints**

The key secondary endpoints are hierarchically ordered as listed below:

1. Proportion of subjects with TTP-related death, a recurrence of TTP, or at least one treatment-emergent major thromboembolic event during the study drug treatment period (including extensions).
2. Proportion of subjects with a recurrence of TTP in the overall study period (including the 4-week follow-up [FU] period).
3. Proportion of subjects with refractory TTP, defined as absence of platelet count doubling after 4 days of standard treatment, and LDH > upper limit of normal range (ULN).



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4. Time to normalization of all 3 of the following organ damage marker levels: LDH, cTnl, serum creatinine.

### 3.3.2.2 Other secondary endpoints

- Proportion of subjects with recurrences of TTP as well as the number of such events during study drug treatment (including extensions) and after study drug treatment.
- Proportion of subjects with treatment-emergent clinically significant TTP-related events, as well as the number of such events in the overall study period (including 4-week FU period). Clinically significant TTP-related events are defined as one of the following events:
  - Neurological
    - Defined as presence of coma, stupor, seizures, disorientation/confusion, hemiparesis/-plegia, focal deficit, agitation, and dysarthria (For more details see CSP Section 3.4.3.3)
  - Cardiovascular
    - Elevated cardiac troponins (value and local upper limit of reference range)
    - Acute myocardial infarction (ECG finding)
    - Conduction abnormality (ECG finding)
    - Repolarization abnormality (ECG finding)
    - Heart failure (severity)
    - Other (to be specified)
  - Exacerbation
  - On study-drug relapse
  - Post-study drug relapse
  - Death due to TTP
  - Other (to be specified)
- Area under the curve (AUC) of platelet count until Day 5, truncated at  $150 \times 10^9/L$  if platelet count is  $150 \times 10^9/L$  or above.
- Mortality rate during 4 analysis periods: double-blind (DB) treatment daily PE period, overall treatment period, follow-up (FU) period and overall study period.
- Organ damage markers: Time to LDH  $\leq 1 \times$  ULN
- Organ damage markers: Time to cTnl  $\leq 1 \times$  ULN
- Organ damage markers: Time to serum creatinine  $\leq 1 \times$  ULN
- Proportion of subjects with increases in organ damage markers (cTnl and serum creatinine) above  $1 \times$  ULN in 4 analysis periods: DB treatment daily PE period, overall treatment period, FU period and overall study period.



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- AUC of cTnI above 1 x ULN during DB treatment daily PE period and during overall treatment period.
- Proportion of subjects with neurological symptoms based on neurological assessment on Day 1, 2, 3, 4, 5 and on Weeks 1 and 5 of the 30-day post-daily PE treatment period, and the first and the final FU visit.
- Change from baseline in Standardized mini mental state examination (SMMSE) total score on Days 1, 2, 3, 4, 5 and on Weeks 1 and 5 of the 30-day post-daily PE treatment period, and on the first and the final FU visit. Where:
  - SMMSE: 30-point validated test used to examine the cognitive mental status of a subject. The SMMSE measures various domains of cognitive functions including orientation to time and place; registration; concentration; short-term memory; naming familiar items; repeating a common expression; and the ability to read and follow written instructions. The resulting total score is corrected for degree of schooling and age.
- Proportion of subjects with evidence of cardiac ischemia and/or arrhythmia/conduction abnormalities on Days 1, 2, 3, and 4, and Weeks 1 and 5 of 30-day post-daily PE treatment period, and the first and final FU visit.
- Proportion of subjects who have a platelet count  $\geq 150 \times 10^9/L$  on Day 1, 2, 3, 4, 5 and Day 10 and at end of study drug treatment (i.e., last weekly visit during the treatment period).
- Proportion of subjects with refractory TTP, defined according to Scully et al. (2016) as lack of sustained platelet count increment or platelet counts  $< 50 \times 10^9/L$  and persistently raised LDH ( $> 1.5 \times ULN$ ) despite 5 plasma exchanges and steroid treatment.
- Time to stop of daily PE.
- Bleeding events.
- (S)AEs, laboratory data, vital signs, ECG and physical examinations.
- PE parameters: number of days and total volume in 2 time periods, i.e. DB treatment daily PE period and overall treatment period.
- Number of days in ICU and in hospital in 4 time periods: DB treatment daily PE period, overall treatment period, FU period (of 4 weeks after stop of study treatment) and overall study period.
- PD parameters: vWF: Ag concentration, FVIII: C activity and RICO activity.
- PK parameters: study drug concentrations.
- Immunogenicity: ADA, mADA, NAb, and alternative NAb.

Note: The components of composite key secondary endpoints (both proportion of subjects and number of events) will also be analyzed separately as 'other secondary endpoint'.



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## 4 GENERAL ASPECTS FOR STATISTICAL ANALYSIS

### 4.1 Analysis populations

This section contains a description of analysis populations considered for analysis of data from adult subjects.

Data of pediatric subjects will be analyzed separately from data of adult subjects. Given the limited number of pediatric subjects expected to be enrolled, and as all pediatric subjects will be enrolled in an open-label caplacizumab arm, the data will be analyzed descriptively, and no comparisons can be made or inferential statistics performed.

#### 4.1.1 *All screened subjects population*

All subjects who signed an informed consent form.

#### 4.1.2 *Intent-to-treat population*

All subjects who were randomized. The intent-to-treat (ITT) population will be used for general outputs and for main efficacy analysis.

#### 4.1.3 *Modified intent-to-treat population*

All randomized subjects who received at least 1 administration of study drug, as randomized (cfr. Section 4.3.5). The modified ITT (mITT) population will be used for selected (sensitivity) analysis of efficacy.

#### 4.1.4 *Per protocol population*

The per protocol (PP) population is a subpopulation of the ITT population, excluding those subjects who have had a major protocol deviation.

#### 4.1.5 *Safety population*

All subjects who received at least 1 administration of study drug, as treated (cfr. Section 4.3.5). The safety population will be used for analysis of safety, PK, PD, disease markers, and immunogenicity data.

#### 4.1.6 *Open-label Caplacizumab population*

All subjects who received at least 1 administration of open-label study drug. The open-label Caplacizumab (OL Caplacizumab) population will be used in cases where a separate analysis of open-label period is performed.





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## 4.2 General Methods

### 4.2.1 Calculation of descriptive statistics

For continuous parameters, descriptive statistics will be presented when  $n \geq 2$ . When  $n=1$ , only sample size ( $n$ ) and mean, i.e. the value itself, are shown. Descriptive statistics will include the number of non-missing data points ( $n$ ), the arithmetic mean, the standard deviation (SD) (for baseline summaries) or standard error (SE) (for post-baseline or change from baseline summaries), the median, minimum and maximum.

For categorical parameters, frequency tabulations are prepared, consisting of frequency counts (non-missing observations) and percentages.

Descriptive statistics of efficacy parameters will additionally include 95% confidence intervals (CI) as appropriate.

Descriptive statistics of PK concentrations and PD data will additionally include 5% and 95% percentiles, coefficient of variation (CV)% of arithmetic mean, geometric mean and geometric SD.

For the graphs showing mean values or percentages, an SE flag will be shown. For PK graphs showing geometric mean values, a geometric SD flag will be shown.

### 4.2.2 Calculation of percentages

Missing values will not be included in the denominator count when computing percentages.

### 4.2.3 Handling of values below (or above) a threshold

Values below (above) the detection limit will be imputed by the value of the detection limit itself, unless indicated otherwise. Listings will always present the original value. Example: if the database contains values like "<0.04", then for the descriptive statistics the value of the detection limit (0.04) shall be used. A value like ">1000" will be imputed by "1000". For categorization of values into discrete classes the original value will be considered if it is a boundary value (e.g. ADAMTS13 <10% will be considered for <10 category)

Individual PK concentrations below the limit of detection or below the quantification limit (BQL) will be reported as BQL. To compute descriptive statistics (i.e. mean (or median or geometric mean), SD, CV%, minimum and maximum), all BQL values will be treated as missing. When the total number of BQL values exceeds 1/3 of the total number of values at that time point, descriptive statistics should not be computed. Descriptive statistics not calculated for the above reasons should be reported as not calculated (NC).



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#### **4.2.4 Handling of missing data**

There is no imputation of missing values, unless specified otherwise. Frequency of missing values will be tabulated for categorical variables.

Handling of missing date (time) or partially known date (time) is described in Section 5.3 for time since TTP diagnosis and in Section 7.1.1 for adverse events.

#### **4.2.5 Handling of outliers**

There will be no outlier detection. All measured values will be included in the analyses.

#### **4.2.6 Rounding of calculated parameters**

Calculated parameters will not be rounded in the derived datasets. The rounding will be done at the reporting level.

### **4.3 Key Definitions and Labels**

#### **4.3.1 Definition of baseline**

Baseline is defined as the last non-missing assessment before first administration of study drug.

For assessments with multiple parameters per subject (such as laboratory assessments), baseline will be determined per parameter individually. It is recognized that baseline assessments may thus come from more than one assessment and not just from the "baseline visit" assessment. Baseline will be calculated for each treatment period separately (double-blind treatment and open-label treatment). The assessment on Day 1 of the open-label treatment period, taken before first administration of open-label caplacizumab, will be taken as baseline value for the open-label part.

#### **4.3.2 Change from baseline and percentage change from baseline**

The change from baseline will be calculated for all post-baseline time points as:

Change from baseline at time point t = value at time point t – baseline value.

Percentage change from baseline at time point t =  $100 * ((\text{value at time point t} - \text{baseline value}) / \text{baseline value})$ .

Change from baseline and percentage change from baseline will be calculated separately for each of the treatment periods from their respective baseline values.



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### **4.3.3 Handling of unscheduled assessments**

Pre-dose unscheduled measurements: the latest non-missing pre-dose unscheduled measurement may be used for the possible imputation of a missing baseline (see Section 4.3.1). In all other cases, the value will only be listed.

Post-dose unscheduled measurements: the original scheduled measurement will be used for the analysis tables. Unscheduled samples will not be used in the descriptive statistics, but will be shown in listings.

Unscheduled measurements will be taken into account for derivation of time to event parameters and area under the curve (AUC). They will also be used if there is a worst-case determination over a period of time.

### **4.3.4 Screening and follow-up visits**

For analyses by visit, screening visits will be shown for each treatment group, not pooled. For subjects who have not switched to open-label caplacizumab after recurrence, follow-up visits will be shown for each treatment group, not pooled. For subjects who have switched to open-label caplacizumab after recurrence, follow-up visits will be shown pooled for subjects who received caplacizumab during the double-blind treatment period and for subjects who received placebo during the double-blind treatment period. See Section 4.3.6. for more details.

### **4.3.5 Randomized versus actual treatment**

Analyses will be handled differently before and after switch to open-label caplacizumab after recurrence, as specified below.

Before switch to open-label caplacizumab the treatment group as assigned by the randomization will be used (i.e., as-randomized analysis) for efficacy. For safety, PK, PD, disease-related markers and immunogenicity analyses the treatment that was actually used by the subject will be applied (i.e., as-treated analysis).

Differences between as-treated and as-randomized will be flagged in the listing on subject allocation.

After switch to open-label caplacizumab an all-treated analysis will be conducted in a separate pooled open-label caplacizumab treatment group, unless specified otherwise. For some specific analyses, e.g. for immunogenicity analyses; see Section 9.1, this pooling is not done. As a consequence, if open label period is represented according to the randomized treatment, the actual treatment (Caplacizumab) can differ from represented treatment group (Placebo or Caplacizumab).



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#### 4.3.6 Presentation of treatment groups

The following treatment group labels will be used in the tables, listings and figures, unless specified otherwise:

- Caplacizumab
- Placebo
- Open-label (OL) Caplacizumab

Treatment groups Caplacizumab and Placebo refer to the initial treatment group prior to a potential switch to open-label caplacizumab, and only data up to the switch are used in the analyses of these treatment groups. The OL Caplacizumab treatment group will only be used for analyses after the switch to open-label caplacizumab.

#### 4.3.7 Totals over groups

Grand total, pooling all subjects, will be displayed in the tables on general characteristics.

#### 4.3.8 General presentation of results

All results will be presented per treatment group, unless specified otherwise.

All listings will be ordered by treatment group, subject, and time point, unless specified otherwise.

The analysis population will always be indicated in a subtitle in the table, listing or figure.

### 4.4 Analysis Periods and Visit Windows

#### 4.4.1 Analysis periods

The following analysis phases are defined for this study: Screening, Treatment, Follow-up. Within these analysis phases, the following analysis periods and subperiods will be considered:

**Table 1: Analysis periods**

Period	Subperiod	Start period	End period
(Screening)		Date of signing the ICF, with 00:00 added as timepart	First DB treatment administration datetime – 1 min
Double-Blind (DB) Treatment	Daily PE	First administration datetime of DB treatment	Start of DB post-daily PE subperiod – 1 min
	Post-daily PE	Date of switch to post-daily PE + 1 day with 00:00 added as timepart	Min(Week 5 visit date if no treatment extension or last visit date of treatment extension period with 23:59 added as timepart, early termination visit date with 23:59 added as timepart, first administration datetime of OL treatment – 1 min)
	Daily PE	First administration datetime of OL treatment	Start of OL post-daily PE subperiod – 1 min



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Open-label (OL) Treatment	Post-daily PE	Date of switch to post-daily PE + 1 day with 00:00 added as timepart	Min(Week 5 visit date if no treatment extension or last visit date of treatment extension period, early termination visit date) with 23:59 added as timepart
(Follow-up)		End of treatment period + 1 min	Trial termination date, with 23:59 added as timepart

Note that the last analysis period in case of early termination will always be ended by the trial termination date.

The 'overall treatment period' corresponds with the treatment analysis phase and covers both the DB treatment analysis period and the OL treatment analysis period. Note that only subjects who experience a relapse or exacerbation will have an OL treatment analysis period. For these subjects, the overall treatment period starts at start of DB treatment period and ends at end of OL treatment period. For subjects with no switch to open-label caplacizumab, the overall treatment period starts at start of DB treatment period and ends at end of DB treatment period.

The 'overall study period' covers both the treatment analysis phase and the follow-up analysis phase.

#### 4.4.2 Relative number of days

The relative day (DY) is calculated as follows:

- = Visit date – reference date + 1 day, when the visit date is on or after the reference date
- = Visit date – reference date, when the visit date is before the reference date.

The reference date is the date of first intake of the study drug, which by definition has DY=1. There is no DY=0.

## 4.5 Software and validation model

### 4.5.1 Software

SAS version 9.2 will be used for programming.

### 4.5.2 Validation model

Currently valid ██████████ SOPs will be followed.

The ADaM datasets and tables will be validated following Model C; listings and figures follow validation model B (██████████):

- Model B: review of the output, source code and program log by an independent person (i.e., somebody different from the developer).
- Model C: independent programming of the parameters indicated in this SAP.



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## 5 GENERAL CHARACTERISTICS

All analyses on general characteristics will be run on the ITT population, unless specified otherwise.

### 5.1 Subject Disposition

Subject disposition will be presented descriptively for the all screened population. This includes the number and percentage of subjects in each of the analysis populations defined in Section 4.1. A disposition summary by country and site and by time point will be given for the Intent-to-treat (ITT) population. The number and percentage of subjects who completed the trial and who prematurely discontinued will be summarized, along with the primary reasons for discontinuation.

A detailed list of tables and listings can be found in Section 14.1 and Section 16.1, respectively.

### 5.2 Protocol Deviations and Eligibility Criteria

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Protocol deviations are considered as major if they can have an impact on the statistical analysis of the study. They concern criteria and disease characteristics that are critical to define the study population and criteria that determine or influence clinical endpoints or criteria that may cause immediate hazard to the subjects (impact on subjects' rights, safety or well-being) or increase the risk to subjects.

The list of (potentially) major protocol deviations will be reviewed by the sponsor and finalized prior to database lock. Detailed information can be found in the trial protocol deviation criteria list.

Major protocol deviations will be tabulated according to their category:

- Selection criteria not met
- Subject not withdrawn as per protocol
- Prohibited concomitant medication
- Treatment non-compliance
- Efficacy assessment deviation
- Other

Additionally, major protocol deviations will be listed including categorization and description. Violation to the in- and exclusion criteria will also be listed separately.

Subjects with major protocol deviations will be excluded from all analyses performed on the PP Population.



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A detailed list of tables and listings can be found in Section 14.1 and Section 16.1, respectively.

### 5.3 Demographic and Other Baseline Characteristics

Demographic data and baseline disease characteristics will be evaluated descriptively using standard statistical tools, including mean, standard deviation, median, minimum and maximum for continuous variables and counts and percentages for categorical variables. Summaries will be presented by treatment group and overall on the ITT population. The following demographic parameters and baseline disease characteristics will be included in the tables and/or listings:

#### Demographic parameters:

- Gender at birth: male / female
- Age at the moment of signing the ICF (years): the age is not recalculated when already available in the database. If not available, it will be calculated as (date of screening – date of birth) / 365.25 and rounded to integer.
- Year of birth: only listed
- Date of signing the ICF: only listed
- Race: not allowed to ask / white / black or African American / Asian / American Indian or Alaska native / native Hawaiian or other Pacific islander / other  
Specifications for Asian and other race: only listed
- Ethnicity: not allowed to ask / Hispanic or Latino / non-Hispanic or non-Latino
- Height (cm)
- Weight (kg)
- Blood group
- Body mass index BMI = (weight in kg) / (height in m)<sup>2</sup> (kg/m<sup>2</sup>): the BMI will be recalculated and rounded to 1 decimal, even when already available in the database. The original BMI will not be listed in that case.

#### Baseline disease characteristics:

- Time since TTP diagnosis (years) = (date of screening visit – date of TTP diagnosis)/365.25. For the calculation of time since TTP diagnosis, partially missing start dates will be imputed as follows:
  - Missing day will be imputed by 15
  - Missing day and month will be imputed by 1JUL
  - Note: If the start date would come later than the randomization date after imputation following this rule, the start date will be imputed with the randomization date instead.
- ADAMTS13 activity at admission or baseline: <10% / ≥10%  
Note: The smallest value of ADAMTS13 activity at admission, as measured by a local laboratory – if available – and ADAMTS13 activity at baseline will be used for this summary, as ADAMTS13 activity levels can be substantially impacted by the prior PE.



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- Previous TTP episode(s): initial / recurrent
- Number of previous TTP episodes: 0 / 1 / 2 / >2
- GCS at randomization: ≤12 / 13-15
- Baseline organ damage markers: LDH, cTnl and serum creatinine
- Baseline organ damage marker categories (LDH, cTnl, serum creatinine): ≤ULN / >ULN
- Baseline platelet count. This parameter is assessed by a local laboratory.
- Baseline SMMSE total score
- Baseline RICO activity, vWF:Ag concentration and FVIII:C activity
- Baseline complement factors C5a and C5b-9
- Severity of disease at baseline category: very severe / less severe. Very severe is defined as French severity score ≥ 3 **or** severe neurological involvement at baseline (i.e., coma, seizures, focal deficit) **or** cardiac involvement (cTnl > 2.5 x ULN). The French severity score (Benhamou, 2012) is a discrete score from 0 to 4, involving evaluation of three parameters: cerebral involvement: yes = 1 / no = 0, LDH: >10 x ULN = 1 / ≤10 x ULN = 0, age: >60 years = 2 / >40 and ≤60 years = 1 / ≤40 years = 0.

A detailed list of tables and listings can be found in Section 14.1 and Section 16.1, respectively.

## 5.4 Medical History

Medical history (i.e. condition no longer present), concomitant diseases (i.e. condition still present) and ADAMTS13 activity at admission will be listed (see Section 16.1). Separate listings will be presented for general medical history and for TTP history.

## 5.5 Prior and Concomitant Medications

### 5.5.1 Analysis

Any concomitant medication taken during the study will be recorded in the eCRF.

All therapies are coded using the latest WHO-DRUG version, no Anatomical therapeutic chemical classification system (ATC) selection is performed.

Based on their start and stop date, previous and concomitant therapies will be reported in each analysis period during which they were applied (i.e. a non-treatment-emergent allocation). This implies that each therapy can be reported more than once. The analysis periods are defined in Section 4.4.1.

If a therapy record misses components of its start and/or stop dates (day and/or month and/or year), a worst-case allocation will be applied:





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- In case of partial start or stop dates, the concomitant therapy records will be allocated to analysis phases or (sub)periods using the available partial information, without imputations. If, for example, only month and year are available, these will be compared to the month and the year of the phases, and the concomitant therapy record will so be allocated to the analysis phase(s) or (sub)period(s) where these date parts match.
- In case of a completely missing start date, the concomitant therapy will be considered as having started before the trial.
- In case of a completely missing end date, the concomitant therapy will be considered as ongoing at the end of the trial.

Previous and concomitant therapies will be tabulated by generic term and by analysis period (DB treatment daily PE period, DB treatment post-daily PE period, OL treatment daily PE period, OL treatment post-daily PE period, overall treatment period, follow-up period, overall study period). Multiple records of the same generic term for the same subject will be counted only once. The table will therefore present subjects, not occurrences. The tables are sorted by decreasing frequency (overall). Immunosuppressive (including rituximab) and non-immunosuppressive concomitant therapies will be tabulated separately. A separate tabulation by analysis period will be made to summarize the number and proportion of subjects who received concomitant antithrombotic therapies (ATC codes starting with B01A) and the number and proportion of subjects to whom transfusions have been given.

The duration of corticosteroids use and the cumulative dose of corticosteroids during the overall treatment period will be summarized by treatment group. The treatment groups for this analysis will be defined as:

- Caplacizumab + OL Caplacizumab
- Placebo + OL Caplacizumab

This definition implies that subjects will be analyzed according to their initial treatment group, both before and after switch to open-label caplacizumab.

