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STATISTICAL ANALYSIS PLAN

Prospective Follow-up Study for Patients who Completed Study ALX0681-C301 (HERCULES) to Evaluate Long-term Safety and Efficacy of Caplacizumab (Post-HERCULES)

ALX0681- LTS16371 (ALX0681-C302)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	Anti-drug antibody
ADaM:	analysis data model
ADAMTS13:	a disintegrin-like and metalloprotease with thrombospondin repeats 13
AE:	adverse event
ALT:	Alanine aminotransferase
AST:	Aspartate aminotransferase
ATC:	Anatomical therapeutic chemical classification system
aTTP:	Acquired thrombotic thrombocytopenic purpura
BQL:	below quantification limit
CDR:	Complementary determining region
CI:	Confidence interval
CRP:	C-reactive protein
CV:	coefficient of variation
DY:	relative day
eCRF:	Electronic case report form
ELISA:	Enzyme-linked immunosorbent assay
FU:	Follow-up
H:	High
Hb:	Hemoglobin
Hct:	Hematocrit
HIT-6:	Headache impact test-6
HLGT:	High level group term
HLT:	High level term
i.v.:	intravenous
ICU:	Intensive Care Unit
ITO:	Intention to Observe
KM:	Kaplan-Meier
L:	Low
LLN:	Lower limit of the normal
LLT:	Lower level term
M:	Month
mADA:	Modified anti drug antibody
MedDRA:	Medical Dictionary for Regulatory Activities
MRD:	Minimum required dilution
MSR:	Minimum significant ratio
N:	Normal
NAb:	Neutralizing antibody
PD:	Pharmacodynamic
PE:	plasma exchange
PK:	Pharmacokinetic
PT:	Preferred term

Q1:	25 percentile
Q3:	75 percentile
Q6M:	Twice yearly
QoL:	Quality of Life
RBANS:	Repeatable Battery for the Assessment of Neurological Status
RBC:	Red blood cell
RICO:	Ristocetin cofactor activity
s.c.:	subcutaneous
SAE:	Serious adverse event
SD:	standard deviation
SDTM:	standard data tabulation method
SE:	standard error
SF-36:	Short Form-36
SOC:	System organ class
TE:	Treatment emergent
TEAE:	Treatment emergent adverse event
TnI:	Troponin I
ULN:	Upper limit of the normal
vWF: Ag:	von Willebrand factor antigen
vWF:	von Willebrand factor
WBC:	White blood cell
WHO-DD:	World Health Organization-Drug Dictionary
Y:	Year

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a long-term follow-up, multicenter, open-label study design, for subjects who completed study ALX0681-C301 (HERCULES) according to the protocol (i.e., completed the Final [28 day] follow-up [FU] visit). The anticipated study duration per subject is approximately 3 years.

In case of recurrence of Acquired thrombotic thrombocytopenic purpura [aTTP], subjects will be treated with standard of care and Caplacizumab.

1.2 OBJECTIVES

The objectives of this study are:

- To evaluate long-term safety and efficacy of caplacizumab
- To evaluate safety and efficacy of repeated use of caplacizumab
- To characterize long term impact of aTTP

1.3 DETERMINATION OF SAMPLE SIZE

The sample size is not based on statistical considerations but rather on the number of subjects who complete Study ALX0681-C301 (HERCULES) and accept the option to participate in this FU study (ALX0681-C302). All subjects who enrolled in this FU study will be included in the safety and efficacy analyses.

1.4 STUDY PLAN

This is a FU study for subjects who completed study ALX0681-C301 (HERCULES) according to the protocol (ie, completed the final [28 day] FU visit).

The study flow is depicted in Figure 1.

Subjects who completed Study ALX0681-C301 will be given the option to participate in this FU study and attend twice yearly [Q6M] visits for 3 years starting with a baseline visit coinciding with or scheduled to take place within 1 month after the Final (28 day) FU visit in study ALX0681-C301. For subjects for whom the Final (28 day) FU visit in Study ALX0681-C301 occurred prior to local approval and site activation for this study, a time window of + 1 month after site activation is permitted to complete the screening/baseline visit. Assessments at these Q6M visits will include patient reported outcome measures, clinical assessments (including adverse events, safety laboratory parameters, vital signs and physical examination), and determination of anti-drug antibody [ADA], von Willebrand factor antigen [vWF:Ag] (PD parameter), and disease-related markers (a disintegrin-like and metalloprotease with thrombospondin repeats 13 [ADAMTS13] activity and Troponin I [TnI]).

Recurrence of TTP episode

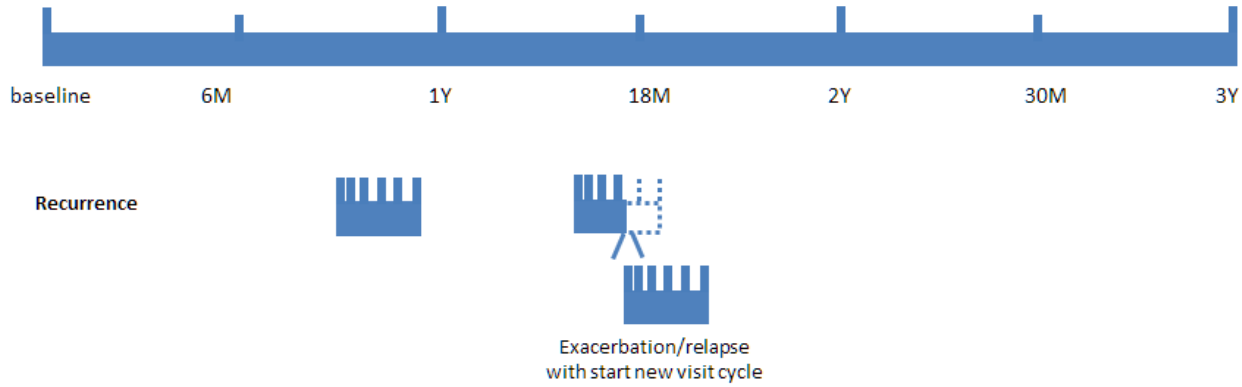
Upon recurrence of TTP, defined as recurrent thrombocytopenia requiring initiation of daily plasma exchange [PE] (1), standard of care treatment consisting of daily PE and immunosuppression is to be initiated. In addition, an intravenous (i.v.) loading dose of open-label caplacizumab will be administered prior to initiation of daily PE followed by daily subcutaneous [s.c.] administration of caplacizumab for the duration of daily PE and for 30 days thereafter. Up to 1 PE (which may be spread over 2 or more sessions in 24 hours) may be given prior to initiation of treatment with caplacizumab as long as considered part of the PE for the treatment of the presenting TTP episode. Treatment with caplacizumab may be extended for a maximum of 4 weeks in case of persistent signs and symptoms of underlying disease activity (eg, ADAMTS13 activity profile remains below 10% based on weekly measurements).

The visit schedule upon initiation of treatment consists of a recurrence visit at presentation, a visit on Day 3 of treatment with caplacizumab, weekly visits during treatment with caplacizumab (starting 1 day after the last daily PE), and a recurrence FU visit 1 week after the end of treatment with caplacizumab. At these visits, information with regard to the TTP recurrence (presenting symptoms, duration, and outcome) and treatment choice will be collected as will safety information (including AEs, safety laboratory parameters, vital signs and physical examination), and determination of pharmacokinetic [PK], ADA, pharmacodynamic [PD] parameters (vWF:Ag and Ristocetin cofactor activity [RICO]), and disease-related markers (ADAMTS13 activity and TnI).

In case of recurrent thrombocytopenia requiring re-initiation of daily PE during an ongoing recurrence period (see Figure 1), a new visit cycle is to be started, with a recurrence visit on the day of the new recurrence followed by all subsequent visits as indicated in Table 5. An i.v. loading dose of caplacizumab needs to be administered prior to re-initiation of PE for the recurrence. All remaining visits of the original schedule are no longer applicable and are not to be performed.

Q6M visits that are scheduled within a recurrence period will not be held as assessments at such visits would be confounded by the concurrent recurrence. Treatment with caplacizumab may not be initiated for subjects who do not fulfil the caplacizumab treatment criteria Hence, these subjects will be treated with standard of care only. The visit schedule in case of initiation of only standard of care treatment includes a recurrence visit at presentation and a recurrence FU visit at 30 days after end of daily PE (see Table 6 for schedule of assessments).