Different types of corticosteroids will be converted to Prednisolone equivalent doses before calculating the cumulative dose of corticosteroids. The cumulative dose will be given in mg/day (Please refer to Appendix C section 17.3 for more details).

A detailed list of tables and listings can be found in Section 14.1 and Section 16.1, respectively.

## 5.6 Exposure to Study Medication

Extent of exposure will be analyzed descriptively by treatment group and overall based on the safety population. The following exposure parameters will be considered:

- DB treatment duration (days) = (date of last administration – date of first administration within the DB treatment period + 1)
- OL treatment duration (for switchers only) (days) = (date of last administration – date of first administration within the OL treatment period + 1)



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- Total treatment duration (days) = (date of last drug administration – date of first drug administration + 1 day). The treatment groups Caplacizumab + OL Caplacizumab and Placebo + OL Caplacizumab will be considered for this analysis. Subjects will thus be analyzed according to their initial treatment group, both before and after switch to open-label caplacizumab.
- Compliance, calculated as (number of study drug administrations received / number of study drug administration planned)\*100% will be tabulated by (sub)period

The number and proportion of subjects with treatment extensions will be summarized by treatment group (Caplacizumab, Placebo, OL Caplacizumab).

A detailed list of tables and listings can be found in Section 14.1 and Section 16.1, respectively.

## 6 EFFICACY

### 6.1 Primary efficacy endpoint evaluation

#### 6.1.1 Primary efficacy analysis

The primary endpoint of the study is: time to platelet count response. Platelet count response is defined as initial platelet count  $\geq 150 \times 10^9/L$  with subsequent stop of daily PE within 5 days. It refers to the first time both conditions, platelet count above  $150 \times 10^9/L$  and the stop of dPE within 5 days, are met; so it is not necessarily the first time the platelet count goes above  $150 \times 10^9/L$ .

Only data from the double blind daily PE period up to the cut-off point will be used for the analysis of the primary endpoint. The data cut-off point is defined by either:

- 45 days of daily PE after the start of study drug,
- The stop of daily PE
- The stop of study treatment drug,

whichever occurs first.

The time to platelet count response is calculated as the time of the event/censor – time of first i.v. loading dose of study drug after randomization + 1 minute. The time to response will be represented by number of days with two decimal digits.

For the platelet count measurements with missing time part, the missing sample time will be imputed using the first dosing time minus 1 minute for the subject.



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Depending on the time of platelet count  $\geq 150 \times 10^9/L$ , the time of stop of daily PE and the stop of study drug treatment, different potential scenarios for the event time and censoring of observations are possible. These are presented in Table 2.

**Table 2: Censoring and event plan**

Scenario	Response	Censored	Time to event / censoring time (days)	Graphical representation (grey bar represents dPE)
1) Initial platelet count $\geq 150 \times 10^9/L$ at day x with subsequent stop of dPE within 5 days, platelet count stays $\geq 150 \times 10^9/L$ as of day x ( $x \leq 45d$ )	Yes	0	x	
2) Initial platelet count $\geq 150 \times 10^9/L$ at day x with subsequent stop of dPE within 5 days. Platelet count dropped below $150 \times 10^9/L$ between day x and stop of dPE on day y ( $y \leq 45d$ ) and was not $\geq 150 \times 10^9/L$ by the stop of dPE	Yes	0	x	
3) No platelet count $\geq 150 \times 10^9/L$ within 45 days of continuous dPE	No	1	45	



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<p>4) No platelet count <math>\geq 150 \times 10^9/L</math> and at day x subject early terminated with no initial platelet count response (<math>x \leq 45d</math>)</p>	<p>No</p>	<p>1</p>	<p>x</p>	
<p>5) Platelet count <math>\geq 150 \times 10^9/L</math> (at day x) after being below <math>150 \times 10^9/L</math>, with subject early terminated within 5 days while on dPE</p>	<p>Yes</p>	<p>0</p>	<p>x</p>	
<p>6) Stop of dPE at day x without platelet count <math>\geq 150 \times 10^9/L</math> (<math>x \leq 45d</math>)</p>	<p>No</p>	<p>1</p>	<p>x</p>	
<p>7) Stop of dPE at day x without platelet count <math>\geq 150 \times 10^9/L</math> and platelet count <math>\geq 150 \times 10^9/L</math> at day x+y (<math>x \leq 45d, y &gt; 0d</math>)</p>	<p>No</p>	<p>1</p>	<p>x</p>	



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<p>8) Platelet count <math>\geq 150 \times 10^9/L</math> at day x with stop of dPE 5+y days later (<math>y &gt; 0d</math>), platelet count stays <math>\geq 150 \times 10^9/L</math> as of day x (<math>x+y \leq 45d</math>)</p>	<p>Yes</p>	<p>0</p>	<p>x+y</p>	
<p>9) Platelet count <math>\geq 150 \times 10^9/L</math> at day x with stop of dPE 5+y days later (<math>y &gt; 0d</math>), platelet count has not been <math>\geq 150 \times 10^9/L</math> between day x+y and day x+y+5 (<math>x+y+5 \leq 45d</math>)</p>	<p>No</p>	<p>1</p>	<p>x+y+5</p>	
<p>10) Study drug withdrawn at day x with no Platelet count <math>\geq 150 \times 10^9/L</math>, and the subject early terminated y days later (<math>y &gt; 0</math>, <math>x+y \leq 45d</math>). The subject was still on dPE until early termination</p>	<p>No</p>	<p>1</p>	<p>x</p>	

Time to platelet count response in the caplacizumab arm and placebo arm will be compared by conducting a two-sided stratified Log-rank test based on a Kaplan-Meier (KM) analysis, with severity of neurological involvement (according to the GCS, stratification factor used in randomization:  $\leq 12 / 13-15$ ) as stratification factor. The resulting p-value will be compared with the significance level  $\alpha$  of 5%. In case the p-value is smaller than 0.05 and the estimated median time to platelet count response in the caplacizumab treatment group is smaller than in the placebo treatment group, a significant reduction of time to platelet count response by caplacizumab will be concluded and the primary endpoint will have been met.

This analysis will be performed on the ITT population. Subjects will be analyzed according to the treatment to which they were assigned. Switch of subjects who experience a recurrence of TTP during the study to open-label caplacizumab will not affect the primary efficacy endpoint analysis as a recurrence can only occur after platelet count response, i.e. initial platelet count  $\geq 150 \times 10^9/L$  with subsequent stop of daily PE within 5 days, has been reached.



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Besides the p-value, the table on the primary analysis will include standard KM estimates such as the median, 25% percentile and 75% percentile of the time to platelet count response by treatment group with associated 95% CIs, as well as the number of events and the number of censored observations. This summary will be presented both by GCS category, and overall, i.e. unadjusted by GCS category.

The KM estimates will also be presented graphically, unadjusted by GCS category.

The data will also be 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 ratio (HR) from the Cox model will be reported along with 95% CI in the table. The adequacy of the Cox model will be tested using the graphical and numerical methods of Lin, Wei, and Ying (1993). The proportional hazards assumption will be checked by using a transform of the martingale residuals known as the empirical score process. The assumption will be tested graphically by plotting for each covariate the simulated score processes, representing score processes under the proportional hazards assumption, and comparing them to the observed score process. In addition, a supremum test will be reported to assess the proportion of simulated score processes that yielded a maximum score larger than the maximum observed score process. A very small proportion (p-value) suggests violation of proportional hazards. In case the proportional hazards assumption does not hold, effect of potential confounding factors such as use of rituximab, disease severity at baseline, and baseline ADAMTS13 activity levels will be explored using stratified proportional hazards model(s), if feasible (i.e. depending on number of subjects in strata).

The following sas code will be used as starting point for the primary analysis.

For the Kaplan-Meier (KM) analysis:

```
proc lifetest data=inputdata;
  time aval*cnsr(1);
  strata trt01p trt01pn / test=(logrank);
  ods output quartiles=quartile CensoredSummary=censor;
run;
```

where

```
INPUTDATA is the input dataset
AVAL is the time to the event variable,
CNRS is 0 (subjects with events) or 1 (subjects without no event,
i.e. subject censored)
TRT01P and TRT01PN are respectively the categorical and numeric
versions of the planned treatment groups used for the subjects during
the DB treatment period
```

For the stratified Log-rank test:

```
proc lifetest data=inputdata;
  time aval*cnsr(1);
  strata gcsscsc / test=(logrank);
  test trt01pn;
  ods output LogUniChiSq=logrank;
run;
```



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where  
 INPUTDATA is the input dataset  
 AVAL is the time to the event variable,  
 CNRS is 0 (subjects with events) or 1 (subjects without no event,  
 i.e. subject censored)  
 TRT01PN is the numeric version of the planned treatment groups used  
 for the subjects during the DB treatment period  
 GCSSCOSC is the Glasgow Coma Scale Category for each subject

#### For the Cox proportional hazards regression model:

```
proc phreg data=inputdata;
  class TREATMENT (ref="1") GCS (ref="1");
  model aval*cnsr(1)= TREATMENT GCS / ties=efron risklimits type3;
  estimate "TREATMENT" TREATMENT 1 / cl;
  estimate "GCS" GCS 1 / cl;
  assess ph / crpanel resample;
  ods output ParameterEstimates=parestimate
  ProportionalHazardsSupTest=proptest Estimates=estimate;
run;
```

where  
 INPUTDATA is the input dataset  
 AVAL is the time to the event variable,  
 CNRS is 0 (subjects with events) or 1 (subjects without no event,  
 i.e. subject censored)  
 TREATMENT is the numeric version of the planned treatment group used  
 for the subjects during the DB treatment period  
 GCS is the Glasgow Coma Scale Category for each subject

A detailed list of tables, listings and figures can be found in [Section 14.2](#), [Section 16.2](#) and [Section 15.1](#), respectively.

Time to platelet count response will be measured from the time of the first i.v. loading dose of study drug after randomization. In the KM analysis an observation will be censored if the defined time interval of 45 days after first administration of study drug is not met, due to any cause (e.g., endpoint not being reached within this time interval or subject lost to follow-up).

### 6.1.2 Sensitivity analyses

The following sensitivity analyses will be performed:

- The primary endpoint analysis will be repeated on the mITT population
- The primary endpoint analysis will be repeated on the PP population.
- The primary endpoint analysis will be repeated on the ITT population with a constrained definition of time to platelet count response. For this analysis, scenarios 2, 5 and 8 will be considered as non response scenarios. The corresponding new censoring time are presented in Table 3 below.



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**Table 3: Constrained censoring and event plan (for scenarios 2, 5 and 8)**

Scenario	Response	Censored	Time to event / censoring time (days)	Graphical representation (grey bar represents dPE)
2) Initial platelet count $\geq 150 \times 10^9/L$ at day x with subsequent stop of dPE within 5 days. Platelet count dropped below $150 \times 10^9/L$ between day x and stop of dPE on day y ( $y \leq 45d$ ) and was not $\geq 150 \times 10^9/L$ by the stop of dPE	No	1	y	
5) Platelet count $\geq 150 \times 10^9/L$ at day x with subject early terminated within 5 days (on day y) while on dPE	No	1	y	
8) Platelet count $\geq 150 \times 10^9/L$ at day x with stop of dPE 5+y days later ( $y > 0d$ ), platelet count stays $\geq 150 \times 10^9/L$ as of day x ( $x+y \leq 45d$ )	No	1	x+y+5	

- The primary endpoint analysis will be repeated on the ITT population with time to platelet count response defined as the first time platelet count is  $\geq 150 \times 10^9/L$  without the requirement to stop daily PE within 5 days. Consequently, only subjects who have no platelet count  $\geq 150 \times 10^9/L$  within 45 days of the first i.v loading dose of study drug after randomization, or who were early terminated before reaching platelet count  $\geq 150 \times 10^9/L$  are censored for the analysis, with time of censoring at 45 days, or at time of early termination, whichever comes first. Time of stop of daily PE will have no





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influence on reaching the endpoint or on censoring time. The scenarios are specified below in Table 4.

**Table 4: Censoring and event plan (dPE stop within 5 days not required)**

Scenario	Response	Censored	Time to event / censoring time (days)
1) Subject has event within 45 days, on day x.	Yes	0	x
2) Subject has no event within 45 days, and subject has no early termination within 45 days.	No	1	45
3) Subject has no event before early termination on day x, before day 45.	No	1	x

A detailed list of tables, listings and figures can be found in Section 14.2, Section 16.2 and Section 15.1, respectively.

## 6.2 Secondary Efficacy Endpoints Evaluation

### 6.2.1 Key secondary endpoints

Key secondary endpoints are defined in Section 3.3.2.1.

Confirmatory hypothesis testing will be conducted only for the key secondary endpoints. In order to control the rate of false positive conclusions with a family-wise error rate of 5%, a fixed sequence approach will be applied. The key secondary endpoints are hierarchically ordered. This allows statistical testing for these endpoints at the same nominal significance level of 5% without adjustment, as long as the tests occur in the pre-defined sequential order, and given that all null hypotheses to be tested for endpoints with a higher rank (including the primary endpoint) are rejected. As soon as a test is not statistically significant for a certain endpoint, i.e. as soon as the sequence breaks, no confirmatory testing will be done for remaining endpoints lower in the ranking. Statistical comparison between the two treatment arms for the key secondary endpoints will be done by means of the following planned analyses (in hierarchical order):

1. Proportion of subjects with TTP-related death, a recurrence of TTP, or at least one treatment-emergent major thromboembolic event (e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism or deep venous thrombosis [DVT]) during the overall treatment period (including extensions). Start and end times of the overall treatment period are defined in Section 4.4.1. A Cochran-Mantel-Haenszel (CMH) test will be conducted with adjustment for GCS category (stratification factor used in randomization). For both treatment groups, only events that have occurred prior to a switch to open-label caplacizumab will be evaluated for this analysis.

This composite endpoint consists of the following components:



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- TTP-related death: adverse event categorized as 'clinically significant TTP event' and documented as 'death due to TTP' and/or adverse events with outcome 'fatal', adjudicated as TTP related (see below).
- TTP recurrence: recurrent thrombocytopenia after initial recovery of platelet count, requiring re-initiation of daily PE. Depending on the timing of recurrence, it is defined as:
  - Exacerbation: recurrence occurring during the first 30-days post-daily PE period
  - Relapse: recurrence occurring after the 30-days post-daily PE period; only relapses within the overall treatment period are taken into account for the key secondary endpoint.Exacerbations and relapses will be documented as serious adverse events. Note that, exceptionally, daily PE may have been stopped before an initial platelet count  $\geq 150 \times 10^9/L$  is reached, by investigator's decision. It is recognized that in this case the subject can still experience an exacerbation or relapse requiring re-initiation of daily PE if documented as described above.
- Treatment-emergent major thromboembolic event: e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism or DVT, confirmed after adjudication (see below).

If a potential major thromboembolic event or TTP-related death occurs, the investigator will be requested to provide additional information for adjudication by a blinded independent committee. Only events that are confirmed after adjudication will be used for the analysis. More details are provided in CSP Section 3.4.3.6 and [Appendix B: Adjudication charter](#).

2. Proportion of subjects with a recurrence of TTP in the overall study period (including the FU period). A CMH test will be conducted with adjustment for GCS category (stratification factor used in randomization). For both treatment groups, only recurrences that have occurred prior to a potential switch to open-label caplacizumab will be evaluated for this analysis.
3. Proportion of subjects with refractory TTP, defined as absence of platelet count doubling after 4 days of standard treatment, and LDH > ULN. A CMH test will be conducted with adjustment for GCS category (stratification factor used in randomization). Refractory TTP is derived as follows: (platelet count after 4 days of standard treatment / platelet count at start of standard treatment) < 2 and LDH > ULN after 4 days of standard treatment. Platelet count and LDH at Day 5 will be used for this analysis. Subjects who have reached platelet count response (primary endpoint) by Day 5 will not be considered as having a refractory TTP.

Subjects discontinued (lost to follow-up, withdrew consent, etc...) before day 5 will be excluded from the analysis.



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Missing values will be imputed using multiple imputation (Markov Chain Monte Carlo) by averaged simulated parameter values. The number of simulation iterations will be adapted to the proportion of missing values (0-10% missing values: 20 iterations, 10-20% missing values: 100 iterations) to keep the relative efficiency (RE) of multiple imputation under control (Rubin, 1987).

The following sas code will be used as starting point for the multiple imputation:

```
proc mi data=original nimpute=number seed=1 out=imputed minimum=0
round=1;
  by studyid trt01pn trt01p;
  mcmc impute=full;
  var _day1 _ day2 _ day3 _ day4 _ day5;
run;
```

where

ORIGINAL is the input dataset

IMPURED is the data after imputation

NUMBER is the number of imputation depending on the percentage of missingness

STUDYID is the study identifier

TRT01P and TRT01PN are respectively the categorical and numeric versions of the planned treatment groups used for the subjects during the DB treatment period

\_DAYx (x=1 to 5) are the measurements for each subjects from day 1 to day 5

4. Time to first normalization of all three organ damage marker levels, i.e. LDH, cTnI and serum creatinine. Time to first normalization of LDH, cTnI and serum creatinine is defined as: first time of  $LDH \leq ULN$  and  $cTnI \leq ULN$  and serum creatinine  $\leq ULN$  - time of first i.v. loading dose of study drug after randomization + 1 minute. The time to normalization will be represented by number of days with two decimal digits. Subjects in either initial treatment group who have switched to open-label caplacizumab before having reached the endpoint will be censored at time of switch. All on-treatment records during DB treatment period will be used. A stratified Log-rank test will be conducted based on a KM analysis with adjustment for GCS category and for an additional factor defining whether the subject has abnormal values at baseline for LDH only (not for cTnI or for serum creatinine) or not.

In addition to the confirmatory statistical tests, standard summary statistics will be provided for all key secondary endpoints. For the first key secondary endpoint 'proportion of subjects with TTP-related death, a recurrence of TTP, or at least one treatment-emergent major thromboembolic event during the overall treatment period (including extensions)' and for the second key secondary endpoint 'proportion of subjects with a recurrence of TTP in the overall study period' separate summary statistics will be included for the OL Caplacizumab treatment group. For these endpoints also the number of events will be reported.

All analyses will be run on the ITT population.



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A detailed list of tables, listings and figures can be found in Section 14.2, Section 16.2 and Section 15.1, respectively.

### 6.2.2 Other secondary efficacy endpoints

Other secondary efficacy endpoints are defined in Section 3.3.2.2.

In general, all endpoints will be summarized using descriptive statistics such as number of observations, means, standard error, and proportions, as appropriate. All analyses will be run on the ITT population.

- Proportion of subjects with at least one treatment-emergent major thromboembolic event (e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism or DVT), confirmed after adjudication, as well as the number of such events, during the overall treatment period (including extensions) (Caplacizumab, Placebo, OL Caplacizumab).
- Proportion of subjects with recurrences of TTP as well as the number of such events during study drug treatment (including extensions) and after study drug treatment (during FU) will be summarized by treatment group (Caplacizumab, Placebo, OL Caplacizumab).
- Proportion of subjects with treatment-emergent clinically significant TTP-related events, as well as the number of such events in the overall study period (including 4-week FU period) as defined in Section 3.3.2.2 will be summarized by treatment group (Caplacizumab, Placebo, OL Caplacizumab).
- Area under the curve (AUC) of platelet count until Day 5, truncated at  $150 \times 10^9/L$  if platelet count is  $150 \times 10^9/L$  or above, will be summarized by treatment group (Caplacizumab, Placebo). The AUC value will be calculated using the linear trapezoidal rule, i.e.  $AUC_{t_i-t_{i+1}} = 1/2 * (C_i + C_{i+1}) * (t_{i+1} - t_i)$  where  $C_i$  is the platelet count at time point  $t_i$ . Missing platelet counts will not be imputed separately as missing values can be bridged by using the trapezoid rule on neighboring (available) timepoints, thereby implicitly interpolating the missing timepoint. If the subject discontinued prior to Day 5, the subject will not be considered in this analysis. Descriptive statistics will include the 25%, 75% and 90% percentiles.
- Mortality rate (number and percentage) will be summarized by treatment group (Caplacizumab, Placebo, OL Caplacizumab) during DB treatment daily PE period (OL Caplacizumab not applicable), overall treatment period, FU period and overall study period.
- Organ damage markers:
  - Time to LDH  $\leq 1 \times$  ULN
  - Time to cTnl  $\leq 1 \times$  ULN
  - Time to serum creatinine  $\leq 1 \times$  ULN

A separate KM analysis for each organ damage marker will be conducted with time to first normalization as dependent variable and treatment group (Caplacizumab, Placebo) as independent variable. Subjects in either initial treatment arm who have switched to open-label caplacizumab before having reached the endpoint will be censored at time of switch.



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Time to first normalization of *organ damage marker* is defined as: first time of *organ damage marker*  $\leq$  ULN - time of first i.v. loading dose of study drug after randomization + 1 minute. All on-treatment records during DB treatment period will be used. The time to first normalization will be represented by number of days with two decimal digits.

- Proportion of subjects with increases in organ damage markers (cTnI and serum creatinine) above 1 x ULN will be summarized by treatment group (Caplacizumab, Placebo, OL Caplacizumab) during DB treatment daily PE period (OL Caplacizumab not applicable), overall treatment period, FU period and overall study period.
- AUC of cTnI above 1 x ULN (cTnI peak) will be summarized by treatment group (Caplacizumab, Placebo, OL Caplacizumab) during DB treatment daily PE period (OL Caplacizumab not applicable) and during overall treatment period. The AUC value will be calculated by the linear trapezoidal rule. The analysis will be repeated including and excluding cTnI peaks at baseline. Descriptive statistics will include the 25%, 75% and 90% percentiles.
- Proportion of subjects with neurological symptoms based on neurological assessment on Day 1, 2, 3, 4, 5 and Weeks 1 and 5 of 30-day post-daily PE treatment period, and the first and final FU visit will be summarized by treatment group (Caplacizumab, Placebo, OL Caplacizumab).
- Actual value and change from baseline in Standardized mini mental state examination (SMMSE) total score on Days 1, 2, 3, 4, 5 and Weeks 1 and 5 of the 30-day post-daily PE treatment period, and the first and final FU visit will be summarized by treatment group (Caplacizumab, Placebo, OL Caplacizumab). For the OL Caplacizumab treatment group change from baseline is based on the Day 1 assessment of the open-label treatment period.
- Proportion of subjects with evidence of cardiac ischemia and/or arrhythmia/conduction abnormalities on Days 1, 2, 3, and 4, and Weeks 1 and 5 of 30-day post-daily PE treatment period, and the first and final FU visit will be summarized by treatment group (Caplacizumab, Placebo, OL Caplacizumab).
- Proportion of subjects who have a platelet count  $\geq 150 \times 10^9/L$  on Day 1, 2, 3, 4, 5 and Day 10 and end of study drug treatment (i.e., last weekly visit during the DB or OL treatment period) will be summarized by treatment group (Caplacizumab, Placebo, OL Caplacizumab).
- Proportion of subjects with refractory TTP, defined according to Scully et al. (2016) as lack of sustained platelet count increment or platelet counts  $< 50 \times 10^9/L$  and persistently raised LDH ( $> 1.5 \times$  ULN) despite 5 plasma exchanges and steroid treatment will be summarized by treatment group (Caplacizumab, Placebo). Refractory TTP is derived as follows: (platelet count at Day x  $<$  platelet count at Day x-1 for at least 1 value of x with x=2,...,5) and (LDH  $> 1.5 \times$  ULN from Day 1 to Day 5). Subjects who have reached platelet count response (primary endpoint) by Day 5 will be considered as not refractory to TTP. Missing values will be imputed by using multiple imputation (Markov Chain Monte Carlo) by



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averaged simulated parameter values, except if the subject discontinued prior to Day 5. In that case, the subject will not be considered in the analysis.

- Time to stop of daily PE: A KM analysis will be conducted with time to stop of daily PE within the DB treatment period as dependent variable and treatment group (Caplacizumab, Placebo) as independent variable. Time to stop of daily PE is defined as: date of daily PE stop - date of first i.v. loading dose of study drug after randomization + 1 day.
- The number of PE days and the total PE volume (absolute and normalized) in the DB treatment daily PE period and the overall treatment period will be summarized by treatment group. For this analysis the treatment groups are defined as
  - Caplacizumab + OL Caplacizumab
  - Placebo + OL Caplacizumab

Subjects will thus be analyzed according to their initial treatment group, both before and after switch to open-label caplacizumab. The number of PE days is defined as the total number of days on which PE is documented. The absolute total PE volume is given by the sum over all PE days of the amount exchanged in liter, while the normalized total PE volume is calculated as the sum over all PE days of the multiple of plasma volume exchanged.

- Number of days in ICU and in hospital will be summarized by treatment group (Caplacizumab + OL Caplacizumab, Placebo + OL Caplacizumab) in the DB treatment daily PE period, in the overall treatment period, in the FU period and in the overall study period. The number of days in ICU is calculated as (ICU discharge date – ICU admission date + 1 day) summed over all stays in ICU. The number of days in hospital is calculated as (discharge date – admission date + 1 day) summed over all hospitalizations (including days in ICU). Subjects will be analyzed according to their initial treatment group, both before and after switch to open-label caplacizumab.

A detailed list of tables, listings and figures can be found in Section 14.2, Section 16.2 and Section 15.1, respectively.

### 6.3 Subgroup analyses

A KM analysis of time to platelet count response (primary endpoint) in function of treatment group (Caplacizumab, Placebo) will be performed separately for the following subgroups:

- ADAMTS13 activity at admission or baseline: < 10% / ≥ 10%
- Previous TTP episode(s): initial / recurrent
- Severity of disease at baseline category: very severe / less severe

Each subgroup analysis will only be conducted if at least 5 data points are available by subgroup in each treatment group.

The number and proportion of subjects with refractory TTP by treatment group (Caplacizumab, Placebo) will be summarized for the following subgroups:









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If the AE start date is completely missing but AE end date and study drug administration are non-missing and AE end date is before the first study drug administration and after signing ICF, then the AE is defined as pre-treatment. All adverse events emerging during the screening period will only be listed and will not be presented in any of the tables. These events are not TEAEs. All tables will thus present TEAEs only.

According to ICH-E3, the drug relatedness as assessed by the investigator will be dichotomized as follows:

- Drug-related: at least possibly drug-related, OR with a missing drug-relatedness (= worst-case).
- Not drug-related: less than possibly drug-related.

In tabulations this dichotomized drug-relatedness will be used, but in the listings the original drug-relatedness will be presented.

Relationship to PE and relationship to corticosteroids are collected as related or not related. Missing relatedness will be considered as related.

When cross-tabulating AE preferred terms versus an AE attribute (e.g., severity), the worst-case is always applied within each analysis period. This means that when a subject has the same AE preferred term twice in the same analysis period, then the subject is reported only once: with the worst severity. If this happens in two different analysis periods, the subject is reported twice: once in each analysis period.

AE onset day and AE duration are defined as follows:

- AE onset day
  - = AE start date – date of first study drug intake + 1 day (when the AE start date is completely known)
  - = missing (when the AE start date is incomplete or unknown).
- AE duration
  - = AE stop date – AE start date + 1 day (when both dates are completely known)
  - = trial termination date – AE start date + 1 day (when the AE start date is fully known but the AE is not resolved at the end of the trial): in this case the duration will be presented as ">x days" in the listing rather than "x days"
  - = missing (when the AE start date is incomplete or unknown, or when the AE has resolved but with an incomplete or unknown end date).

These derived parameters will only be presented in the listings. Note that the start and stop times of the AE are not used.

All percentages will be calculated against the total number of subjects (within each treatment group) that are still in the study in that particular analysis period.



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### **7.1.2 Analysis**

The following analysis periods will be considered for all AE tables:

- DB treatment daily PE period
- DB treatment post-daily PE period
- OL treatment daily PE period
- OL treatment post-daily PE period
- Overall treatment period
- FU period
- Overall study period

Summaries on AEs will be presented by treatment group (Caplacizumab, Placebo, OL Caplacizumab, Caplacizumab Total) and by analysis period. The 'Caplacizumab Total' group will combine events that have occurred for all caplacizumab-treated subjects. For subjects who received placebo in the DB treatment period, only events after switch to open-label caplacizumab will be counted for the Caplacizumab Total group.

A general summary table will be presented by treatment group and analysis period, reporting the number and percentage of subjects, the number of events and the incidence per 100 patient months, which will be calculated as:  $100 \times (\text{Number of subjects with AE}) / (\text{Total number of months observed within analysis period, summed for all subjects})$ . The following categories will be included in the summary table:

- Subjects with at least one TEAE
- Subjects with at least one serious TEAE
- Subjects with at least one TEAE leading to death
- Subjects with at least one TEAE for which the study drug was interrupted
- Subjects with at least one TEAE for which the study drug was withdrawn
- Subjects with at least one TEAE that was considered at least possibly treatment-related by the investigator
- Subjects with at least one serious TEAE that was considered at least possibly treatment-related by the investigator
- Subjects with at least one bleeding event, i.e. an event documented as event indicating an increased bleeding tendency
- Subject with at least one bleeding event, based on the Standardized MedDRA Query (SMQ) 'Haemorrhage terms (excluding laboratory terms)'
- Subjects with at least one thromboembolic event, based on the SMQ 'Embolism and thrombotic events (arterial, venous, and vessel type unspecified and mixed arterial and venous)'
- Subjects with at least one hypersensitivity reaction, based on the SMQs 'Hypersensitivity' (Narrow), 'Anaphylactic reaction' (Narrow) and 'Angioedema' (Narrow)
- Subjects with at least one hypersensitivity reaction, based on the SMQs 'Hypersensitivity' (Narrow), 'Anaphylactic reaction' (Narrow) and 'Angioedema' (Narrow), considered at least possibly treatment-related by the investigator.



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TEAEs, serious TEAEs, non-serious TEAEs and clinically significant TTP and bleeding events will be summarized for each treatment group (Caplacizumab, Placebo, OL Caplacizumab, Caplacizumab Total) by system organ class and preferred term. This will be done for each analysis period. The number of events and the number and percentage of subjects having an event will be presented.

TEAEs and serious TEAEs will be summarized for each treatment group (Caplacizumab, Placebo, OL Caplacizumab, Caplacizumab Total) by system organ class, preferred term and severity. This will be done for each analysis period. The number of events and the number and percentage of subjects having an event will be presented for the worst severity reported for each event (within the same analysis period – see also Section 7.1.1). This analysis will be repeated for the bleeding events.

TEAEs considered at least possibly treatment-related by the investigator and serious TEAEs considered at least possibly treatment-related by the investigator will be summarized for each treatment group (Caplacizumab, Placebo, OL Caplacizumab, Caplacizumab Total) by system organ class and preferred term. This will be done for each analysis period. The number of events and the number and percentage of subjects having an event will be presented. This analysis will be repeated for the bleeding events.

TEAEs leading to study drug withdrawal and TEAEs leading to study drug interruption will be summarized separately and combined for each treatment group (Caplacizumab, Placebo, OL Caplacizumab, Caplacizumab Total) by system organ class and preferred term. This will be done for each analysis period. The number of events and the number and percentage of subjects having an event will be presented.

Treatment-emergent thromboembolic events, based on the SMQ 'Embolic and thrombotic events (arterial, venous, and vessel type unspecified and mixed arterial and venous)', will be summarized for each treatment group (Caplacizumab, Placebo, OL Caplacizumab, Caplacizumab Total) by system organ class and preferred term. This will be done for each analysis period. The number of events and the number and percentage of subjects having an event will be presented.

Hypersensitivity reactions (including anaphylaxis and angioedema) will be summarized for each treatment group (Caplacizumab, Placebo, OL Caplacizumab, Caplacizumab Total) by system organ class and preferred term. This will be done for each analysis period. The number of events and the number and percentage of subjects having an event will be presented. This analysis will be repeated for hypersensitivity reactions considered at least possibly treatment-related by the investigator.

The tables by system organ class and preferred term are sorted by decreasing frequency of system organ class and preferred term overall.

All recorded adverse events will be listed.



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A detailed list of tables and listings can be found in Section 14.6 and Section 16.6 respectively.

### 7.1.3 Exploratory analysis

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[Redacted text block]

## 7.2 Laboratory Evaluations

### 7.2.1 Available data

The following parameters will be available:

- **Biochemistry:** sodium, potassium, chloride, urea (BUN), glucose, total bilirubin, alkaline phosphatase, AST, ALT, haptoglobin, total protein, albumin, calcium, C-reactive protein (CRP), globulin.
- **Hematology:** hemoglobin, hematocrit, reticulocytes, erythrocytes, leukocytes, partial automated differentiation: neutrophils, lymphocytes, monocytes, eosinophils, basophils, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC).
- **Coagulation:** activated partial prothrombin time.

### 7.2.2 Laboratory units

The statistical analysis will only present results in Standard International (SI) units. Other units will not be presented.

In the tables, the number of significant digits of the original values will be used to determine the number of decimals that will be printed.



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### 7.2.3 Abnormalities

All values will be compared to their matching normal ranges. The classification available in the standard data tabulation method (SDTM) dataset will not be used for the statistical analysis. The classification will be re-calculated in the analysis data model (ADaM) dataset by using the values and normal ranges in SI units.

Values will be scored as abnormally low (L), normal (N) or abnormally high (H). A value is classified as abnormally low when the value < lower limit of the normal range. A value is classified as abnormally high when the value > upper limit of the normal range. Tests without normal ranges will not be scored. An original value like "<X" where X equals the lower limit of the normal range will be classified as abnormally low (L). An original value like ">X" where X equals the upper limit of the normal range will be classified as abnormally high (H).

### 7.2.4 Worst-case abnormality

The worst-case abnormality is derived for each parameter separately.

All non-missing post-baseline values (including unscheduled measurements and follow-up measurements) will be used to derive the following worst-case:

- H = abnormally high: at least one post-dose measurement is above the normal range, and there are no values below the normal range.
- L = abnormally low: at least one post-dose measurement is below the normal range, and there are no values above the normal range.
- H+L = abnormally high and low: at least one post-dose measurement is above the normal range, and at least one other post-dose measurement is below the normal range.
- N = normal: all post-dose measurements are within normal limits

### 7.2.5 Analysis

For laboratory parameters, descriptive statistics (mean, median, standard error, minimum, and maximum) will be computed on the actual values and the change from baseline for each parameter. All laboratory values will be categorized according to their normal ranges as below, within or above normal. A shift table versus baseline will be created. For selected parameters a shift table will also be created according to an additional categorization:

- AST and ALT:  $\leq 1 \times \text{ULN}$  /  $> 1 \times \text{ULN}$  and  $\leq 3 \times \text{ULN}$  /  $> 3 \times \text{ULN}$  and  $\leq 5 \times \text{ULN}$  /  $> 5 \times \text{ULN}$  and  $\leq 20 \times \text{ULN}$  /  $> 20 \times \text{ULN}$
- Hb:  $\leq 8 \text{ g/dL}$  /  $> 8 \text{ g/dL}$  and  $\leq 10 \text{ g/dL}$  /  $> 10 \text{ g/dL}$
- Leukocytes:  $\geq 3000/\text{mm}^3$  /  $< 3000/\text{mm}^3$  and  $\geq 2000/\text{mm}^3$  /  $< 2000/\text{mm}^3$  and  $\geq 1000/\text{mm}^3$  /  $< 1000/\text{mm}^3$
- Serum creatinine:  $\leq 1 \times \text{ULN}$  /  $> 1 \times \text{ULN}$  and  $\leq 1.5 \times \text{ULN}$  /  $> 1.5 \times \text{ULN}$  and  $\leq 3 \times \text{ULN}$  /  $> 3 \times \text{ULN}$  and  $\leq 6 \times \text{ULN}$  /  $> 6 \times \text{ULN}$

A detailed list of tables, listings and figures can be found in Section 14.7, Section 16.8 and Section 15.6, respectively.



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### 7.3 Physical Examination

Abnormal findings in physical examinations will be listed (see Section 16.7).

### 7.4 Vital Signs

The available parameters are: pulse rate, diastolic and systolic blood pressure, weight, temperature. These will be summarized using descriptive statistics (for actual values and changes from baseline).

A detailed list of tables and listings can be found in Section 14.9 and Section 16.10, respectively.

### 7.5 ECG

Investigator's conclusion on the ECG profile will be summarized descriptively.

A detailed list of tables and listings can be found in Section 14.8 and Section 16.9, respectively.

## 8 ANALYSIS OF PHARMACOKINETICS, PHARMACODYNAMICS AND DISEASE-RELATED MARKERS

### 8.1 Analysis of pharmacokinetics

The analysis of caplacizumab in plasma samples will be performed at PRA International using a validated method. The results of the analysis will be transferred to SGS Secure Data Office in Excel format. Individual pharmacokinetic concentrations will be reported in ng/mL. Concentrations will be converted to µg/mL.

Individual study drug concentrations will be listed. In addition, a listing of the actual sampling times relative to the study drug administration times will be presented. Drug concentrations will be summarized by scheduled sampling time using descriptive statistics and will be listed and summarized in tabular and graphical form.

All analyses will be run on the safety population.

Pharmacokinetic concentrations and descriptive statistics will be reported to 3 significant digits for values up to, but not including 1000. Values equal to and above 1000 will be reported as the value without decimal signs.

A detailed list of tables, listings and figures can be found in Section 14.3, Section 16.3 and Section 15.3, respectively.



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## 8.2 Analysis of pharmacodynamics

Available parameters: RICO activity, vWF:Ag concentration and FVIII:C activity.

The sample analysis of the pharmacodynamics samples will be performed at ACM using validated methods. The results of the analysis will be transferred to SGS SD Office in Excel format. Concentrations will be reported in % with one decimal.

RICO activity, vWF:Ag concentration and FVIII:C activity will be summarized using descriptive statistics and will be listed and summarized in tabular and graphical form.

RICO activity will also be categorized and represented as a frequency tabulation (number of subjects and percentages) by timepoint using following categories: <20% / ≥20%.

All analyses will be run on the safety population. Pharmacodynamic concentrations or activity and their descriptive statistics will be reported to 3 significant digits.

A detailed list of tables, listings and figures can be found in Section 14.4, Section 16.4 and Section 15.3, respectively.

## 8.3 Analysis of pharmacokinetics/pharmacodynamics

The planned population PK/PD analysis will be described in a separate data analysis plan. The results of this analysis will be reported in an independent Modeling and Simulation report.

A figure will be made of the RICO activity in function of the PK concentration/vWF:Ag ratio (for matching samples). The PK/vWF:Ag ratio will be expressed in molarity. The conversion factor to molarity for PK is given by PK concentration (ng/mL)/14. The conversion factor to molarity for vWF:Ag is given by vWF:Ag concentration (%) x 0.4.

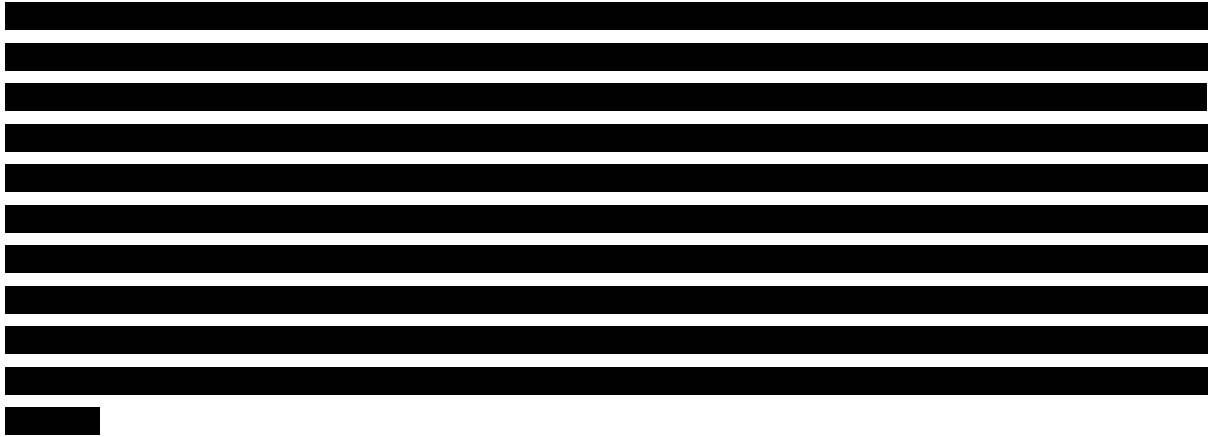
## 8.4 Analysis of disease-related markers

ADAMTS13 activity levels ( <10%/ ≥10% ) will be summarized by treatment group (Caplacizumab, Placebo, OL Caplacizumab) and by time point using the safety population.

The number and proportion of subjects with ADAMTS13 activity < 10% at Week 5 will be summarized by treatment group (Caplacizumab, Placebo, OL Caplacizumab) for the following subgroups: rituximab use during daily PE period: yes / no, other immunosuppressive treatment (not including rituximab) during daily PE period: yes / no. The effect of duration of daily PE will be analyzed by means of a logistic regression model with ADAMTS13 activity < 10% at Week 5 as dependent variable and treatment group (Caplacizumab, Placebo) and duration of daily PE as independent variables.



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## 9 IMMUNOGENICITY ANALYSIS

### 9.1 Available data

#### 9.1.1 ADA and mADA analysis

##### 9.1.1.1 ADA analysis

Immunogenicity samples will be evaluated in the bridging ADA assay. All samples scoring positive in the ADA assay will be titrated. The  $\log_{10}(\text{titer})$  will be reported. The titer represents the last dilution factor of the sample's titration series still scoring positive in the ADA assay. Samples scoring negative in the ADA assay are not titrated and the respective  $\log_{10}(\text{titer})$  is reported as  $<\log_{10}(\text{Minimal required dilution [MRD]})$  with  $\text{MRD}=96$ , i.e.  $\log_{10}(\text{titer}) < 1.98$ . The latter are not included in descriptive statistics on titers.

Subjects will be classified as follows based on the ADA assay results:

- ADA negative: no positive ADA samples at any of the sampling time points
- ADA positive: positive ADA samples at one or more sampling time points
- Inconclusive: no positive ADA samples and drug is present at levels higher than the drug tolerance characteristics of the assay
- Missing: relevant samples are missing

No statement will be made on pre-existing antibody (pre-Ab) positivity pre-dose due the plasma exchange (PE) procedure. During PE (i) pre-Ab present in donor plasma can be transferred to the patient and/or (ii) pre-Ab might be diluted during PE treatment. Since all the patients will be treated with one PE before the first caplacizumab administration, no ADA pre-PE sample will be available to determine the pre-Ab status of the patient.





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### 9.1.1.2 mADA

All positive ADA samples will be further evaluated using the modified ADA (mADA) assay. This assay employs a modified caplacizumab molecule as detection reagent in the bridging format, i.e. caplacizumab-Ala variant. The modification constitutes of a single alanine extension at the C-terminus of caplacizumab. The mADA assay allows detection of drug-induced treatment-emergent (TE) ADA, whereas pre-Ab are not detected. In other words, drug-induced TE ADA will score positive in the mADA assay. Only TE ADA responses with a restricted repertoire, directed against the C-terminal part of the Nanobody (i.e. C-terminal part of the last Nanobody domain), which might be shielded by the presence of the additional alanine on the detector reagent might be left undetected using this mADA assay. All samples scoring positive in the mADA assay will be titrated and reported as  $\log_{10}(\text{titer})$  using the same approach as for the ADA assay (see above).