Figure 1 - Study flow of study ALX0681-C302



M: month; Y : year

Treatment in case of recurrence:

Initiation of treatment with caplacizumab is for subjects with a clinical diagnosis of an episode of recurrent acquired TTP requiring initiation of daily PE treatment and who had a baseline visit.

Treatment with caplacizumab is not permitted for subjects who:

- Are pregnant or intend to get pregnant in the near future
- Have a history of a severe and/or serious hypersensitivity reaction to investigational medicinal product (IMP) in Study ALX0681-C301 or Study ALX0681-C302.

Standard of care treatment (per standard site practice) can include:

- PE with plasma (eg, fresh frozen plasma, solvent detergent/viral-inactivated plasma, cryosupernatant)
- Corticosteroid treatment
- Use of other immunosuppressive agents (eg, rituximab)

Initiation of treatment with caplacizumab:

Daily PE period

- Loading i.v. dose: subjects will receive a single loading dose of 10 mg study drug by i.v. bolus injection from 6 hours to 15 minutes prior to start of daily PE treatment
- Daily s.c. dose: within 2 hours after completing each daily PE, a s.c. injection of 10 mg study drug will be administered daily throughout the full duration of PE treatment.

30-day post-daily PE period

Daily s.c. administration of 10 mg study drug will continue for a period of 30 days after stop of daily PE. No adjustment to this period will be made for tapering of PE. Subjects (and/or

caregivers) will be trained on preparing and administering caplacizumab and are to administer the study drug after discharge from the hospital.

Treatment extension period:

Treatment with caplacizumab beyond these 30 days will be guided by a number of risk factors for relapse of the presenting TTP episode and may be accompanied by an optimization of the immunosuppressive treatment. The risk factors will include the ADAMTS13 activity profile, as well as other signs and symptoms of continued underlying disease activity, such as presence of inhibitors if measured as routine practice by the site. Continued caplacizumab treatment should be given 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/or exhibit other clinical signs or symptoms of underlying disease. Caplacizumab treatment should be stopped when ADAMTS13 activity shows a sustained upward trend of >10% and/or when there is an improvement in other signs and symptoms of underlying disease activity and at the latest on Day 28 of the study drug treatment extension period.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The statistical section of the protocol was never changed in an amendment.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

The endpoint refractory to disease, defined as absence of platelet count doubling after 4 days of standard treatment, and lactate dehydrogenase (LDH) > upper limit of normal (ULN), is not calculated. Patients are missing the necessary timepoints to calculate the endpoint.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

For analysis related to the on-study period, the baseline is defined as the screening/baseline visit.

For analysis related to the recurrence period, the baseline value is defined as the recurrence visit of that recurrence episode.

All baseline parameters are presented along with the on-treatment summary statistics in the sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

Demographic variables are:

- Gender at birth: (Male, Female),
- Race: (not allowed to ask / white / black or African American / Asian / American Indian or Alaska native / native Hawaiian or other Pacific islander / other),
- Age in years at inform consent
- Ethnicity (Hispanic, non-Hispanic),

Medical or surgical history

Medical history includes:

- General medical history
- TTP-related medical history: TTP episodes and major thromboembolic events (e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism, deep venous thrombosis, transient ischemic attack, heart failure, unstable angina, coronary revascularization)
- History of hypersensitivity to IMP in study ALX0681-C301

This information will be coded using version 22.0 of Medical Dictionary for Regulatory Activities (MedDRA).

Vital signs

Vital signs at baseline are weight in kilograms, height, blood pressure and pulse (assessed after 5 min in supine position).

Baseline disease characteristics

Baseline disease characteristics are measured at the recurrence visit. It includes:

- ADAMTS13 activity at admission or baseline: <10% / ≥10%
- Baseline organ damage markers: (LDH, TnI and serum creatinine): <=ULN / >ULN
- Baseline platelet count.
- Baseline RICO activity, vWF:Ag concentration

Any technical details related to computation, dates, and imputation for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

All medications taken from signing of informed consent form until the subject's last visit, immunosuppressive therapies and antithrombotic therapies, are to be reported in the case report form pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) version B3 2019. Based on their start and stop date, prior and concomitant medications will be reported in each analysis period during which they applied (ie, non-treatment emergent (TE) allocation). This implies that each therapy can be reported more than once.

Non-investigational medicinal product

Following medications are the non-investigational medicinal products as the standard of care.