Based on the mADA assay results, subjects will be classified based on pre-Ab and drug-induced TE ADA status as follows:

- Pre-Ab positive – Drug-induced TE ADA negative: all ADA positive samples analyzed in the mADA assay score negative (i)
- Pre-Ab negative – Drug-induced TE ADA positive: all ADA positive samples analyzed in the mADA assay score positive (ii).
- Pre-Ab positive – Drug-induced TE ADA positive: from the ADA positive samples analyzed in the mADA assay, some are positive and some are negative (ii)
- Inconclusive: no positive ADA samples in the mADA assay and drug is present at levels higher than the drug tolerance characteristics of the assay
- Missing: relevant samples are missing

(i) Pre-Ab can originate from the donor plasma introduced during PE procedure or can originate from the patient itself.

(ii) Subjects will be classified as pre-Ab negative, drug-induced TE ADA positive, in case all ADA positive samples analyzed in the mADA assay are positive in the latter assay. However, it cannot be excluded that in addition of the drug-induced TE ADA, pre-Ab against caplacizumab is present in those subjects.

The overall subject classification is based on the ADA and/or mADA assay results, hereafter indicated as “overall subject classification”, and is indicated below:

Overall subject classification:

- Pre-Ab negative – Drug-induced TE ADA negative: no positive ADA samples
- Pre-Ab positive – Drug-induced TE ADA negative: all ADA positive samples analyzed in the mADA assay score negative
- Pre-Ab negative – Drug-induced TE ADA positive: all ADA positive samples analyzed in the mADA assay are positive
- Pre-Ab positive – Drug-induced TE ADA positive: from the ADA positive samples analyzed in the mADA assay, some are positive and some are negative



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- Inconclusive: no positive ADA samples and drug is present at levels higher than the drug tolerance characteristics of the assay
- Missing: relevant samples are missing

Subjects classified as ADA negative based on ADA assay results will per default be classified as pre-Ab negative – Drug-induced TE ADA negative.

Given the possible switch to open-label caplacizumab in case of TTP recurrence, subjects will be classified based on the ADA samples available during the DB period, and the OL period separately. For the latter subject classification, the Day 1 visit of the OL treatment period will be used as baseline visit. In addition, patients who switch to open-label caplacizumab after having received double-blind caplacizumab treatment will be classified based on the samples collected during the overall study period. This will be done based on ADA assay results, mADA assay results and for the overall subject classification. Table 5 below provides an overview of the treatment groups for which the incidence in the different classes of the ADA, mADA and overall subject classification will be calculated, and the analysis periods for which this will be done.

**Table 5: Overview of treatment groups in the ADA, mADA and overall subject classification**

Treatment group	DB period*	OL Caplacizumab period*	Overall study period
Placebo (no OL Caplacizumab)	X		
Caplacizumab (no OL Caplacizumab)	X (i)		
OL Caplacizumab (after Placebo)	X	X (i)	
OL Caplacizumab (after Caplacizumab)	X	X	X (i)
Placebo	Combination of 'Placebo (no OL Caplacizumab)' and 'OL Caplacizumab (after Placebo)'		
Caplacizumab	Combination of 'Caplacizumab (no OL Caplacizumab)' and 'OL Caplacizumab (after Caplacizumab)'		
Caplacizumab Total	Combination of 'Caplacizumab (no OL Caplacizumab)' (DB period), 'OL Caplacizumab (after Placebo)' (OL Caplacizumab period), and 'OL Caplacizumab (after Caplacizumab)' (Overall study period), as indicated by (i)		

\* FU samples are included in the DB period if the patients are not switching to OL caplacizumab; in the latter case the FU sample is considered part of the OL Caplacizumab period.



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### 9.1.2 NAb (neutralizing antibody)

The NAb assay is based on vWF-platelet interaction. As this assay is not sufficiently drug tolerant to detect NAb under treatment, only pre-dose samples (before first caplacizumab administration, i.e. baseline visit) and wash out samples (FU samples) will be analyzed.

All samples scoring positive in the ADA assay at baseline visit or FU samples will be analyzed in the NAb assay. Samples scoring positive in the NAb assay are titrated. The titer per sample is reported as  $\log_{10}(\text{titer})$ . Samples scoring negative in the NAb assay will be reported as  $<\log_{10}(\text{MRD})$  with  $\text{MRD}=2.30$  i.e.  $\log_{10}(\text{titer}) < 0.36$ . Positive samples for which no titration can be done due to insufficient sample volume will be reported as  $>\log_{10}(\text{MRD})$ . These positive samples (for which no titration could be done) should be plotted as  $\log(\text{MRD})$  equal to 0.36 in the figure.

Subjects will be classified based on their pre-dose status (i.e. baseline visit) and treatment-emergent (TE) status. Subject classification based on NAb is as follows:

- Pre-dose negative, TE negative: no positive samples
- Pre-dose negative, TE positive: negative baseline visit and one or more positive samples post-dose
- Pre-dose positive, TE negative: positive baseline visit and no titer increase post-dose or all samples scoring negative post-dose
- Pre-dose positive, TE positive: positive baseline visit and titer increase post-dose
- Missing: relevant ADA samples are missing

Subjects with no positive NAb samples will be classified as NAb pre-dose negative, TE negative. In listings, samples not evaluated in the NAb assay will be indicated as not analyzed (NA). In graphical presentations, these samples will be presented as negative results.

Given the possible switch to OL Caplacizumab treatment in case of TTP recurrence, subjects will be classified based on the ADA samples available during the DB period, and the OL period, separately. For the latter subject classification, the Day 1 visit of the OL treatment period will be used as baseline visit. Table 6 below provides an overview of the treatment groups for which the incidence in the different classes of the subject classification based on NAb will be calculated, and the analysis periods for which this will be done.

**Table 6: Overview of treatment groups in the subject classification based on NAb**

Treatment group	DB period*	OL Caplacizumab period*	Overall study period
Placebo (no OL Caplacizumab)	X		
Caplacizumab (no OL Caplacizumab)	X		
OL Caplacizumab (after Placebo)		X	



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OL Caplacizumab (after Caplacizumab)			X
Caplacizumab Total	Combination of 'Caplacizumab (no OL Caplacizumab)' (DB period), 'OL Caplacizumab (after Placebo)' (OL Caplacizumab period), and 'OL Caplacizumab (after Caplacizumab)' (Overall study period)		

\* Pre-dose and FU samples only.

### **9.1.3 Alternative NAb (epitope characterization; null variant assay): ADA with neutralizing potential**

To detect ADA with potential neutralizing activity during treatment an alternative NAb assay will be used, consisting of the bridging ADA assay in which an altered caplacizumab molecule (i.e. caplacizumab with mutated complementary determining region [CDR] regions) is added in excess to capture all non-CDR binding ADA. Consequently, using this assay, only ADA binding to the CDRs of the Nanobody are detected. Those ADA are considered to have neutralizing potential, although clinical relevance (i.e., ability to block binding of vWF) will be dependent on affinity and titer level and should be related to PK, PD and efficacy read-outs.

All samples scoring positive in the ADA assay, will be analyzed in alternative nAb assay. Samples scoring positive in the alternative nAb assay are titrated. The titer per sample is reported as log<sub>10</sub>(titer). Samples scoring negative in the alternative NAb assay are not titrated and the respective titer is reported as <log<sub>10</sub>(MRD) with MRD=96, i.e. log<sub>10</sub>(titer)<1.98.

Subjects will be classified based on their pre-dose status (i.e. baseline visit) and treatment-emergent status. Subject classification based on alternative NAb assay is as follows:

- Pre-dose negative, TE negative: no positive samples
- Pre-dose negative, TE positive: negative baseline visit and one or more positive samples post-dose.
- Pre-dose positive, TE negative: positive baseline visit and no titer increase post-dose or all samples scoring negative post-dose
- Pre-dose positive, TE positive: positive baseline visit and titer increase post-dose
- Inconclusive: no positive samples and drug is present at levels higher than the drug tolerance characteristics of the assay
- Missing: relevant ADA samples are missing

Subjects with no positive ADA sample will be classified as pre-dose negative, TE negative in the alternative NAb assay. In listings, samples not evaluated in the alternative NAb assay will be indicated as not analyzed (NA). In graphical presentations they will be presented as negative results at the specific sample time points.

Given the possible switch to open-label caplacizumab in case of TTP recurrence, subjects will be classified based on the ADA samples available during the DB period, and the OL period separately. For the latter subject classification, the Day 1 visit of the OL treatment period will be used as baseline visit. Patients who switch to open-label caplacizumab after having received double-blind caplacizumab treatment will be classified based on the DB period and



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the overall study period, but not on the OL Caplacizumab period, as the OL Day 1 baseline visit cannot be considered a proper baseline visit for this analysis. Table 7 below provides an overview of the treatment groups for which the incidence in the different classes of the subject classification based on alternative NAb will be calculated, and the analysis periods for which this will be done.

**Table 7: Overview of the treatment groups based on alternative NAb**

Treatment group	DB period*	OL Caplacizumab period*	Overall study period
Placebo (no OL Caplacizumab)	X		
Caplacizumab (no OL Caplacizumab)	X (i)		
OL Caplacizumab (after Placebo)	X	X (i)	
OL Caplacizumab (after Caplacizumab)	X	Not done	X (i)
Placebo	Combination of 'Placebo (no OL Caplacizumab)' and 'OL Caplacizumab (after Placebo)'		
Caplacizumab	Combination of 'Caplacizumab (no OL Caplacizumab)' and 'OL Caplacizumab (after Caplacizumab)'		
Caplacizumab Total	Combination of 'Caplacizumab (no OL Caplacizumab)' (DB period), 'OL Caplacizumab (after Placebo)' (OL Caplacizumab period), and 'OL Caplacizumab (after Caplacizumab)' (Overall study period), as indicated by (i)		

\* FU samples are included in the DB period if the patients are not switching to OL caplacizumab; in the latter case the FU sample is considered part of the OL Caplacizumab period.

## 9.2 Analysis

Immunogenicity will be assessed through summary tables and figures, and listing of individual results by subject. Immunogenicity data will be correlated with PK, PD and efficacy endpoints. In addition, immunogenicity will be correlated with possible safety findings. No formal inferential statistics (p-values) will be derived.

All analyses will be run on the safety population, unless specified otherwise.

A detailed list of tables, figures and listings can be found in Section 14.10, Section 15.7 and Section 16.11, respectively.

The immunogenicity results for the pediatric substudy will be reported via listings only.



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### **9.2.1 Subgroup analyses**

Analysis of incidence based on ADA/mADA results (overall subject classification) are planned for the following subgroups:

- Hypersensitivity reaction, with categories
  - No hypersensitivity reaction
  - At least 1 hypersensitivity reaction

### **9.2.2 Exploratory analyses**

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

## **10 INTERIM ANALYSES**

There are no interim analyses in this study.

## **11 DSMB REVIEWS FOR SAFETY**

A Data Safety Monitoring Board (DSMB) has been appointed by the Sponsor, consisting of an independent group of clinical experts, who are not participating in the study. They are supplemented by an independent statistician. The objective of the DSMB is to review unblinded safety data on SAEs with a focus on mortality rate. The composition, objectives, and role and responsibilities of the independent DSMB are described in a DSMB charter, agreed with the DSMB members and Sponsor. The DSMB charter also defines and document the content of the safety summaries, and general procedures (including communications).

## **12 CHANGE FROM ANALYSIS PLANNED IN PROTOCOL**

### **12.1 Changes before database lock**

No shift tables for Vital signs are produced as they are not representing essential information that is not available elsewhere in the outputs.

In order to reduce any possible bias in the estimation of the effectiveness of Caplacizumab versus Placebo, the main efficacy analysis will be performed on the ITT population instead of



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mITT. For the primary endpoint a separate analysis on mITT will be performed as sensitivity analysis.

Per protocol, all samples will be analyzed by a central laboratory, except for pregnancy, screening creatinine and samples of platelet count. However, some extra local laboratory creatinine samples have been analyzed for visits after screening. Those results will only be listed and will not be used for analysis. The extra local creatinine taken for safety reason will not be considered as protocol deviation. Those taken for reasons other than safety will be captured as protocol deviation. The same will apply for the extra PE assessments performed outside of the time point indicated in the schedule of assessment.

## 12.2 Changes after database lock

Not applicable.

## 13 REFERENCE LIST

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- Webb R, Singer M. Oxford Handbook of Critical Care. Oxford ; New York : *Oxford University Press*, 2005.



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## 14 INDEX OF TABLES

### 14.1 General

**Table 14.1.1.1: Subject disposition: Tabulation by analysis population**

Tabulation of the number of subjects in each of the analysis populations defined in Section 4.1.

Population: all screened population.

**Table 14.1.1.2: Subject disposition: Tabulation by country and site**

Tabulation of the number of subjects per country and site.

Population: ITT population.

**Table 14.1.1.3: Subject disposition: Tabulation by time point**

Tabulation of the number of subjects per time point.

Population: ITT population.

**Table 14.1.1.4: Subject disposition: First and last contact in the trial**

Tabulation of the following 3 dates:

- Date of the first signature on trial ICF or pre-trial ICF
- Last visit date (all visits; including unscheduled visits)
- Last date of contact in the study with any subject (i.e., the last DM.RFENDTC).

Population: all screened population.

**Table 14.1.1.5: Subject disposition: Descriptive statistics of the analysis period duration (days)**

Descriptive statistics of the analysis period duration. The duration (days) is derived as follows: period end date – period start date + 1. This table will represent phases, periods and subperiods.

Population: ITT population.

**Table 14.1.1.6: Trial termination: Tabulation**

Tabulation of completion/discontinuations and the reasons for discontinuation.

Population: ITT population.

**Table 14.1.1.7: Major protocol deviations: Tabulation**

Tabulation of the major protocol deviations per category (DVDECOD) (see Section 5.2 for more details).

Population: ITT population.

**Table 14.1.2.1: Demographic data: Tabulation and descriptive statistics**

Continuous parameters: descriptive statistics.

Categorical parameters: frequency tabulation.

Population: ITT population.

**Table 14.1.2.2: Baseline disease characteristics: Tabulation and descriptive statistics**





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Continuous parameters: descriptive statistics.

Categorical parameters: frequency tabulation.

Population: ITT population.

**Table 14.1.2.3: Concomitant immunosuppressive therapies**

Tabulation of type of immunosuppressive therapies (corticosteroid / rituximab / other immunosuppressive).

Population: ITT population.

**Table 14.1.2.4: Concomitant immunosuppressive therapies by generic term**

Tabulation of the generic terms of immunosuppressive therapies.

Population: ITT population.

**Table 14.1.2.5: Concomitant non-immunosuppressive therapies by generic term**

Tabulation of the generic terms of non-immunosuppressive therapies.

Population: ITT population.

**Table 14.1.2.6: Concomitant antithrombotic therapies by generic term**

Tabulation of the generic terms of immunosuppressive therapies.

Population: ITT population.

**Table 14.1.2.7: Transfusions**

Tabulation of transfusions.

Population: ITT population.

**Table 14.1.2.8: Duration of corticosteroids use and cumulative dose of corticosteroids**

Tabulation by treatment group during the overall treatment period. Corticosteroids will be reported as prednisolone equivalent dose.

Population: ITT population.

**Table 14.1.2.9: Exposure to study medication: Descriptive statistics**

Descriptive statistics of treatment duration and compliance, present by sub-period (dPE and post dPE) and overall for the DB treatment period.

Population: safety population.

## 14.2 Efficacy

### 14.2.1 Platelet count

**Table 14.2.1.1.1: EFF: Platelet count - Primary endpoint: Time to platelet count response**

Kaplan-Meier analysis stratified for GCS at randomization, including a two-sided stratified Log-rank test. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs and p-value of the log-rank test



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as well as the hazard ratio (including CI) of the corresponding Cox proportional hazards model (see table 14.2.1.1.2 below for more details on the Cox model).

The table will be presented both by GCS category, and overall, i.e. unadjusted by GCS category.

Population: ITT population.

**Table 14.2.1.1.2: EFF: Platelet count – Primary endpoint: Cox proportional hazards model on Time to platelet count response**

Cox proportional hazards regression model with time to platelet count response as dependent variable and treatment group and GCS category as independent variables. Table consists of 3 parts:

Part 1: Results of the Cox proportional hazards model including hazard ratio and CI on hazard ratio.

Part 2: Assumption testing including supremum test on proportion of simulated score processes that yielded a maximum score larger than the maximum observed score and a graphical representation of observed score processes per covariate

Part 3 (conditional): Results of the expanded Cox proportional hazards model including hazard ratio and CI on hazard ratio. This part will only be reported when the original assumption of proportional hazards does not hold and time interaction(s) need to be added.

Population: ITT population.

**Table 14.2.1.1.3: EFF: Platelet count – Sensitivity: Time to platelet count response (mITT)**

Kaplan-Meier analysis stratified for GCS at randomization, including a two-sided stratified Log-rank test. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs and p-value of the log-rank test as well as the hazard ratio (including CI) of the corresponding Cox proportional hazards model (see table 14.2.1.1.4 below for more details on the Cox model).

The table will be presented both by GCS category, and overall, i.e. unadjusted by GCS category.

Population: mITT population.

**Table 14.2.1.1.4: EFF: Platelet count – Sensitivity: Cox proportional hazards model on Time to platelet count response (mITT)**

Cox proportional hazards regression model with time to platelet count response as dependent variable and treatment group and GCS category as independent variables. Table consists of 3 parts:

Part 1: Results of the Cox proportional hazards model including hazard ratio and CI on hazard ratio.

Part 2: Assumption testing including supremum test on proportion of simulated score processes that yielded a maximum score larger than the maximum observed score and a graphical representation of observed score processes per covariate

Part 3 (conditional): Results of the expanded Cox proportional hazards model including hazard ratio and CI on hazard ratio. This part will only be reported when the original assumption of proportional hazards does not hold and time interaction(s) need to be added.

Population: mITT population.



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**Table 14.2.1.1.5: EFF: Platelet count – Sensitivity: Time to platelet count response (Per protocol)**

Kaplan-Meier analysis stratified for GCS at randomization, including a two-sided stratified Log-rank test. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs and p-value of the log-rank test as well as the hazard ratio (including CI) of the corresponding Cox proportional hazards model (see table 14.2.1.1.6 below for more details on the Cox model).

The table will be presented both by GCS category, and overall, i.e. unadjusted by GCS category.

Population: PP population.

**Table 14.2.1.1.6: EFF: Platelet count – Primary endpoint: Cox proportional hazards model on Time to platelet count response (Per protocol)**

Cox proportional hazards regression model with time to platelet count response as dependent variable and treatment group and GCS category as independent variables. Table consists of 3 parts:

Part 1: Results of the Cox proportional hazards model including hazard ratio and CI on hazard ratio.

Part 2: Assumption testing including supremum test on proportion of simulated score processes that yielded a maximum score larger than the maximum observed score and a graphical representation of observed score processes per covariate

Part 3 (conditional): Results of the expanded Cox proportional hazards model including hazard ratio and CI on hazard ratio. This part will only be reported when the original assumption of proportional hazards does not hold and time interaction(s) need to be added.

Population: PP population.

**Table 14.2.1.1.7: EFF: Platelet count – Sensitivity: Time to platelet count response (ITT - Constrained response definition)**

Similar to primary endpoint with constrained definition of response by considering efficacy scenario 2, 5 and 8 as non-responders. Kaplan-Meier analysis stratified for GCS at randomization, including a two-sided stratified Log-rank test. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs and p-value of the log-rank test as well as the hazard ratio (including CI) of the corresponding Cox proportional hazards model (see table 14.2.1.1.8 below for more details on the Cox model).

The table will be presented both by GCS category, and overall, i.e. unadjusted by GCS category.

Population: ITT population.

**Table 14.2.1.1.8: EFF: Platelet count – Sensitivity: Cox proportional hazards model on Time to platelet count response (ITT - Constrained response definition)**

Similar to primary endpoint with constrained definition of response by considering efficacy scenario 2, 5 and 8 as non-responders



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Cox proportional hazards regression model with time to platelet count response as dependent variable and treatment group and GCS category as independent variables. Table consists of 3 parts:

Part 1: Results of the Cox proportional hazards model including hazard ratio and CI on hazard ratio.

Part 2: Assumption testing including supremum test on proportion of simulated score processes that yielded a maximum score larger than the maximum observed score and a graphical representation of observed score processes per covariate

Part 3 (conditional): Results of the expanded Cox proportional hazards model including hazard ratio and CI on hazard ratio. This part will only be reported when the original assumption of proportional hazards does not hold and time interaction(s) need to be added.

Population: ITT population.

**Table 14.2.1.1.9: EFF: Platelet count – Sensitivity: Time to first platelet count  $\geq 150 \times 10^9/L$  (ITT - dPE stop within 5 days not required)**

Similar to primary endpoint without the requirement to stop daily PE within 5 days. Kaplan-Meier analysis stratified for GCS at randomization, including a two-sided stratified Log-rank test. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs and p-value of the log-rank test as well as the hazard ratio (including CI) of the corresponding Cox proportional hazards model (see table 14.2.1.1.10 below for more details on the Cox model).

The table will be presented both by GCS category, and overall, i.e. unadjusted by GCS category.

Population: ITT population.

**Table 14.2.1.1.10: EFF: Platelet count – Sensitivity: Cox proportional hazards mode: Time to first platelet count  $\geq 150 \times 10^9/L$  (ITT - dPE stop within 5 days not required)**

Similar to primary endpoint without the requirement to stop daily PE within 5 days.