- Plasma exchange (PE)
- Corticosteroid treatment
- Other immunosuppressive treatment

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

2.1.3.1 TTP recurrence information endpoints

2.1.3.1.1 TTP recurrence presenting symptoms:

TTP recurrence presenting symptoms are assessed at the recurrence visit and collected in the electronic case report form (eCRF). The symptoms categories are fever, fatigue, neurological, gastro-intestinal, bleeding symptoms, cardiac symptoms and others.

2.1.3.1.2 Duration of the TTP recurrence

The duration of TTP recurrence in days (time to platelet count response) is defined as initial platelet count ≥ 150×10^9/L with subsequent stop of daily PE within 5 days. The start and end date time of the recurrence, for the calculation of the duration of TTP recurrence, are captured in the eCRF. There will be no imputation of missing data.

2.1.3.1.3 Outcome of the TTP recurrence:

The outcome of the TTP recurrence is assessed at the recurrence follow-up visit and is collected in the eCRF.

2.1.3.2 Treatment outcome endpoints

2.1.3.2.1 Time to platelet count ≥ 150×10^9/L

Time to platelet count ≥ 150×10^9/L is defined as the time from the recurrence visit to the first time the platelet count is ≥ 150×10^9/L in the recurrence episode. Patients without an event during the study are censored at the end of the recurrence episode

2.1.3.2.2 Duration of daily PE

Duration of daily PE in a recurrence episode is calculated as end date of daily PE – start date of daily PE +1 day.

2.1.3.2.3 Number of days in hospital:

The number of days in hospital is calculated as hospitalization discharge date – hospitalization admission date + 1 day.

2.1.3.2.4 Number of days in intensive care unit:

The number of days in intensive care unit (ICU) is calculated as ICU discharge date – ICU admission date + 1 day.

2.1.3.3 Cognitive assessment

2.1.3.3.1 Repeatable Battery for the assessment of Neurological Status (RBANS)

The RBANS is a 30-min comprehensive screening test with five individual domains (immediate memory, delayed memory, attention, language, and visuospatial ability) to examine the cognitive mental status of a subject. The results of the RBANS are reported as a total scale (overall score) and scores for each individual domain, based on the normal population values adjusted for age, provided by the RBANS manual. The overall score is a summary of performance across all five

individual domain scores. Scores are standardized to a mean score of 100 with a standard deviation of 15.

2.1.3.4 Quality of life

2.1.3.4.1 Headache impact test-6 (HIT-6)

The HIT-6 questionnaire is an easy to administer assessment that can be used as a clinical evaluation of the impact of headache on a patient's quality of life in both clinical practice and clinical research.

The questionnaire includes 6 questions covering the 6 areas of functioning most impacted in headache sufferers including pain, role functioning (the ability to carry out usual activities), social functioning, vitality (energy/ fatigue), cognitive functioning, and psychological/emotional distress. Scores range from 36 to 78, with higher scores reflecting worse condition.

2.1.3.4.2 Short Form Health Survey (SF-36)

The Short Form-36 (SF-36) version 2.0 is a 36 items questionnaire that measures Quality of Life (QoL). It has eight multi-item scales:

- Physical Functioning (10 items)
- Social Functioning (2 items)
- Role Functioning/Physical (4 items)
- Role Functioning/Emotional (3 items)
- Emotional Well-Being (5 items)
- Energy/Fatigue (4 items)
- Pain (2 items)
- General Health (5 items).

There is an additional single item covering change in health status over the last year.

Scales are set up so that a higher score indicates better health. Eleven items are reverse scored so that a higher precoded item value indicates a poorer health state. Those items are recoded before being added to other items on the same scale. Therefore, for each dimension, item scores are coded, summed, and transformed on to a scale from 0 (worst possible health state measured by the questionnaire) to 100 (best possible health state).

2.1.3.5 Other efficacy endpoints

2.1.3.5.1 TTP-related events

TTP related event is defined as:

- TTP-related death,
- recurrence of TTP
- or reported major thromboembolic event [e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism or deep venous thrombosis] based on SMQ based on the SMQ 'Embolic and thrombotic events (arterial, venous, and vessel type unspecified and mixed arterial and venous)'.

2.1.3.5.2 Time to TTP-related events:

The time to TTP related event (in days) is defined as the date from screening/baseline visit to the date of the first TTP related event. Patients without an event during the ALX0681-C302 study are censored at the end of the study.