Cox proportional hazards regression model with time to platelet count response as dependent variable and treatment group and GCS category as independent variables. Table consists of 2 parts:

Part 1: Results of the Cox proportional hazards model including hazard ratio and CI on hazard ratio.

Part 2: Assumption testing including supremum test on proportion of simulated score processes that yielded a maximum score larger than the maximum observed score and a graphical representation of observed score processes per covariate

Part 3 (conditional): Results of the expanded Cox proportional hazards model including odds hazard ratio and CI on hazard ratio. This part will only be reported when the original assumption of proportional hazards does not hold and time interaction(s) need to be added.

Population: ITT population.

**Table 14.2.1.1.11: EFF: Platelet count – Proportion of subjects with platelet count  $\geq 150 \times 10^9/L$**



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Frequency tabulation of having a platelet count  $\geq 150 \times 10^9/L$ . The following time points will be shown: Day 1, Day 2, Day 3, Day 4, Day 5, Day 10 and end of study drug treatment (i.e., last weekly visit during the DB or OL treatment period).

Population: ITT population.

**Table 14.2.1.1.12: EFF: Platelet count – AUC until Day 5**

Descriptive statistics of AUC of platelet count until Day 5.

Population: ITT population.

**Table 14.2.1.1.13: EFF: Platelet count – Actual values at each time point**

Descriptive statistics of platelet count at each time point including (5% 10% 25% 75% 90% and 95% percentiles).

Population: ITT population.

## **14.2.2 TTP**

**Table 14.2.1.2.1: EFF: TTP – Key secondary endpoint: Proportion of subjects with TTP-related death, a recurrence of TTP, or at least one treatment-emergent major thromboembolic event during the study drug treatment period**

Frequency table of TTP-related death, a recurrence of TTP, or at least one treatment-emergent major thromboembolic event during the study drug treatment period and p-value of the Cochran-Mantel-Haenszel test with adjustment for GCS at randomization. Within the treatment emergent major thromboembolic events category the frequency tabulation of different preferred terms will be shown.

Population: ITT population.

**Table 14.2.1.2.2: EFF: TTP – Key secondary endpoint: Proportion of subjects with a recurrence of TTP in the overall study period**

Frequency table of recurrence of TTP in the overall study period and p-value of the Cochran-Mantel-Haenszel test with adjustment for GCS at randomization.

Population: ITT population.

**Table 14.2.1.2.3: EFF: TTP – Key secondary endpoint: Proportion of subjects with refractory TTP**

Frequency table of refractory TTP and p-value of the Cochran-Mantel-Haenszel test with adjustment for GCS at randomization.

Population: ITT population.

**Table 14.2.1.2.4: EFF: TTP – Proportion of subjects with refractory TTP according to Scully et al. (2016)**

Frequency table of refractory TTP according to Scully et al. (2016).

Population: ITT population.

**Table 14.2.1.2.5: EFF: TTP – Proportion of subjects with treatment-emergent clinically significant TTP-related events**



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Number and percentage of subjects with and number of events of treatment-emergent clinically significant TTP-related events in the overall study period.

Population: ITT population.

### **14.2.3 Organ damage markers**

#### **Table 14.2.1.3.1: EFF: Organ damage marker levels – Key secondary endpoint: Time to normalization of all 3 of the organ damage marker levels**

Kaplan-Meier analysis stratified for GCS at randomization and LDH status ( $\leq$  ULN /  $>$  ULN) at baseline, including a two-sided stratified Log-rank test. The output will include number of events, number of censored values, median, 25% and 75% time to event with 95% CIs and p-value of the log-rank test. If the model does not allow parameter estimation due to limited observations in subcategory combinations, GCS stratification factor will be omitted from the analysis.

Population: ITT population.

#### **Table 14.2.1.3.2: EFF: Organ damage marker levels – Time to normalization of LDH**

Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% and 75% time to event with 95% CIs.

Population: ITT population.

#### **Table 14.2.1.3.3: EFF: Organ damage marker levels – Time to normalization of cTnI**

Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% and 75% time to event with 95% CIs.

Population: ITT population.

#### **Table 14.2.1.3.4: EFF: Organ damage marker levels – Time to normalization of serum creatinine**

Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% and 75% time to event with 95% CIs.

Population: ITT population.

#### **Table 14.2.1.3.5: EFF: Organ damage marker levels – Proportion of subjects with increases in organ damage markers**

Frequency tabulation of increased organ damage markers ( $>$  ULN), by marker (cTnI and serum creatinine) and analysis period (DB treatment daily PE period, overall treatment period, FU period and overall study period).

Population: ITT population.

#### **Table 14.2.1.3.6: EFF: Organ damage marker levels – AUC of cTnI $>$ ULN**

Descriptive statistics of AUC(cTnI)  $>$  ULN during DB treatment daily PE period and during overall treatment period. Separate tabulation including and excluding cTnI peaks at baseline.

Population: ITT population.

#### **Table 14.2.1.3.7: EFF: Organ damage marker levels – Actual values at each time point**

Descriptive statistics of LDH, cTnI and serum creatinine at each time point.



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Population: ITT population.

#### **14.2.4 Neurology**

##### **Table 14.2.1.4.1: EFF: Neurology – Proportion of subjects with neurological symptoms**

Frequency tabulation of neurological symptoms based on neurological assessment on Day 1, 2, 3, 4, 5 and Weeks 1 and 5 of 30-day post-daily PE treatment period, and the first and final FU visit.

Population: ITT population.

##### **Table 14.2.1.4.2: EFF: Neurology – SMMSE actual values**

Descriptive statistics of SMMSE total score on Days 1, 2, 3, 4, 5 and Weeks 1 and 5 of the 30-day post-daily PE treatment period, and the first and final FU visit.

Population: ITT population.

##### **Table 14.2.1.4.3: EFF: Neurology – SMMSE change from baseline**

Descriptive statistics of change from baseline in SMMSE total score on Days 2, 3, 4, 5 and Weeks 1 and 5 of the 30-day post-daily PE treatment period, and the first and final FU visit.

Population: ITT population.

#### **14.2.5 Plasma exchange**

##### **Table 14.2.1.5.1: EFF: Plasma Exchange – Time to stop of daily PE**

Kaplan-Meier analysis. The output will include number of events, number of censored values, median, 25% and 75% time to event with 95% CIs.

Population: ITT population.

##### **Table 14.2.1.5.2: EFF: Plasma Exchange – Number of days of PE**

Descriptive statistics of the number of days of PE, in the DB treatment daily PE period and in the overall treatment period separately.

Population: ITT population.

##### **Table 14.2.1.5.3: EFF: Plasma Exchange – Total volume of PE (absolute)**

Descriptive statistics of the total volume of PE (absolute), in the DB treatment daily PE period and in the overall treatment period separately.

Population: ITT population.

##### **Table 14.2.1.5.4: EFF: Plasma Exchange – Total volume of PE (normalized)**

Descriptive statistics of the total volume of PE (normalized), in the DB treatment daily PE period and in the overall treatment period separately.

Population: ITT population.



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### **14.2.6 Safety parameters**

#### **Table 14.2.1.6.1: EFF: Safety related parameters – Mortality rate**

Number and percentage of subjects who died and mortality rate during each of the 4 time periods: DB treatment daily PE period, overall treatment period, FU period and overall study period.

Population: ITT population.

#### **Table 14.2.1.6.2: EFF: Safety related parameters – Proportion of subjects with evidence of cardiac ischemia and/or arrhythmia/conduction abnormalities**

Frequency tabulation of evidence of cardiac ischemia and/or arrhythmia/conduction abnormalities on Days 1, 2, 3, and 4, and Weeks 1 and 5 of 30-day post-daily PE treatment period, and the first and final FU visit.

Population: ITT population.

#### **Table 14.2.1.6.3: EFF: Safety related parameters – Number of days in hospital**

Descriptive statistics of the number of days in hospital in 4 time periods: DB treatment daily PE period, overall treatment period, FU period and overall study period.

Population: ITT population.

#### **Table 14.2.1.6.4: EFF: Safety related parameters – Number of days in ICU**

Descriptive statistics of the number of days in ICU in 4 time periods: DB treatment daily PE period, overall treatment period, FU period and overall study period.

Population: ITT population.

### **14.2.7 Subgroup analyses**

#### **Table 14.2.1.7.1: EFF: Subgroup analyses - Time to platelet count response**

Kaplan-Meier analysis stratified for GCS at randomization. The output will include number of events, number of censored values, median, 25% percentile and 75% percentile of time to event with 95% CIs.

The table will be presented both by GCS category, and overall, i.e. unadjusted by GCS category.

Following subgroups will be analyzed if at least 5 data points per category are available:

ADAMTS13 activity at admission or baseline <10% / ≥10%

Previous TTP episode(s): initial/recurrent

Baseline severity of disease: very severe/ less severe

Population: ITT population.

#### **Table 14.2.1.7.2: EFF: Subgroup analyses - Proportion of subjects with refractory TTP**

Frequency table of refractory TTP Following subgroups will be analyzed if at least 5 data points per category are available:

ADAMTS13 activity at admission or baseline <10% / ≥10%

Previous TTP episode(s): initial/recurrent





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Baseline severity of disease: very severe/ less severe  
Population: ITT population.

**Table 14.2.1.7.3: EFF: Subgroup analyses - Proportion of subjects with a recurrence of TTP in the overall study period**

Frequency table of recurrence of TTP in the overall study period.

Following subgroups will be analyzed if at least 5 data points per category are available:

Baseline severity of disease: very severe/ less severe

Population: ITT population.

**Table 14.2.1.7.4: EFF: Subgroup analyses – Proportion of subjects with at least one treatment-emergent major thromboembolic event during overall treatment period**

Number and percentage of subjects with at least one treatment-emergent major thromboembolic event (adjudicated) during the overall treatment period, as well as the number of events. Within the treatment emergent major tromboembolic events category the frequency tabulation of different preferred terms will be shown.

Following subgroups will be analyzed if at least 5 data points per category are available:

Baseline severity of disease: very severe/ less severe

Population: ITT population.

**14.2.8 Exploratory analyses**

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### 14.3 Pharmacokinetics

#### Table 14.2.2.1: PK: Descriptive statistics of drug concentrations

Descriptive statistics of drug concentrations by scheduled sampling time and treatment group.  
Population: safety population.

### 14.4 Pharmacodynamics

#### Table 14.2.3.1: PD: Descriptive statistics of PD concentrations



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Descriptive statistics of the vWF:Ag concentrations and FVIII:C activity and RICO activity by treatment group and by time point.

Population: safety population.

**Table 14.2.3.2: PD: Tabulation of RICO activity per timepoint**

Tabulation of number and percentage of subjects in RICO activity category (<20%, ≥20%) by treatment group and timepoint.

Population: safety population.

## 14.5 Disease related markers

**Table 14.2.4.1: Disease related markers: Descriptive statistics of ADAMTS13 activity**

Descriptive statistics of ADAMTS13 activity levels by treatment group and by time point.

Population: safety population.

**Table 14.2.4.2: Disease related markers: Logistic regression: proportion of subjects with ADAMTS13 activity < 10% at Week 5.**

Frequency tabulation of number and percentage of subjects with ADAMTS13 activity <10% including Logistic regression results on model with ADAMTS13 <10% at Week 5 as dependent variable and treatment group and duration of daily PE (including interaction) as independent variables. The analysis will be repeated for following subgroups:

-Overall

-Rituximab immunosuppressive use during daily PE yes/no

-Non-Rituximab immunosuppressive use during daily PE yes/no

Population: safety population.

**Table 14.2.4.3: Disease related markers: Cox proportional hazards model: Time to sustained ADAMTS13 activity ≥ 10%.**

Cox proportional hazards regression model with Time to sustained ADAMTS13 activity ≥10% as dependent variable. Time to sustained ADAMTS13 activity ≥ 10% is defined as 2 consecutive weekly visits during treatment or follow-up with reported ADAMTS13 activity ≥ 10% (first visit will be used to calculate time to event).

Following covariates will be tested:

-Rituximab immunosuppressive use during daily PE yes/no

-Non-Rituximab immunosuppressive use during daily PE yes/no

-Duration of daily PE

-Tapering of daily PE yes/no

Population: safety population.

## 14.6 Safety: Adverse Events

**Table 14.3.1.1: Treatment-emergent adverse events: Summary table**



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Tabulation of the number and percentage of subjects, the number of events and the incidence per 100 patient months for the following:

- Subjects with at least one TEAE
- Subjects with at least one serious TEAE
- Subjects with at least one TEAE leading to death
- Subjects with at least one TEAE for which the study drug was interrupted
- Subjects with at least one TEAE for which the study drug was withdrawn
- Subjects with at least one TEAE that was considered at least possibly treatment-related by the investigator
- Subjects with at least one serious TEAE that was considered at least possibly treatment-related by the investigator
- Subjects with at least one bleeding event (i.e. event documented as event indicating an increased bleeding tendency)
- Subjects with at least one bleeding event, based on SMQ 'Haemorrhage terms (excluding laboratory terms)'
- Subjects with at least one hypersensitivity reaction, based on the SMQs 'Hypersensitivity' (Narrow), 'Anaphylactic reaction' (Narrow) and 'Angioedema' (Narrow)
- Subjects with at least one hypersensitivity reaction, based on the SMQs 'Hypersensitivity' (Narrow), 'Anaphylactic reaction' (Narrow) and 'Angioedema' (Narrow), considered at least possibly treatment-related by the investigator

Population: safety population.

**Table 14.3.1.2: Treatment-emergent adverse events: Tabulation of all adverse events**

Tabulation of TEAE preferred terms per system organ class.

Population: safety population.

**Table 14.3.1.3: Treatment-emergent adverse events: Tabulation of all adverse events by severity**

Tabulation of TEAE preferred terms per system organ class by severity.

Population: safety population.

**Table 14.3.1.4: Treatment-emergent adverse events: Tabulation of serious adverse events**

Tabulation of serious TEAE preferred terms per system organ class.

Population: safety population.

**Table 14.3.1.5: Treatment-emergent adverse events: Tabulation of serious adverse events by severity**

Tabulation of serious TEAE preferred terms per system organ class by severity.

Population: safety population.

**Table 14.3.1.6: Treatment-emergent adverse events: Tabulation of non-serious adverse events**

Tabulation of non-serious TEAE preferred terms per system organ class.

Population: safety population.



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**Table 14.3.1.7: Treatment-emergent adverse events: Tabulation of all treatment-related adverse events**

Tabulation of TEAE preferred terms per system organ class. Selecting only the TEAEs that were treatment-related (as defined in Section 7.1.1).

Population: safety population.

**Table 14.3.1.8: Treatment-emergent adverse events: Tabulation of all treatment-related serious adverse events**

Tabulation of TEAE preferred terms per system organ class. Selecting only the serious TEAEs that were treatment-related (as defined in Section 7.1.1).

Population: safety population.

**Table 14.3.1.9: Treatment-emergent adverse events: Tabulation of all treatment-related bleeding events**

Tabulation of TEAE preferred terms per system organ class. Selecting only the bleeding events, based on event documented as event indicating an increased bleeding tendency, that were treatment-related (as defined in Section 7.1.1).

Population: safety population.

**Table 14.3.1.10: Treatment-emergent adverse events: Tabulation of all treatment-related serious bleeding events**

Tabulation of TEAE preferred terms per system organ class. Selecting only the serious bleeding events, based on event documented as event indicating an increased bleeding tendency, that were treatment-related (as defined in Section 7.1.1).

Population: safety population.

**Table 14.3.1.11: Treatment-emergent adverse events: Tabulation of all treatment-related bleeding events (SMQ)**

Tabulation of TEAE preferred terms per system organ class. Selecting only the bleeding events, based on SMQ 'Haemorrhage terms (excluding laboratory terms)', that were treatment-related (as defined in Section 7.1.1).

Population: safety population.

**Table 14.3.1.12: Treatment-emergent adverse events: Tabulation of all treatment-related serious bleeding events (SMQ)**

Tabulation of TEAE preferred terms per system organ class. Selecting only the serious bleeding events, based on SMQ 'Haemorrhage terms (excluding laboratory terms)', that were treatment-related (as defined in Section 7.1.1).

Population: safety population.

**Table 14.3.1.13: Treatment-emergent adverse events: Tabulation of the events for which the trial or the study medication were discontinued or interrupted**

Tabulation of TEAE preferred terms per system organ class and per analysis period. Selecting only the TEAEs for which the study treatment was permanently discontinued or interrupted, or for which the study was discontinued.

Population: safety population.



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**Table 14.3.1.14: Treatment-emergent adverse events: Tabulation of all thromboembolic events**

Tabulation of TEAE preferred terms per system organ class and per analysis period. Selecting only the thromboembolic TEAEs.

Population: safety population.

**Table 14.3.1.15: Treatment-emergent adverse events: Tabulation of all hypersensitivity reactions**

Tabulation of TEAE preferred terms per system organ class and per analysis period. Selecting only the hypersensitivity reactions.

Population: safety population.

**Table 14.3.1.16: Treatment-emergent adverse events: Tabulation of all treatment-related hypersensitivity reactions**

Tabulation of TEAE preferred terms per system organ class and per analysis period. Selecting only the hypersensitivity reactions that were treatment-related (as defined in Section 7.1.1).

Population: safety population.

**Table 14.3.1.17: Treatment-emergent adverse events: Tabulation of all adverse events by subgroup**

Tabulation of TEAE preferred terms per system organ class by subgroup. Following subgroups will be shown:

- Treatment extension ( yes/ no )
- Baseline disease severity ( very severe/ less severe )

Population: safety population.

**Table 14.3.1.18: Treatment-emergent adverse events: Tabulation of all serious adverse events by subgroup**

Tabulation of serious TEAE preferred terms per system organ class by subgroup. Following subgroups will be shown:

- Treatment extension ( yes/ no )
- Baseline disease severity ( very severe/ less severe )

Population: safety population.

**Table 14.3.1.19: Treatment-emergent adverse events: Tabulation of all bleeding events by subgroup**

Tabulation of bleeding event preferred terms per system organ class by subgroup. Following subgroups will be shown:

- Treatment extension ( yes/ no )
- Baseline disease severity ( very severe/ less severe )
- Antithrombotic agents (yes / no), this subgroup will be based on MedDRA coding (ATC term Antithrombotic Agents, ATC codes starting with B01A).

Population: safety population.



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**Table 14.3.1.20: Treatment-emergent adverse events: Tabulation of all thromboembolic events by subgroup.**

Tabulation of TEAE preferred terms per system organ class and per analysis period (including number of events and incidence per 100 patient months) by subgroup. Following subgroups will be shown:

Refractory TTP (yes / no)

Population: safety population.

**14.7 Safety: Laboratory****Table 14.3.2.1: Laboratory data: Descriptive statistics of the actual values per time point**

Descriptive statistics per lab test category (hematology, biochemistry and coagulation), lab test and unit and time point. Table sorted first by treatment group, then by time point. Each lab test will begin on a new page.

Population: safety population.

**Table 14.3.2.2: Laboratory data: Descriptive statistics of the absolute changes from baseline per time point**

Descriptive statistics per lab test category (hematology, biochemistry and coagulation), lab test and unit and time point. Table sorted first by treatment group, then by time point. Each lab test will begin on a new page.

Population: safety population.

**Table 14.3.2.3: Laboratory data: Descriptive statistics of the percentage changes from baseline per time point**

Descriptive statistics per lab test category (hematology, biochemistry and coagulation), lab test and unit and time point. Table sorted first by treatment group, then by time point. Each lab test will begin on a new page.

Population: safety population.

**Table 14.3.2.4: Laboratory data: Cross-tabulation of the abnormalities per time point**

Cross-tabulation per lab test category (hematology, biochemistry and coagulation), lab test and time point. Table sorted first by treatment group, then by time point. Each lab test will begin on a new page. The table will present the shift in abnormality (L/N/H) at each post-baseline time point versus the baseline abnormality (L/N/H). Tests without normal ranges will not be presented in this table.

Population: safety population.

**Table 14.3.2.5: Laboratory data: Additional cross-tabulation of the abnormalities per time point for key parameters**

Cross-tabulation per lab test and time point. Table sorted first by treatment group, then by time point. Each lab test will begin on a new page. The table will present the shift in abnormality at each post-baseline time point versus the baseline abnormality, according to the additional categorization described in Section [7.2.5](#).





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ALT, AST, hemoglobin, leukocytes and serum creatinine will be presented in this table.  
Population: safety population.

**Table 14.3.2.6: Laboratory data: Cross-tabulation of the worst-case abnormalities**

Cross-tabulation per lab test category (hematology, biochemistry and coagulation) and lab test. Each lab test will begin on a new page. The table will present the shift in abnormality (L/N/H/L+H) at the worst post-baseline time point versus the baseline abnormality (L/N/H). Tests without normal ranges will not be presented in this table.  
Population: safety population.

**Table 14.3.2.7: Laboratory data: Additional cross-tabulation of the worst-case abnormalities for key parameters**

Cross-tabulation per lab test. The table will present the shift in abnormality at the worst post-baseline time point versus the baseline abnormality, according to the additional categorization described in Section 7.2.5.  
ALT, AST, hemoglobin, leukocytes and serum creatinine will be presented in this table.  
Population: safety population.

## 14.8 Safety: ECG

**Table 14.3.3.1: ECG: Cross-tabulation of the investigator's conclusion per time point**

Cross-tabulation per time point. Table sorted first by treatment group, then by time point. The table will present the shift in conclusion (normal/abnormal NCS/abnormal CS) at each post-baseline time point versus the baseline conclusion (normal/abnormal NCS/abnormal CS).  
Population: safety population.

## 14.9 Safety: Vital Signs

**Table 14.3.4.1: Vital signs: Descriptive statistics of the actual values per time point**

Descriptive statistics per test and unit and time point. Table sorted first by treatment group, then by time point. Each test will begin on a new page.  
Population: safety population.

**Table 14.3.4.2: Vital signs: Descriptive statistics of the changes from baseline per time point**

Descriptive statistics per test and unit and time point. Table sorted first by treatment group, then by time point. Each test will begin on a new page.  
Population: safety population.

## 14.10 Immunogenicity

**Table 14.3.5.1: Immunogenicity: ADA incidence based on ADA assay results**

The table will present the number and percentage of subjects per ADA subject category by treatment group and by analysis period. Subject categories, treatment groups and analysis periods are given in Section 9.1.1.1.



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Population: safety population.

**Table 14.3.5.2: Immunogenicity: Incidence of drug-induced TE ADA status and pre-Ab status based on mADA assay results**

The table will present a summary by treatment group and analysis period of (1) the number and percentage of subjects within each mADA subject category, (2) the number and percentage of subjects classified as TE ADA within the pre-Ab negative and within the pre-Ab positive population, and (3) the number and percentage of subjects classified as pre-Ab negative, pre-Ab positive, drug-induced TE negative and drug-induced TE positive. Subject categories, treatment groups and analysis periods are given in Section 9.1.1.2.

Population: subset of safety population consisting of subjects who were classified as ADA positive based on ADA data.

Population: safety population.

**Table 14.3.5.3: Immunogenicity: Incidence of drug-induced TE ADA status and pre-Ab status based on ADA/mADA assay results (overall subject classification)**

The table will present a summary by treatment group and analysis period of (1) the number and percentage of subjects within each overall subject category, (2) the number and percentage of subjects classified as TE ADA within the pre-Ab negative and within the pre-Ab positive population, and (3) the number and percentage of subjects classified as pre-Ab negative, pre-Ab positive, drug-induced TE negative and drug-induced TE positive. Subject categories, treatment groups and analysis periods are given in Section 9.1.1.2.

Population: safety population.

**Table 14.3.5.4: Immunogenicity: Incidence of pre-dose NAb status and TE NAb status based on NAb assay result**

The table will present a summary by treatment group and analysis period of (1) the number and percentage of subjects within each NAb subject category, and (2) the number and percentage of subjects classified as pre-dose negative, pre-dose positive, TE negative and TE positive. Subject categories, treatment groups and analysis periods are given in Section 9.1.2.

Population: safety population.

**Table 14.3.5.5: Immunogenicity: Incidence of pre-dose NAb status and TE NAb status based on alternative NAb (null variant) assay result**

The table will present a summary by treatment group and analysis period of (1) the number and percentage of subjects within each alternative NAb subject category, and (2) the number and percentage of subjects classified as pre-dose negative, pre-dose positive, TE negative and TE positive. Subject categories, treatment groups and analysis periods are given in Section 9.1.3.

Population: safety population.

**Table 14.3.5.6: Immunogenicity: Incidence of drug-induced TE ADA status and pre-Ab status based on ADA and mADA assay results (overall subject classification) by hypersensitivity reaction**

Table 14.3.5.3, repeated for each category of hypersensitivity reaction.



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Population: safety population.

**Table 14.3.5.7: Immunogenicity: Incidence of drug-induced TE ADA status and pre-Ab status based on ADA and mADA assay results (overall subject classification) by treatment extension (Y/ N)**

Table 14.3.5.3, repeated for each category of hypersensitivity reaction.

Population: safety population.

**Table 14.3.5.8: Immunogenicity: Incidence of drug-induced TE ADA status and pre-Ab status based on ADA and mADA assay results (overall subject classification) by Rituximab use**

Table 14.3.5.3, repeated for each category of hypersensitivity reaction.

Population: safety population.

**Table 14.3.5.9: Immunogenicity: drug concentration by overall subject category (based on ADA/mADA assay results)**

Descriptive statistics of drug concentrations by visit and by overall subject category for (1) Caplacizumab during DB period, (2) OL Caplacizumab (after Caplacizumab) during OL Caplacizumab period, and (3) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section [9.1.1.2](#).

Population: safety population

**Table 14.3.5.10: Immunogenicity: RICO activity by overall subject category (based on ADA/mADA assay results)**

Descriptive statistics of RICO activity by visit and by overall subject category for (1) Caplacizumab during DB period, (2) Placebo during DB period, (3) OL Caplacizumab (after Caplacizumab) during OL Caplacizumab period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section [9.1.1.2](#).

Population: safety population

**Table 14.3.5.11: Immunogenicity: Percent change from baseline in vWF:Ag concentration by overall subject category (based on ADA/mADA assay results)**

Descriptive statistics of percent change from baseline of vWF:Ag concentrations by visit and by overall subject category for (1) Caplacizumab during DB period, (2) Placebo during DB period, (3) OL Caplacizumab (after Caplacizumab) during OL Caplacizumab period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section [9.1.1.2](#).

Population: safety population

**Table 14.3.5.12: Immunogenicity: Time to platelet count response by overall subject category (based on ADA/mADA assay results)**

Descriptive statistics of time to platelet count response, based on KM analysis, by overall subject category for (1) Caplacizumab during DB period, (2) Placebo during DB period, (3) OL Caplacizumab (after Caplacizumab) during OL Caplacizumab period, and (4) OL



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Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section 9.1.1.2.

Population: safety population

**Table 14.3.5.13: Immunogenicity: drug concentration by NAb assay subject category**

Descriptive statistics of drug concentrations by visit and by NAb subject category for (1) Caplacizumab (no OL Caplacizumab) during DB period, (2) OL Caplacizumab (after Caplacizumab) during overall study period, and (3) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section 9.1.2.

Population: safety population

**Table 14.3.5.14: Immunogenicity: RICO activity by NAb assay subject category**

Descriptive statistics of RICO activity by visit and by NAb subject category for (1) Caplacizumab (no OL Caplacizumab) during DB period, (2) Placebo (no OL Caplacizumab) during DB period, (3) OL Caplacizumab (after Caplacizumab) during overall study period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section 9.1.2.

Population: safety population

**Table 14.3.5.15: Immunogenicity: Percent change from baseline in vWF:Ag concentration by NAb assay subject category**

Descriptive statistics of percent change from baseline of vWF:Ag concentrations by visit and by NAb subject category for (1) Caplacizumab (no OL Caplacizumab) during DB period, (2) Placebo (no OL Caplacizumab) during DB period, (3) OL Caplacizumab (after Caplacizumab) during overall study period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section 9.1.2.

Population: safety population

**Table 14.3.5.16: Immunogenicity: Time to platelet count response by NAb assay subject category**

Descriptive statistics of time to platelet count response, based on KM analysis, by NAb subject category for (1) Caplacizumab during DB period, (2) Placebo during DB period, (3) OL Caplacizumab (after Caplacizumab) during OL Caplacizumab period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section 9.1.2.

Population: safety population

**Table 14.3.5.17: Immunogenicity: drug concentration by alternative NAb assay subject category**

Descriptive statistics of drug concentrations by visit and by alternative NAb subject category for (1) Caplacizumab during DB period, (2) OL Caplacizumab (after Caplacizumab) during overall study period, and (3) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section 9.1.3.

Population: safety population

**Table 14.3.5.18: Immunogenicity: RICO activity by alternative NAb assay subject category**



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Descriptive statistics of RICO activity by visit and by alternative NAb subject category for (1) Caplacizumab during DB period, (2) Placebo during DB period, (3) OL Caplacizumab (after Caplacizumab) during overall study period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section 9.1.3.

Population: safety population

**Table 14.3.5.19: Immunogenicity: Percent change from baseline in vWF:Ag concentration by alternative NAb assay subject category**

Descriptive statistics of percent change from baseline of vWF:Ag concentrations by visit and by alternative NAb subject category for (1) Caplacizumab during DB period, (2) Placebo during DB period, (3) OL Caplacizumab (after Caplacizumab) during overall study period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section 9.1.3.

Population: safety population

**Table 14.3.5.20: Immunogenicity: Time to platelet count response by alternative NAb subject category**

Descriptive statistics of time to platelet count response, based on KM analysis, by alternative NAb subject category for (1) Caplacizumab during DB period, (2) Placebo during DB period, (3) OL Caplacizumab (after Caplacizumab) during overall study period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section 9.1.3.

Population: safety population

**Table 14.3.5.21: Immunogenicity: ADA/mADA log<sub>10</sub>(titer) over time**

Descriptive statistics of ADA/mADA log<sub>10</sub>(titer) by visit and by treatment group (Caplacizumab during DB period, Placebo during DB period, OL Caplacizumab [after Caplacizumab] during OL Caplacizumab period, and OL Caplacizumab [after Placebo] during OL Caplacizumab period).

Population: safety population

**Table 14.3.5.22: Immunogenicity: NAb log<sub>10</sub>(titer) over time**

Descriptive statistics of NAb log<sub>10</sub>(titer) by visit and by treatment group (Caplacizumab [no OL Caplacizumab] during DB period, Placebo [no OL Caplacizumab] during DB period, OL Caplacizumab [after Caplacizumab] during overall study period, and OL Caplacizumab [after Placebo] during OL Caplacizumab period).

Population: safety population

**Table 14.3.5.23: Immunogenicity: Alternative NAb log<sub>10</sub>(titer) over time**

Descriptive statistics of alternative NAb log<sub>10</sub>(titer) by visit and by treatment group (Caplacizumab during DB period, Placebo during DB period, OL Caplacizumab [after Caplacizumab] during overall study period, and OL Caplacizumab [after Placebo] during OL Caplacizumab period).

Population: safety population



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**Table 14.3.5.24: Immunogenicity: ADA/mADA incidence over time**

Incidence of positive ADA or mADA samples by visit and by treatment group (Caplacizumab during DB period, Placebo during DB period, OL Caplacizumab [after Caplacizumab] during OL Caplacizumab period, and OL Caplacizumab [after Placebo] during OL Caplacizumab period).

Population: safety population

**Table 14.3.5.25: Immunogenicity: NAb incidence over time**

Incidence of positive NAb samples by visit and by treatment group (Caplacizumab [no OL Caplacizumab] during DB period, Placebo [no OL Caplacizumab] during DB period, OL Caplacizumab [after Caplacizumab] during overall study period, and OL Caplacizumab [after Placebo] during OL Caplacizumab period).

Population: safety population

**Table 14.3.5.26: Immunogenicity: Alternative NAb incidence over time**

Incidence of positive alternative NAb samples by visit and by treatment group (Caplacizumab during DB period, Placebo during DB period, OL Caplacizumab [after Caplacizumab] during overall study period, and OL Caplacizumab [after Placebo] during OL Caplacizumab period).

Population: safety population

## 15 INDEX OF FIGURES

### 15.1 General

**Figure 14.1.1.1: Consort Flow diagram.**

CONSORT diagram showing the flow of participants through each stage of the randomized trial (Screened, excluded, randomized, treated, discontinued, and analyzed)

Population: all screened population.

### 15.2 Efficacy

**Figure 14.2.1.1.1: EFF: Platelet count - Time to platelet count response**

Kaplan-Meier plot of the time to platelet count response by treatment group.

Population: ITT population.

**Figure 14.2.1.1.2: EFF: Platelet count – Sensitivity: Time to platelet count response (mITT population)**

Kaplan-Meier plot of the time to platelet count response by treatment group. Sensitivity analysis on modified intent-to-treat (mITT) population.

Population: mITT population.



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**Figure 14.2.1.1.3: EFF: Platelet count – Sensitivity: Time to platelet count response (Per protocol)**

Kaplan-Meier plot of the time to platelet count response by treatment group. Sensitivity analysis on PP population.

Population: PP population.

**Figure 14.2.1.1.4: EFF: Platelet count - Sensitivity: Time to platelet count response (ITT - Constrained response definition)**

Kaplan-Meier plot of the time to platelet count response by treatment group using the constrained response definition.

Population: ITT population.

**Figure 14.2.1.1.5: EFF: Platelet count - Sensitivity: Time to first platelet count  $\geq 150 \times 10^9/L$  (ITT - dPE stop within 5 days not required)**

Kaplan-Meier plot of the time to initial platelet count  $\geq 150 \times 10^9/L$  by treatment group.

Population: ITT population.

**Figure 14.2.1.1.6: EFF: Platelet count – Mean (SE) plot**

Line plot of the mean platelet count values, including SE bars, with one line per treatment group.

Population: ITT population.

**Figure 14.2.1.2.1: EFF: Organ damage marker levels – Time to normalization of all 3 of the organ damage marker levels**

Kaplan-Meier plot of the time to normalization of all 3 of the organ damage marker levels by treatment group.

Population: ITT population.

**Figure 14.2.1.2.2: EFF: Organ damage marker levels - Time to normalization of LDH**

Kaplan-Meier plot of the time to normalization of LDH by treatment group.

Population: ITT population.

**Figure 14.2.1.2.3: EFF: Organ damage marker levels - Time to normalization of cTnl**

Kaplan-Meier plot of the time to normalization of cTnl by treatment group.

Population: ITT population.

**Figure 14.2.1.2.4: EFF: Organ damage marker levels - Time to normalization of serum creatinine**

Kaplan-Meier plot of the time to normalization of serum creatinine by treatment group.

Population: ITT population.

**Figure 14.2.1.3.1: EFF: Plasma Exchange - Time to stop of daily PE**

Kaplan-Meier plot of the time to stop of daily PE by treatment group.

Population: ITT population.

**Figure 14.2.1.4.1: Subgroup analyses - Time to platelet count response**

Kaplan-Meier plot of the time to platelet count response by treatment group.

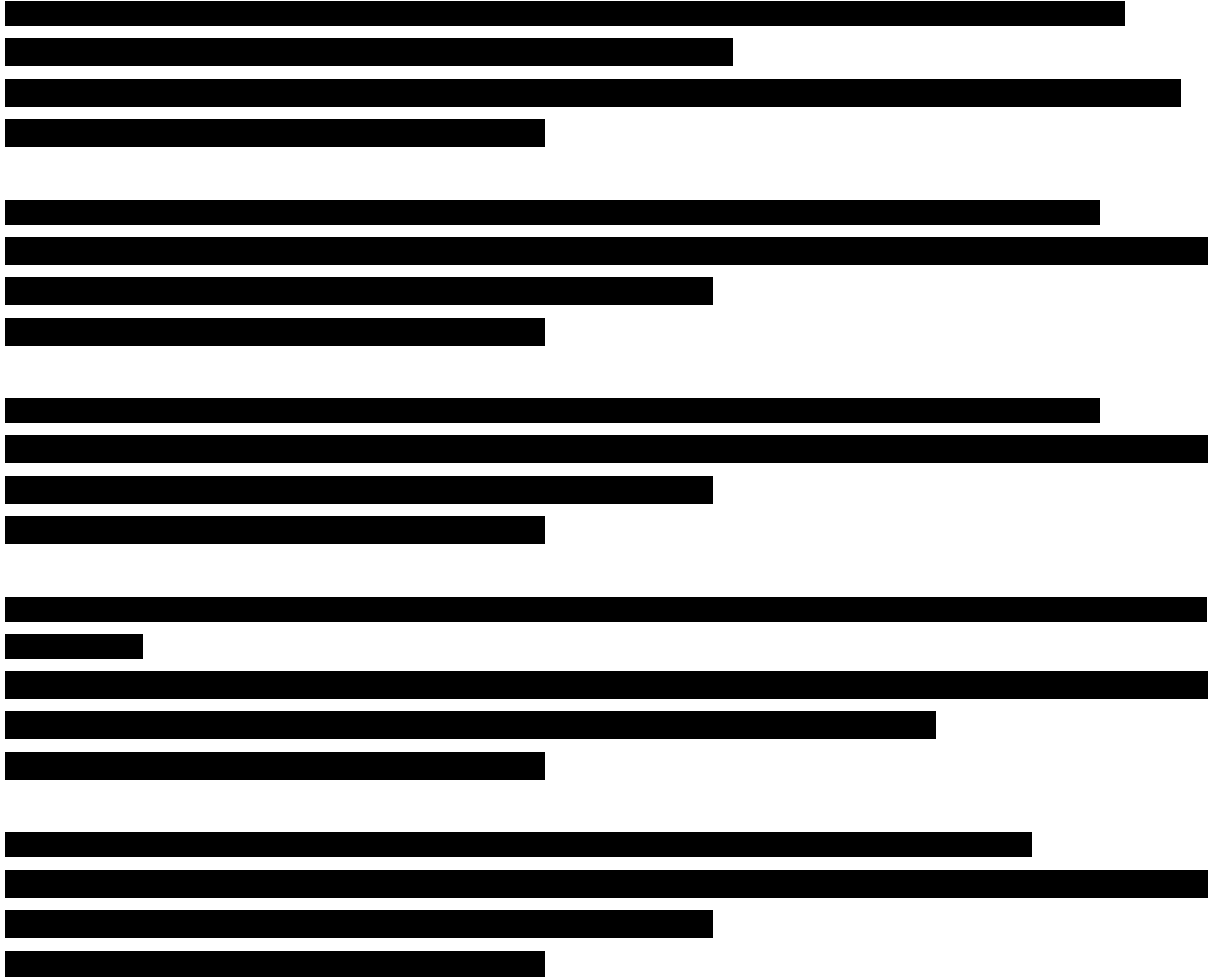
Following subgroups will be analyzed if at least 5 data points per category are available:

ADAMTS13 activity at admission or baseline  $<10\%$  /  $\geq 10\%$



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Previous TTP episode(s): initial/recurrent  
Baseline severity of disease: very severe/ less severe  
Population: ITT population.



### 15.3 Pharmacokinetics

#### Figure 14.2.2.1: PK: Individual drug concentrations – time profiles

For each treatment group separately, spaghetti plot of individual drug concentrations over time. Y-axis scales can be independent per treatment group to allow better interpretation of the results. Nominal sampling times are used. Plots will be created with both linear and semi-logarithmic PK profiles. Both graphs will be displayed on the same page.

Population: safety population.

#### Figure 14.2.2.2: PK: Mean drug concentrations

Line plot of the mean drug concentrations, including SE bars, with one line per treatment group. Plots will be created with both linear and semi-logarithmic PK profiles. Figure will consist of 3 separate parts:





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Part 1: All subjects from start of trial up to potential recurrence or trial termination/discontinuation (if earlier).

Part 2: All subjects with potential recurrence from timepoint of recurrence onwards.

Part 3: All caplacizumab-treated subjects with visits in DB treatment period synchronized with visits in OL treatment period by treatment group (Caplacizumab during DB treatment period, OL Caplacizumab [after Caplacizumab] during OL treatment period, OL Caplacizumab [after Placebo] during OL treatment period).

X-axis of the plot will represent study visit, Y-axis drug concentration

Population: safety population.

**Figure 14.2.2.3: PK: Mean drug concentrations (geometric mean)**

Line plot of the geometric mean drug concentrations, including geometric SD bars, with one line per treatment group. Plots will be created with both linear and semi-logarithmic PK profiles. Both graphs will be displayed on the same page. Figure will consist of 3 separate parts:

Part 1: All subjects from start of trial up to potential recurrence or trial termination/discontinuation (if earlier).

Part 2: All subjects with potential recurrence from timepoint of recurrence onwards.

Part 3: All caplacizumab-treated subjects with visits in DB treatment period synchronized with visits in OL treatment period by treatment group (Caplacizumab during DB treatment period, OL Caplacizumab [after Caplacizumab] during OL treatment period, OL Caplacizumab [after Placebo] during OL treatment period).

X-axis of the plot will represent study visit, Y-axis drug concentration

Population: safety population.

## 15.4 Pharmacodynamics

**Figure 14.2.3.1: PD: Mean time profiles of PD concentrations**

Line plots of the RICO activity, vWF:Ag concentrations and FVIII:C activity vs. time points, including SE bars, with one line per treatment group.

Figure will consist of 3 separate parts:

Part 1: All subjects from start of trial up to potential recurrence or trial termination/discontinuation (if earlier).

Part 2: All subjects with potential recurrence from timepoint of recurrence onwards.

Part 3: All caplacizumab-treated subjects with visits in DB treatment period synchronized with visits in OL treatment period by treatment group (Caplacizumab during DB treatment period, OL Caplacizumab [after Caplacizumab] during OL treatment period, OL Caplacizumab [after Placebo] during OL treatment period).

X-axis of the plot will represent study visit, Y-axis PD concentration/activity.

Population: safety population.

**Figure 14.2.3.2: PD: Scatterplot of RICO activity in function of PK/vWF:AG ratio**

Scatter plot of the RICO activity in function of the PK concentration/vWF:Ag ratio (for matching samples). The PK/vWF:Ag ratio will be expressed in molarity. Each treatment group will be represented by a different color/symbol.

Population: safety population.



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## 15.5 Disease related markers

### Figure 14.2.4.1: Disease related markers: Mean ADAMTS13 activity over time

Line plots of the ADAMTS13 activity including SE bars, with one line per treatment group.

Population: safety population.

### Figure 14.2.4.2: Disease related markers: Cox Proportional hazards model Survival curves

Plots of the survival curves per treatment group (corrected for covariates) based on the Cox proportional hazards model.

Population: safety population.

## 15.6 Safety: Laboratory

### Figure 14.3.2.1: Laboratory data: Parameters of interest – actual values

Mean time profile, showing the mean actual values (with SE) for each treatment group at each scheduled time point. The following parameters will be plotted: AST, ALT, hemoglobin, leukocytes, neutrophils.

Figure will consist of 2 separate parts:

Part 1: All subjects from start of trial up to potential recurrence or trial termination/discontinuation (if earlier).

Part 2: All subjects with potential recurrence from timepoint of recurrence onwards.

X-axis of the plot will represent study visit, Y-axis parameter actual value

Population: safety population.

### Figure 14.3.2.2: Laboratory data: Parameters of interest – changes from baseline

Mean time profile, showing the mean actual changes from baseline (with SE) for each treatment group at each scheduled post-baseline time point. The following parameters will be plotted: AST, ALT, hemoglobin, leukocytes, neutrophils.