2.1.3.5.3 Death

Adverse event with a fatal outcome.

2.1.3.5.4 Recurrence of aTTP

A recurrence of aTTP is defined as recurrent thrombocytopenia requiring initiation of daily plasma exchange (PE).

2.1.3.5.5 Time to first recurrence of aTTP

The event of interest is the first recurrence of aTTP experienced by the patients in the ALX681-C302 study. Time to first recurrence (in days) is defined as the date from end of previous aTTP episode in the ALX0681-C301 study to the date of the event. Patients without an aTTP recurrence during the ALX0681-C302 study are censored at the end of the study. This endpoint is only computed for subjects who did not have any recurrence in the ALX0681-C301, or between the end of ALX0681-C301 trial and the beginning of the ALX-0681C302 trial.

2.1.3.5.6 Time to major thromboembolic events:

The time to the first major thromboembolic event (in days) is defined as the date from screening/baseline visit to the date of the first thromboembolic event. Patient without a thromboembolic event are censored at the end of the study.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data, vital signs and physical examination.

Observation period

The observation period will be divided into 2 non mutually exclusive periods: the on-study period and the recurrence period.

The on-study observation period is defined as the time from informed consent until the end of the study (defined as last protocol planned visit).

The recurrence period is from the start of the recurrence episode, defined as recurrent thrombocytopenia requiring initiation of daily PE, until the last recurrence follow-up visit of that episode. In case of treatment with the IMP, the recurrence period is divided into 2 epochs:

- the **treatment epoch** is defined as the time from the first administration of the IMP to the last administration of the IMP.
- the **residual treatment** epoch is defined as the time from the last administration of the IMP to the last administration of the IMP + 30 days.

The treatment-emergent adverse event (TEAE) period will include both treatment and residual treatment epochs.

In case treatment with the IMP is not initiated during the recurrence episode, there is no subdivision of the recurrence period into the treatment epoch and the residual treatment epoch. The adverse event occurring during that period are not identified as treatment-emergent adverse events.

2.1.4.1 Adverse events variables

Adverse event observation period

- On-study adverse events are adverse events that developed or worsened or became serious during the on-study period
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period

All adverse events (including serious adverse events (SAE)) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version 22.0 of Medical Dictionary for Regulatory Activities (MedDRA).

2.1.4.2 Deaths

The deaths observation period is per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period
- Death on-treatment: deaths occurring during the treatment-emergent adverse event period

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be analyzed into standard international units and international units will be used in all listings and tables.

Blood samples for clinical laboratories will be taken according to the schedule of assessments. The laboratory parameters will be classified as follows:

- Hematology

Red blood cells and platelets and coagulation: hemoglobin [Hb], hematocrit [Hct], red blood cells [RBC], platelets)

White blood cells: white blood cells [WBC]

- Clinical chemistry

Metabolism: total cholesterol, total protein, C-reactive protein [CRP],

Renal function: creatinine

eGFR will be calculated using the CKD-EPI creatinine equation from Levey et al. (2009) (2):

eGFR = 141 * min(SCr/κ, 1)α * max(SCr /κ, 1)-1.209 * 0.993Age *1.018 [if female] *1.159 [if Black]

Where:
eGFR (estimated glomerular filtration rate) = mL/min/1.73 m2
SCr (standardized serum creatinine) = mg/dL
κ = 0.7 if females or 0.9 if males
α = -0.329 if females or -0.411 if males
min = indicates the minimum of SCr/κ or 1
max = indicates the maximum of SCr/κ or 1
age = years

Liver function: alanine aminotransferase [ALT], aspartate aminotransferase [AST], lactate dehydrogenase [LDH]

Pregnancy test: Serum β-human chorionic gonadotropin (all female patients)
Urine samples will be collected as follows:

Urinalysis - quantitative analyses: albumin

- Disease related marker

  Troponin, ADAMTS13 activity and time to sustained ADAMTS13 normalization ≥ 10%. will be analyzed.

  Sustained ADAMTS13 activity ≥ 10% is defined as two consecutive weekly visits during post-daily plasma exchange or follow-up visits at which ADAMTS13 activity is ≥ 10%. The first of these consecutive visits will be used to determine the event. The time to sustained ADAMTS13 activity ≥ 10% is the time from the recurrence visit to the event. In case the event does not occur before the last visit in the recurrence episode, the patient is censored at the last visit.