Figure will consist of 2 separate parts:

Part 1: All subjects from start of trial up to potential recurrence or trial termination/discontinuation (if earlier).

Part 2: All subjects with potential recurrence from timepoint of recurrence onwards.

X-axis of the plot will represent study visit, Y-axis parameter change from baseline

Population: safety population.

## 15.7 Immunogenicity

### Figure 14.4.1.1: Immunogenicity: Mean plot of PK concentration by overall subject category based on ADA/mADA assay results

Line plot of the mean PK concentrations vs. time point (visit), including SE bars, with one line per overall subject category, repeated by treatment group, for (1) Caplacizumab during DB period, (2) OL Caplacizumab (after Caplacizumab) during OL Caplacizumab period, and (3) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section [9.1.1.2](#).



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Population: safety population.

**Figure 14.4.1.2: Immunogenicity: Scatter plot of PK concentration by overall subject category based on ADA/mADA assay results**

Scatter plot of the PK concentrations vs. time point (visit), with overall subject category represented by different plotting symbols, repeated by treatment group, for (1) Caplacizumab during DB period, (2) OL Caplacizumab (after Caplacizumab) during OL Caplacizumab period, and (3) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section 9.1.1.2.

Population: safety population.

**Figure 14.4.1.3: Immunogenicity: Mean plot of percent change from baseline in vWF:Ag concentration by overall subject category based on ADA/mADA assay results**

Line plot of the mean percentage change from baseline of vWF:Ag concentration vs time point (visit), including SE bars, with one line per overall subject category, repeated by treatment group, for (1) Caplacizumab during DB period, (2) Placebo during DB period, (3) OL Caplacizumab (after Caplacizumab) during OL Caplacizumab period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section 9.1.1.2.

Population: safety population.

**Figure 14.4.1.4: Immunogenicity: Scatter plot of percent change from baseline in vWF:Ag concentration by overall subject category based on ADA/mADA assay results**

Scatter plot of the percentage change from baseline of vWF:Ag concentrations vs. time point (visit), with overall subject category represented by different plotting symbols, repeated by treatment group, for (1) Caplacizumab during DB period, (2) Placebo during DB period, (3) OL Caplacizumab (after Caplacizumab) during OL Caplacizumab period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section 9.1.1.2.

Population: safety population.

**Figure 14.4.1.5: Immunogenicity: Mean plot of RICO activity by overall subject category based on ADA/mADA assay results**

Line plot of the mean RICO activity vs. time point (visit), including SE bars, with one line per overall subject category, repeated by treatment group, for (1) Caplacizumab during DB period, (2) Placebo during DB period, (3) OL Caplacizumab (after Caplacizumab) during OL Caplacizumab period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section 9.1.1.2.

Population: safety population.

**Figure 14.4.1.6: Immunogenicity: Scatter plot of RICO activity by overall subject category based on ADA/mADA assay results**

Scatter plot of the RICO activity vs. time point (visit), with overall subject category represented by different plotting symbols, repeated by treatment group, for (1) Caplacizumab during DB



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period, (2) Placebo during DB period, (3) OL Caplacizumab (after Caplacizumab) during OL Caplacizumab period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section [9.1.1.2](#).

Population: safety population.

**Figure 14.4.1.7: Immunogenicity: KM plot of time to platelet count response by overall subject category based on ADA/mADA assay results**

KM plot of the time to platelet count response, with one line per overall subject category, repeated by treatment group, for (1) Caplacizumab during DB period, (2) Placebo during DB period, (3) OL Caplacizumab (after Caplacizumab) during OL Caplacizumab period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section [9.1.1.2](#).

Population: safety population.

**Figure 14.4.1.8: Immunogenicity: Scatter plot of PK concentration by NAb assay subject category**

Scatter plot of the PK concentrations vs. time point (visit), with NAb subject category represented by different plotting symbols, repeated by treatment group, for (1) Caplacizumab (no OL Caplacizumab) during DB period, (2) OL Caplacizumab (after Caplacizumab) during overall study period, and (3) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject categories, treatment groups and analysis periods are given in Section [9.1.2](#).

Population: safety population.

**Figure 14.4.1.9: Immunogenicity: Scatter plot of vWF:Ag concentration by NAb assay subject category**

Scatter plot of vWF:Ag concentration vs. time point (visit), with NAb subject category represented by different plotting symbols, repeated by treatment group, for (1) Caplacizumab (no OL Caplacizumab) during DB period, (2) Placebo (no OL Caplacizumab) during DB period, (3) OL Caplacizumab (after Caplacizumab) during overall study period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject classes, treatment groups and analysis periods are given in Section [9.1.2](#).

Population: safety population.

**Figure 14.4.1.10: Immunogenicity: Scatter plot of RICO activity by NAb assay subject category**

Scatter plot of the RICO activity vs. time point (visit), with NAb subject category represented by different plotting symbols, repeated by treatment group, for (1) Caplacizumab (no OL Caplacizumab) during DB period, (2) Placebo (no OL Caplacizumab) during DB period, (3) OL Caplacizumab (after Caplacizumab) during overall study period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject classes, treatment groups and analysis periods are given in Section [9.1.2](#).

Population: safety population.

**Figure 14.4.1.11: Immunogenicity: Scatter plot of PK concentration by alternative NAb assay subject category**



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Scatter plot of the PK concentrations vs. time point (visit), with alternative NAb subject category represented by different plotting symbols, repeated by treatment group, for (1) Caplacizumab during DB period, (2) OL Caplacizumab (after Caplacizumab) during overall study period, and (3) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject classes, treatment groups and analysis periods are given in Section 9.1.3.

Population: safety population.

**Figure 14.4.1.12: Immunogenicity: Scatter plot of vWF:Ag concentration by alternative NAb assay subject category**

Scatter plot of vWF:Ag concentration vs. time point (visit), with alternative NAb subject category represented by different plotting symbols, repeated by treatment group, for (1) Caplacizumab during DB period, (2) Placebo during DB period, (3) OL Caplacizumab (after Caplacizumab) during overall study period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject classes, treatment groups and analysis periods are given in Section 9.1.3.

Population: safety population.

**Figure 14.4.1.13: Immunogenicity: Scatter plot of RICO activity by alternative NAb assay subject category**

Scatter plot of the RICO activity vs. time point (visit), with alternative NAb subject category represented by different plotting symbols, repeated by treatment group, for (1) Caplacizumab during DB period, (2) Placebo during DB period, (3) OL Caplacizumab (after Caplacizumab) during overall study period, and (4) OL Caplacizumab (after Placebo) during OL Caplacizumab period. Subject classes, treatment groups and analysis periods are given in Section 9.1.3.

Population: safety population.

**Figure 14.4.1.14: Immunogenicity: Mean plot of ADA log<sub>10</sub>(titer) over time**

Line plot of the mean ADA log<sub>10</sub>(titer) vs. time point (visit), including SE bars, with one line per treatment group (Caplacizumab during DB period, Placebo during DB period, OL Caplacizumab [after Caplacizumab] during OL Caplacizumab period, and OL Caplacizumab [after Placebo] during OL Caplacizumab period). Calculated mean ADA negative values will be visualized on the graphs as 1.80 (arbitrarily chosen) to allow plotting. The MRD (or sensitivity of the assay) will be visualized as horizontal line at log<sub>10</sub>(titer)=1.98. Different plots will be made for DB period and OL Caplacizumab period.

Population: safety population.

**Figure 14.4.1.15: Immunogenicity: Mean plot of mADA log<sub>10</sub>(titer) over time**

Line plot of the mean mADA log<sub>10</sub>(titer) vs. time point (visit), including SE bars, with one line per treatment group (Caplacizumab during DB period, Placebo during DB period, OL Caplacizumab [after Caplacizumab] during OL Caplacizumab period, and OL Caplacizumab [after Placebo] during OL Caplacizumab period). Calculated mean mADA negative values will be visualized on the graphs as 1.80 (arbitrarily chosen) to allow plotting. The MRD (or sensitivity of the assay) will be visualized as horizontal line at log<sub>10</sub>(titer)=1.98. Different plots will be made for DB period and OL Caplacizumab period.

Population: safety population.



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**Figure 14.4.1.16: Immunogenicity: Mean plot of NAb log<sub>10</sub>(titer) over time**

Line plot of the mean NAb log<sub>10</sub>(titer) vs. time point (visit), including SE bars, with one line per treatment group (Caplacizumab [no OL Caplacizumab] during DB period, Placebo [no OL Caplacizumab] during DB period, OL Caplacizumab [after Caplacizumab] during overall study period, and OL Caplacizumab [after Placebo] during OL Caplacizumab period). Calculated mean negative values for the NAb assay (reported as log<sub>10</sub>(titer)<0.36) will be visualized on the graphs as 0.20 (arbitrarily chosen) to allow plotting. The MRD of the NAb assay will be visualized as a horizontal line at log<sub>10</sub>(titer)=0.36. Different plots will be made for DB period and OL Caplacizumab period.

Population: safety population.

**Figure 14.4.1.17: Immunogenicity: Mean plot of alternative NAb log<sub>10</sub>(titer) over time**

Line plot of the mean alternative NAb log<sub>10</sub>(titer) vs. time point (visit), including SE bars, with one line per treatment group (Caplacizumab during DB period, Placebo during DB period, OL Caplacizumab [after Caplacizumab] during overall study period, and OL Caplacizumab [after Placebo] during OL Caplacizumab period). Calculated mean negative values for the alternative NAb assay (reported as log<sub>10</sub>(titer)<1.98) will be visualized on the graphs as 1.80 (arbitrarily chosen) to allow plotting. The MRD of the alternative NAb assay will be visualized as a horizontal line at log<sub>10</sub>(titer)=1.98. Different plots will be made for DB period and OL Caplacizumab period.

Population: safety population.

**Figure 14.4.1.18: Immunogenicity: Spaghetti plot of ADA log<sub>10</sub>(titer) over time.**

Spaghetti plot of ADA log<sub>10</sub>(titer) vs. time. Negative values for ADA (reported as log<sub>10</sub>(titer)<1.98) will be visualized on the graphs as 1.80 (arbitrarily chosen) to allow plotting. The MRD (or sensitivity of the assay) will be visualized as horizontal line at log<sub>10</sub>(titer)=1.98. Different plots will be made for different treatment groups and analysis periods (Caplacizumab during DB period, Placebo during DB period, OL Caplacizumab [after Caplacizumab] during OL Caplacizumab period, and OL Caplacizumab [after Placebo] during OL Caplacizumab period).

Population: safety population

**Figure 14.4.1.19: Immunogenicity: Spaghetti plot of mADA log<sub>10</sub>(titer) over time.**

Spaghetti plot of ADA log<sub>10</sub>(titer) vs. time. Negative values for mADA (reported as log<sub>10</sub>(titer)<1.98) will be visualized on the graphs as 1.80 (arbitrarily chosen) to allow plotting. The MRD (or sensitivity of the assay) will be visualized as horizontal line at log<sub>10</sub>(titer)=1.98. Different plots will be made for different treatment groups and analysis periods (Caplacizumab during DB period, Placebo during DB period, OL Caplacizumab [after Caplacizumab] during OL Caplacizumab period, and OL Caplacizumab [after Placebo] during OL Caplacizumab period).

Population: safety population

**Figure 14.4.1.20: Immunogenicity: Spaghetti plot of NAb log<sub>10</sub>(titer) over time.**



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Spaghetti plot of NAb log<sub>10</sub>(titer) vs. time. Negative values for NAb (reported as log<sub>10</sub>(titer)<0.36) will be visualized on the graphs as 0.20 (arbitrarily chosen) to allow plotting. The MRD (or sensitivity of the assay) will be visualized as horizontal line at log<sub>10</sub>(titer)=0.36. Different plots will be made for different treatment groups and analysis periods (Caplacizumab [no OL Caplacizumab] during DB period, Placebo [no OL Caplacizumab] during DB period, OL Caplacizumab [after Caplacizumab] during overall study period, and OL Caplacizumab [after Placebo] during OL Caplacizumab period).

Population: safety population

**Figure 14.4.1.21: Immunogenicity: Spaghetti plot of alternative NAb log<sub>10</sub>(titer) over time.**

Spaghetti plot of alternative NAb log<sub>10</sub>(titer) vs. time. Negative values for alternative NAb (reported as log<sub>10</sub>(titer)<1.98) will be visualized on the graphs as 1.80 (arbitrarily chosen) to allow plotting. The MRD (or sensitivity of the assay) will be visualized as horizontal line at log<sub>10</sub>(titer)=1.98. Different plots will be made for different treatment groups and analysis periods (Caplacizumab during DB period, Placebo during DB period, OL Caplacizumab [after Caplacizumab] during overall study period, and OL Caplacizumab [after Placebo] during OL Caplacizumab period).

Population: safety population

**Figure 14.4.1.22: Immunogenicity: Individual line plots of ADA log<sub>10</sub>(titer), mADA log<sub>10</sub>(titer), NAb log<sub>10</sub>(titer), alternative NAb log<sub>10</sub>(titer), PK, RICO activity, vWF:Ag concentration over time with indication of PE treatment days and treatment with rituximab.**

For each subject presenting positive ADA samples separately, line plot of ADA log<sub>10</sub>(titer), mADA log<sub>10</sub>(titer), NAb log<sub>10</sub>(titer), alternative NAb log<sub>10</sub>(titer), PK, RICO activity, vWF:Ag concentration vs. time point (visit). PE and rituximab treatment days should be visualized on the plot. For ADA, mADA, and alternative NAb titer plotting, negative values (reported as log<sub>10</sub>(titer)<1.98) will be visualized on the graphs as 1.8 (arbitrarily chosen) to allow plotting. The MRD (or sensitivity of the assay) will be visualized as horizontal line at log<sub>10</sub>(titer)=1.98. Negative values for NAb assay (reported as log<sub>10</sub>(titer)<0.36) will be visualized on the graphs as 0.20. The MRD of the NAb assay will be visualized as a horizontal line at log<sub>10</sub>(titer)=0.36.

Population: safety population

## 16 INDEX OF LISTINGS

### 16.1 General

**Listing 16.2.1.1: Subject disposition: Allocation**

Listing of medication numbers, subject numbers and randomization groups. Listing sorted by randomization number. Stratification factors, population indicators, country and investigator are on this list as well. All discrepancies (as-randomized versus as-treated, or discrepancies in stratification factors) will be flagged.

Population: ITT population.

**Listing 16.2.1.2: Subject disposition: Code-breaking information**



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Listing of the code-breaking information. Only subjects for which the code was broken are presented in this listing.

Population: ITT population.

**Listing 16.2.1.3: Subject disposition: Trial analysis periods**

Listing of the analysis periods in the trial, together with the start and end dates, and the duration of each analysis period. The date of first and last use of trial medication, and the trial termination date will also be added. (Analysis periods: see Section [4.4.1](#))

Population: ITT population.

**Listing 16.2.1.4: Trial termination**

Listing of the reason for completion/discontinuation, the number of days since first study drug administration and date of last study drug intake at trial termination. In case the discontinuation was due to AE, the AE will be presented in this listing. If there is another explanation on the discontinuation reason collected in the CRF, this will also be presented in this listing.

Population: ITT population.

**Listing 16.2.1.5: Major protocol deviations**

Listing of all major protocol deviations including category (DVDECOD) and description (DVTERM).

Population: ITT population.

**Listing 16.2.1.6: No-treatment subjects**

Listing of all subjects that were not treated: all subjects never randomized, and all subjects randomized but never treated. Note that this also includes the screening failures.

The trial termination reason and/or the reason for being a no-treatment subject will be listed, whichever is available.

Population: all screened population, minus the safety population.

**Listing 16.2.1.7: Violations on eligibility criteria**

Only violated in- and exclusion criteria will be listed.

Population: ITT population.

**Listing 16.2.2.1: Demographic data**

Listing of all demographic parameters.

Population: ITT population.

**Listing 16.2.2.2: Baseline disease characteristics**

Listing of all baseline disease characteristics.

Population: ITT population.

**Listing 16.2.2.3: Screening tests**

Listing of all results of pregnancy tests, complement C5a and C5b-9 levels and creatinine assessment.

Population: ITT population.





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**Listing 16.2.2.4: Medical history**

Listing of the medical history data findings available in the CRF (i.e., condition no longer present). Listing will consist of two parts:

Part 1: General Medical history

Part 2: TTP related Medical history

Population: ITT population.

**Listing 16.2.2.5: ADAMTS13 Activity at admission and at baseline**

Listing of ADAMTS3 activity data findings available including date/time, actual value, clinical significance and comments

Population: ITT population.

**Listing 16.2.2.6: Concomitant diseases**

Listing of the concomitant diseases data findings available in the CRF (i.e., condition still present).

Population: ITT population.

**Listing 16.2.2.7: Plasma exchange**

Listing of all data on plasma exchange.

Population: ITT population.

**Listing 16.2.2.8: Previous and concomitant therapies**

Listing of all data on previous and concomitant therapies, including coding information.

Population: ITT population.

**Listing 16.2.2.9: Exposure to study medication: Actual data**

Listing of all data collected in the CRF related to the use of medication.

Population: safety population.

**Listing 16.2.2.10: Exposure to study medication: Derived data**

Listing of all derived data related to the use of medication.

Population: safety population.

**Listing 16.2.2.11: Comments**

Listing of remarks and comments written in the CRF.

Population: ITT population.

**16.2 Efficacy****Listing 16.2.3.1: EFF: Platelet count**

Listing per subject and time point of platelet count, including time to response and AUC.

Population: ITT population.

**Listing 16.2.3.2: EFF: TTP**



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Listing per subject of TTP related parameters (TTP related death, recurrence, TTP related AE).

Population: ITT population.

**Listing 16.2.3.3: EFF: Organ damage marker levels**

Listing per subject and time point of LDH, cTnl and serum creatinine values and abnormality flags and of the time to normalization parameters.

Population: ITT population.

**Listing 16.2.3.4: EFF: Neurology**

Listing per subject and time point of neurological symptoms, neurological assessment results and of SMMSE total score.

Population: ITT population.

**Listing 16.2.3.5: EFF: Plasma Exchange**

Listing per subject and time point of volume (absolute and normalized) of plasma exchange and of number of days of PE, total volume of PE and time to stop daily PE.

Population: ITT population.

**Listing 16.2.3.6: EFF: Safety related parameters**

Listing per subject of all safety related parameters.

Population: ITT population.

## 16.3 Pharmacokinetics

**Listing 16.2.4.1: PK: Study drug concentrations**

Listing of all individual study drug concentrations.

Population: safety population.

**Listing 16.2.4.2: PK: Sampling times**

Listing of nominal sampling times, actual sampling times and sampling time deviations.

Population: safety population.

## 16.4 Pharmacodynamics

**Listing 16.2.5.1: PD: Individual PD concentrations**

Listing of all individual RICO activity values, vWF:Ag concentrations and FVIII:C activity values.

Population: safety population.

## 16.5 Disease related markers

**Listing 16.2.6.1: Disease related markers: Individual ADAMTS13 activity**

Listing of all individual ADAMTS13 activity values.

Population: safety population.



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## 16.6 Safety: Adverse Events

### Listing 16.2.7.1: Adverse events

Listing of all adverse events of the following:

- Period start and end
- AE preferred term (flagging serious TEAEs with an asterisk \*)
- AE start and end
- AE onset day
- AE duration
- AE severity
- AE drug relatedness: relation to study drug, to PE and to corticosteroids
- AE outcome
- AE action taken
- Concomitant therapy started (yes/no)
- Serious AE (yes/no)

In such a way that all information fits on one line for each AE.

Periods without an AE will be included as "no AE" records.

Population: safety population.

### Listing 16.2.7.2: Adverse events: Serious adverse events

Same as the previous listing, but only selecting SAEs (irrespective their treatment-emergence). Additionally, the reason(s) for SAE will be listed as well.

Population: safety population.

### Listing 16.2.7.3: Adverse events leading to discontinuation

Same as the previous listing, but only selecting TEAEs that lead to a stop of trial medication, interruption of trial medication, or stop of the trial itself.

Population: safety population.

### Listing 16.2.7.4: Adverse events leading to death

Same as the previous listing, but only selecting adverse events leading to death (irrespective their treatment-emergence).

### Listing 16.2.7.5: Adverse events: coding information

Listing presenting the coding information of all adverse events.

### Listing 16.2.7.6: Adverse events: bleeding events

Same as the previous listing, but only selecting bleeding events. Additionally flags will be added to indicate increased bleeding tendency and membership of Haemorrhage SMQ.

### Listing 16.2.7.7: Adverse events: severe/serious hypersensitivity adverse events

Listing of severe/serious hypersensitivity adverse events (irrespective their treatment emergence), including ADA/mADA log<sub>10</sub>(titer) and biomarker test results (tryptase, total complement CH50 and circulation immune complexes CIC-IgM and CIC-IgG).



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Population: safety population.

## 16.7 Safety: Physical Examinations

### Listing 16.2.7.8: Physical examinations: Abnormalities

Listing of all abnormal findings, including the clinically significance status.

Population: safety population.

## 16.8 Safety: Laboratory

### Listing 16.2.8.1: Laboratory data: Full listing

Listing of all data. Comments are not included in this listing but are presented in a separate listing.

Population: safety population.

### Listing 16.2.8.2: Laboratory data: Abnormalities

Listing of all data scored as out-of-normal-range or clinically significant, plus also the baseline reference time point. Comments are not included in this listing but are presented in a separate listing.

Population: safety population.

### Listing 16.2.8.3: Laboratory data: Comments

Listing of all comments. This listing will be linked to the Full listing and the Abnormalities listing via numbered entries like "[C13]".

Population: safety population.

## 16.9 Safety: ECG

### Listing 16.2.9.1: ECG: Full listing

Listing of the investigator's conclusion on the ECG profile.

Population: safety population.

## 16.10 Safety: Vital Signs

### Listing 16.2.10.1: Vital signs: Full listing

Listing of all parameters: actual values, changes from baseline, and flagging clinically significant results.

Population: safety population.

### Listing 16.2.10.2: Vital signs: Abnormalities

Listing of all data scored as clinically significant, plus also the baseline reference time point.

Population: safety population.



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## 16.11 Immunogenicity

### Listing 16.2.11.1: Immunogenicity: Full listing

Listing of all immunogenicity parameters (ADA log<sub>10</sub>(titer), mADA log<sub>10</sub>(titer), nAb result log<sub>10</sub>(titer), alternative NAb result log<sub>10</sub>(titer)) at each time point. Listing of subject classification based on ADA assay, mADA assay, overall subject classification (based on ADA and mADA assay results) and listing of subject classification based on nAb assay and alternative NAb assay with treatment group and analysis period for the classification indicated. Population: safety population.



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## 17 APPENDICES

### 17.1 Appendix A: Schedule of Assessments

#### *Schedules of Assessments for Adults (≥ 18 years)*

**Table 1: Time and events schedule for adults: screening**

Study Visit	Screening
Written informed consent	x
Demographics	x
Medical history <sup>a</sup>	x
Review of eligibility criteria	x
Collection of hospitalization information	x
Glasgow Coma Scale <sup>b</sup>	x
Bleeding assessment <sup>c</sup>	x
Adverse events	x
Concomitant medication	x
Pregnancy test (urine or blood) <sup>d</sup>	x
Platelet count and blood smear <sup>e</sup>	x
Serum creatinine <sup>e</sup>	x

<sup>a</sup> General medical history and TTP-specific medical history. The result of an ADAMTS13 activity test performed as per standard of care upon admission will be collected in the eCRF, if available.

<sup>b</sup> To be assessed within 2 hours prior to randomization.

<sup>c</sup> Bleeding assessment is a clinical assessment of signs and symptoms of bleeding (e.g., petechiae, hematuria, epistaxis, meno-metrorrhagia, bruises) performed by the Investigator.

<sup>d</sup> Only for women of childbearing potential. Pregnancy test (urine or blood) will be assessed locally.

<sup>e</sup> Samples for platelet count, blood smear and serum creatinine will be assessed by a local laboratory (values of samples taken as part of standard of care can be used, if available).



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**Table 2: Time and events schedule for adults: Daily PE period a**

Study Visit	Day 1 (Baseline)	Day 2	Day 3	Day 4	DAILY from Day 5 to end of daily PE	WEEKLY b on Day 8, 15, ... (± 1 day)
Complement C5a and C5b-9 (initial daily PE period only)	x					
Randomization	x					
Study drug administration c	x	x	x	x	x	x
Plasma exchange + corticosteroidsd	x	x	x	x	x	x
Neurologic assessments e	x	x	x	x	x	x
SMMSE	x	x	x	x	x	x
Clinically significant TTP event	x	x	x	x	x	x
Bleeding assessment f	x	x	x	x	x	x
Physical examination	x					x
Height and weight (initial daily PE period only)	x					
Vital signs g	x					x
12-lead ECG h	x	x	x	x		
Adverse events	→					
Concomitant medication	→					
Platelet count j	x	x	x	x	x	x
Blood smear j	x					
Clinical laboratory analyses i	x					x
Organ damage markers k	x	x	x	x	x	x
ADAMTS13 activity	x					
PK	x	x	x			
PD parameters l	x	x	x			
Immunogenicity (ADA)m	x					

<sup>a</sup> The following guidance with regard to timing of assessments planned at a single visit should be followed: 1) ECG and vital signs should be assessed prior to blood sampling, 2) assessments should be done prior to start of PE (and on Day 1, prior to the i.v. dose administration), and 3) s.c. study drug should be dosed after end of the day's PE.



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- This time and events schedule is also applicable for open-label caplacizumab in case of a first exacerbation or relapse (relapse during the treatment extension period). Of note, complement (C5a and C5b-9) and height and weight are to be assessed at the initial daily PE period only.
- <sup>b</sup> All assessments to be done on Day 8, 15,... include assessments done on daily basis plus extra weekly assessments.
  - <sup>c</sup> Study drug is to be administered daily s.c. post PE, in addition on Day 1 an i.v. loading dose of study drug will also be administered prior to the first PE after randomization.
  - <sup>d</sup> PE with plasma (e.g., fresh frozen plasma, solvent detergent/viral-inactivated plasma, cryosupernatant) at 1 to 1.5 x estimated plasma volume daily as of randomization) (the PE prior to randomization should have been given with volume and intensity at the discretion of the Investigator). Of note, PE with 1 to 1.5 x estimated plasma volume may be spread over multiple sessions within 24 hours.
  - <sup>e</sup> Neurological assessment will include assessment of the neurological system (including coma, stupor, seizures, disorientation/confusion, hemiparesis/-plegia, focal deficit, agitation, dysarthria).
  - <sup>f</sup> Bleeding assessment is a clinical assessment of signs and symptoms of bleeding (e.g., petechiae, hematuria, epistaxis, meno-metrorrhagia, bruises) performed by the Investigator.
  - <sup>g</sup> Vital signs (assessment after 5 min in supine position): blood pressure, pulse and temperature.
  - <sup>h</sup> To be performed after 5 min in supine position.
  - <sup>i</sup> Clinical laboratory analyses include blood chemistry, hematology and blood coagulation parameters.
  - <sup>j</sup> Samples for platelet count and blood smear that will be assessed by a local laboratory.
  - <sup>k</sup> Organ damage markers include LDH, Troponin I, creatinine.
  - <sup>l</sup> PD parameters include RICO, vWF:Ag, and FVIII:C.
  - <sup>m</sup> In case of a severe and/or serious hypersensitivity reaction, an additional blood sample to characterize the reaction should be collected as soon as possible after the start of the event.





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**Table 3: Time and events schedule for adults: 30-day post-daily PE period, early termination and follow-up period a**

Study Period	30-Day Post-Daily PE Period					Early Termination Visit	Follow-up	
	Week 1 Day 1 (1 day after last daily PE)	Week 2 Day 8 (8 days after last daily PE) (± 1 day)	Week 3 Day 15 (15 days after last daily PE) (± 1 day)	Week 4 Day 22 (22 days after last daily PE) (± 1 day)	Week 5 Day 30 End of 30-day post-daily PE Period (± 1 day)		First FU visit 7 days after last dosing (± 1 day)	Final FU visit 28 days after last dosing (± 1 day)
Study drug administration (daily) <b>b</b>	x	x	x	x	x			
Corticosteroids	x	x	x	x	x			
Review of patient diary	x	x	x	x	x			
Neurologic assessments <b>c</b>	x				x	x	x	x
SMMSE	x				x	x	x	x
Clinically significant TTP event	x	x	x	x	x	x	x	x
Bleeding assessment <b>d</b>	x	x	x	x	x	x	x	x
Physical examination	x				x	x	x	x
Vital signs <b>e</b>	x				x	x	x	x
12-lead ECG <b>f</b>	x				x	x	x	x
Adverse events								
Concomitant medication								
Platelet count <b>h</b>	x	x	x	x	x	x	x	x
Clinical laboratory analyses <b>g</b>	x				x	x	x	x
Organ damage markers <b>i</b>	x	x	x	x	x	x	x	x
ADAMTS13 Activity	x	x	x	x	x	x	x	x
PK	x	x	x	x	x	x		
PD parameters <b>j</b>	x	x	x	x	x	x	x	x
Immunogenicity (ADA) <b>k</b>	x				x		x	x

<sup>a</sup> The following guidance with regard to timing of assessments planned at a single visit should be followed: 1) ECG and vital signs should be assessed prior to blood sampling, and 2) s.c. study drug should be dosed after all other assessments have been performed.

<sup>b</sup> Study drug is to be administered daily s.c. for 30 days. Of note, no study drug is to be administered at the Week 5 visit in case of no treatment extensions.

<sup>c</sup> Neurological assessment will include assessment of the neurological system (including coma, stupor, seizures, disorientation/confusion, hemiparesis/-plegia, focal deficit, agitation, dysarthria).

<sup>d</sup> Bleeding assessment is a clinical assessment of signs and symptoms of bleeding (e.g., petechiae, hematuria, epistaxis, meno-metrorrhagia, bruises) performed by the Investigator.

<sup>e</sup> Vital signs (assessment after 5 min in supine position): including blood pressure, pulse and temperature.

<sup>f</sup> To be performed after 5 min in supine position.



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- <sup>g</sup> Clinical laboratory analyses include blood chemistry, hematology and blood coagulation parameters.
- <sup>h</sup> Samples for platelet count will be assessed by a local laboratory.
- <sup>i</sup> Organ damage markers include LDH, Troponin I, creatinine.
- <sup>j</sup> PD parameters include RICO, vWF:Ag, and FVIII:C.
- <sup>k</sup> In case of a severe and/or serious hypersensitivity reaction, an additional blood sample to characterize the reaction should be collected as soon as possible after the start of the event.



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**Table 4: Time and events schedule for adults: Treatment extension period a**

Study Visit	Week 6 (+ 7 days after end of 30-day post-daily PE period) (± 1 day)	Week 7 (+14 days after end of 30-day post-daily PE period) (± 1 day)	Week 8 (+ 21 days after end of 30-day post-daily PE period) (± 1 day)	Week 9 (+ 28 days after end of 30-day post-daily PE period) (± 1 day)	Second or subsequent recurrence visit (At the time of initiating daily PE) <sup>b</sup>
Study drug administration (daily) <sup>c</sup>	x	x	x		
Corticosteroids	x	x	x	x	
Review of patient diary	x	x	x	x	x
Neurologic assessment <sup>d</sup>	x	x	x	x	x
SMMSE	x	x	x	x	x
Clinically significant TTP event	x	x	x	x	x
Bleeding assessment <sup>e</sup>	x	x	x	x	x
Adverse events					→
Concomitant medication					→
Platelet count <sup>f</sup>	x	x	x	x	x
Organ damage markers <sup>g</sup>	x	x	x	x	x
ADAMTS13 Activity	x	x	x	x	x
PK	x	x	x	x	x
PD parameters <sup>h</sup>	x	x	x	x	x
Immunogenicity (ADA) <sup>i</sup>				x	x

<sup>a</sup> The following guidance with regard to timing of assessments planned at a single visit should be followed: s.c. study drug should be dosed after all other assessments have been performed.

After the last dosing in the treatment extension period, subjects are to complete assessments of the first and last FU visit as specified in [Table 3](#).

<sup>b</sup> Also see Protocol Section 3.1.1

<sup>c</sup> Study drug treatment should be administered s.c. for additional 7-day periods with a maximum of 28 days for subjects whose ADAMTS13 activity profile remains below 10% based on weekly measurements and for subjects with other clinical signs of underlying disease.

<sup>d</sup> Neurological assessment will include assessment of the neurological system (including coma, stupor, seizures, disorientation/confusion, hemiparesis/-plegia, focal deficit, agitation, dysarthria).

<sup>e</sup> Bleeding assessment is a clinical assessment of signs and symptoms of bleeding (e.g., petechiae, hematuria, epistaxis, meno-metrorrhagia, bruises) performed by the Investigator.

<sup>f</sup> Samples for platelet count will be assessed by a local laboratory.

<sup>g</sup> Organ damage markers include LDH, Troponin I, creatinine.

<sup>h</sup> PD parameters include RICO, vWF:Ag, and FVIII:C.

<sup>i</sup> In case of a severe and/or serious hypersensitivity reaction, an additional blood sample to characterize the reaction should be collected as soon as possible after the start of the event.

### **Schedules of Assessments for Pediatric Subjects (Children/Adolescents)**



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**Table 5: Time and events schedule for pediatric subjects: screening**

Study Visit	Screening
Written informed consent /assent	x
Demographics	x
Medical history <b>a</b>	x
Review of eligibility criteria	x
Collection of hospitalization information	x
Bleeding assessment <b>b</b>	x
Adverse events	x
Concomitant medication	x
Pregnancy test (urine or blood) <b>c</b>	x
Platelet count and blood smear <b>d</b>	x
Serum creatinine <b>d</b>	x

<sup>a</sup> General medical history and TTP-specific medical history. The result of an ADAMTS13 activity test performed as per standard of care upon admission will be collected in the CRF, if available.

<sup>b</sup> Bleeding assessment is a clinical assessment of signs and symptoms of bleeding (e.g., petechiae, hematuria, epistaxis, meno-metrorrhagia, bruises) performed by the Investigator.

<sup>c</sup> Only for female subjects of childbearing potential (i.e., post-menarche). Pregnancy test (urine or blood) will be assessed locally.

<sup>d</sup> Samples for platelet count, blood smear and serum creatinine will be assessed by a local laboratory (values from samples taken as part of standard of care can be used, if available).



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**Table 6: Time and events schedule for pediatric subjects: Daily PE period <sup>a</sup>**

Study Visit	Day 1 (Baseline)	Day 2	Day 3	Day 4	DAILY from Day 5 to end of daily PE	WEEKLY <sup>b</sup> on Day 8, 15, ... (± 1 day)
Study drug administration <sup>c</sup>	x	x	x	x	x	x
Plasma exchange + corticosteroids	x	x	x	x	x	x
Neurologic assessments <sup>e</sup>	x	x	x	x	x	x
Clinically significant TTP event	x	x	x	x	x	x
Bleeding assessment <sup>f</sup>	x	x	x	x	x	x
Physical examination	x					x
Height and weight (initial daily PE period only)	x					
Vital signs <sup>g</sup>	x					x
12-lead ECG <sup>h</sup>	x	x	x	x		
Adverse events						→
Concomitant medication						→
Platelet count <sup>j</sup>	x	x	x	x	x	x
Blood smear <sup>j</sup>	x					
Clinical laboratory analyses <sup>i</sup>	x					
ADAMTS13 activity	x					
PK	x					
PD parameter <sup>k</sup>	x					
Immunogenicity (ADA) <sup>l</sup>	x					

<sup>a</sup> The following guidance with regard to timing of assessments planned at a single visit should be followed: 1) ECG and vital signs should be assessed prior to blood sampling, 2) assessments should be done prior to start of PE (and on Day 1, prior to the i.v. dose administration), and 3) s.c. study drug should be dosed after end of the day's PE.

This time and events schedule is also applicable in case of a first exacerbation or relapse (relapse during the treatment extension period). Of note, height and weight are to be assessed at the initial daily PE period only.

<sup>b</sup> All assessments to be done on Day 8, 15,... include assessments done on daily basis plus extra weekly assessments.

<sup>c</sup> Study drug is to be administered daily s.c. post PE, in addition on Day 1 an i.v. loading dose of study drug will also be administered prior to start of PE.

<sup>d</sup> Standard of care treatment will be determined by the Investigator (or his/her designee) according to local practice. One PE (with volume and intensity as per local practice) should have been given prior to start of first study drug administration (i.e., loading i.v. dose).

<sup>e</sup> Neurological assessment will include assessment of the neurological system (including coma, stupor, seizures, disorientation/confusion, hemiparesis/-plegia, focal deficit, agitation, dysarthria).



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- f Bleeding assessment is a clinical assessment of signs and symptoms of bleeding (e.g., petechiae, hematuria, epistaxis, meno-metrorrhagia, bruises) performed by the Investigator.
- g Vital signs (assessment after 5 min in supine position): blood pressure, pulse and temperature.
- h To be performed after 5 min in supine position.
- i Clinical laboratory analyses include blood chemistry, hematology and blood coagulation parameters.
- j Samples for platelet count and blood smear will be assessed by a local laboratory.
- k PD parameter includes vWF:Ag.
- l In case of a severe and/or serious hypersensitivity reaction, an additional blood sample to characterize the reaction should be collected as soon as possible after the start of the event.



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**Table 7: Time and events schedule for pediatric subjects: 30-day post-daily PE period, early termination and follow-up period a**

Study Period	30-Day Post-Daily PE Period					Early Termination Visit	Follow-up	
	Week 1 Day 1 (1 day after last daily PE)	Week 2 Day 8 (8 days after last daily PE) (± 1 day)	Week 3 Day 15 (15 days after last daily PE) (± 1 day)	Week 4 Day 22 (22 days after last daily PE) (± 1 day)	Week 5 Day 30 End of 30-day post-daily PE Period (± 1 day)		First FU visit 7 days after last dosing (± 1 day)	Final FU visit 28 days after last dosing (± 1 day)
Study drug administration (daily) <b>b</b>	x	x	x	x	x			
Corticosteroids	x	x	x	x	x			
Review of patient diary	x	x	x	x	x			
Neurologic assessments <b>c</b>	x				x	x	x	x
Clinically significant TTP event	x	x	x	x	x	x	x	x
Bleeding assessment <b>d</b>	x	x	x	x	x	x	x	x
Physical examination	x				x	x	x	x
Vital signs <b>e</b>	x				x	x	x	x
12-lead ECG <b>f</b>	x				x	x	x	x
Adverse events								→
Concomitant medication								→
Platelet count <b>h</b>	x	x	x	x	x	x	x	x
Clinical laboratory analyses <b>g</b>	x				x	x		x
ADAMTS13 Activity	x		x	x	x	x		x
PK	x		x	x	x	x		x
PD parameter <b>i</b>	x		x	x	x	x		x
Immunogenicity (ADA) <b>j</b>	x				x			x

<sup>a</sup> The following guidance with regard to timing of assessments planned at a single visit should be followed: 1) ECG and vital signs should be assessed prior to blood sampling, and 2) s.c. study drug should be dosed after all other assessments have been performed.

<sup>b</sup> Study drug is to be administered daily s.c. for 30 days. Of note, no study drug is to be administered at the Week 5 visit in case of no treatment extensions.

<sup>c</sup> Neurological assessment will include assessment of the neurological system (including coma, stupor, seizures, disorientation/confusion, hemiparesis/-plegia, focal deficit, agitation, dysarthria).

<sup>d</sup> Bleeding assessment is a clinical assessment of signs and symptoms of bleeding (e.g., petechiae, hematuria, epistaxis, meno-metrorrhagia, bruises) performed by the Investigator.

<sup>e</sup> Vital signs (assessment after 5 min in supine position): including blood pressure, pulse and temperature.

<sup>f</sup> To be performed after 5 min in supine position.

<sup>g</sup> Clinical laboratory analyses include blood chemistry, hematology and blood coagulation parameters.

<sup>h</sup> Samples for platelet count will be assessed by a local laboratory.

<sup>i</sup> PD parameter includes vWF:Ag.



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- j In case of a severe and/or serious hypersensitivity reaction, an additional blood sample to characterize the reaction should be collected as soon as possible after the start of the event.





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**Table 8: Time and events schedule for pediatric subjects: Treatment extension period a**

Study Visit	Week 6 (+ 7 days after end of 30-day post-daily PE period) (± 1 day)	Week 7 (+14 days after end of 30-day post-daily PE period) (± 1 day)	Week 8 (+ 21 days after end of 30-day post-daily PE period) (± 1 day)	Week 9 (+ 28 days after end of 30-day post-daily PE period) (± 1 day)	Second or subsequent recurrence visit (At the time of initiating daily PE) b
Study drug administration (daily) c	x	x	x		
Corticosteroids	x	x	x	x	
Review of patient diary	x	x	x	x	x
Neurologic assessment d	x	x	x	x	x
Clinically significant TTP event	x	x	x	x	x
Bleeding assessment e	x	x	x	x	x
Adverse events					→
Concomitant medication					→
Platelet count f	x	x	x	x	x
ADAMTS13 Activity	x	x	x	x	x
PK	x	x	x	x	x
PD parameter g	x	x	x	x	x
Immunogenicity (ADA) h				x	x

a The following guidance with regard to timing of assessments planned at a single visit should be followed: s.c. study drug should be dosed after all other assessments have been performed.

After the last dosing in the treatment extension period, subjects are to complete assessments of the first and last FU visit as specified in [Table 7](#).

b Also see Protocol Section 3.1.1

c Study drug treatment should be administered s.c. for additional 7-day periods with a maximum of 28 days for subjects whose ADAMTS13 activity profile remains below 10% based on weekly measurements and for subjects with other clinical signs of underlying disease.

d Neurological assessment will include assessment of the neurological system (including coma, stupor, seizures, disorientation/confusion, hemiparesis/-plegia, focal deficit, agitation, dysarthria).

e Bleeding assessment is a clinical assessment of signs and symptoms of bleeding (e.g., petechiae, hematuria, epistaxis, meno-metrorrhagia, bruises) performed by the Investigator.

f Samples for platelet count will be assessed by a local laboratory.

g PD parameter includes vWF:Ag.

h In case of a severe and/or serious hypersensitivity reaction, an additional blood sample to characterize the reaction should be collected as soon as possible after the start of the event.



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## **17.2 Appendix B: Adjudication charter**



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### 17.3 Appendix C: Prednisolone equivalent dose chart

	Approx. equivalent dose (mg/day)*	Conversion factor
<b>Cortisone</b>	25	0.20
<b>Hydrocortisone</b>	20	0.25
<b>Methylprednisolone</b>	4	1.25
<b>Prednisolone</b>	5	1.00
<b>Prednisone</b>	5	1.00
<b>Triamcinolone</b>	4	1.25
<b>Betamethasone</b>	0.70	7.15
<b>Dexamethasone</b>	0.75	6.67
<b>Deflazacort</b>	6	0.83

\* Based on Prednisolone dose of 5 mg/day.

#### References:

Dixon JS (1991), Meikle AW and Tyler FH (1977), Webb R, Singer M. and Nayal S et al. (2005)