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs include blood pressure and pulse (assessed after 5 min in supine position) and weight.

2.1.4.5 Physical examination variables

Physical examination includes the following body systems:

- General appearance
- Head, eyes, ears, nose, throat
- Central and peripheral nervous system
- Respiratory
- Cardiovascular
- Gastrointestinal
- Musculoskeletal
- Skin
- Lymph node palpation
- Other

2.1.4.6 Immunogenicity variables

Antibodies to caplacizumab will be evaluated in blood samples collected from all participants as specified in the protocol. In case of a severe and/or serious hypersensitivity reaction, judged to be related to study drug, an additional blood sample will be collected as soon as possible after the start of the event to characterize the reaction.

2.1.5 Pharmacokinetic variables

Pharmacokinetic variable includes the caplacizumab concentration in case of treatment with the IMP.

2.1.6 Pharmacodynamic endpoints

Pharmacodynamic parameters include vWF:Ag concentration and RICO activity (in case of recurrence and treatment with the IMP).

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Enrolled participants are defined as all participants who signed the inform consent form [ICF].

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report, in summary table for the Intention to Observe [ITO] and recurrence populations (see Section 2.3 for more details on the populations):

- Enrolled patients
- Patients with a recurrence
- Patients with a recurrence and not treated with IMP
- Patients with a recurrence and treated with IMP
- Patients who completed the study
- Patients who discontinued the study, with the primary reason
- Status at last study contact
- Lost to follow-up

For all categories of patients (except for the enrolled) percentages will be calculated using the number of exposed patients divided by the number of patients enrolled patients as the denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by analysis group.

A patient is considered lost to follow-up under the following circumstances:

- A patient missed 2 consecutive 6-monthly follow-up visits and did not reply to site staff contact attempts;
- The site contacted the patient at least three times before each of the 6-monthly visits without success, and all contact attempts were documented in the source documents;
- A certified letter was sent to the patient (where possible following site/country procedure/regulations) before the second visit last planned date to inform the patient that if

the second visit would be missed the patient would be withdrawn from the trial without access to future IMP treatment.

All critical or major deviations potentially impacting efficacy analyses, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group.

Trial termination data including reason for completion/discontinuation, the number of days since screening, date of first study drug intake and date of last study drug intake at trial termination will be listed.

- A tabulation of the number and percentage of participants by analysis period, subperiod, and time point will be given for the recurrence population and the ITO population.
- The following 3 dates will be presented on the enrolled participants.
  - Date of the first signature on the ICF
  - Last visit date (all visit; including unscheduled visits)
- A descriptive statistics of the analysis period duration will be provided by phase, analysis period on the ITO and Recurrence population. Analysis period including start and end dates, and duration of each analysis period will be listed. The duration (days) is derived as follows:
  - Period end date – period start date + 1
- A tabulation of the number and percentage of participants in each of the analysis populations will be provided.

2.2.1 Drug dispensing irregularities

Drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis. All drug-dispensing irregularities will be documented in the clinical study report.

2.3 ANALYSIS POPULATIONS

2.3.1 Intention-to Observe (ITO) Population

All subjects who enrolled in study ALX0681-C302. Unless otherwise specified, the ITO population will be used for the analysis of the Q6M FU data on efficacy, disease-related markers, PD, immunogenicity and safety.

2.3.2 Recurrence population

All subjects in the ITO population who have experienced at least one recurrence in study ALX0681-C302. The recurrence population will be used for analysis of data collected during recurrence periods.

2.4 STATISTICAL METHODS

For continuous parameters, descriptive statistics will be presented when n ≥ 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, change from baseline, or percentage change summaries), the median, minimum and maximum.

For categorical parameters, frequency tabulations are prepared, consisting of frequency counts (non-missing observations) and percentages. Missing values will not be included in the denominator count when computing percentages.

Descriptive statistics of PK concentrations and PD data will additionally include 5% and 95% percentiles, SD of arithmetic mean, 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.

- 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*[[value at time point t – baseline value]/ baseline value].
- Change from baseline and percentage change from baseline will be calculated separately for each of the analysis periods from their respective baseline values.

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.

2.4.1 Demographics and baseline characteristics

Demographic and baseline data will be evaluated descriptively. Summaries will be presented on the ITO population and each recurrence episode on the Recurrence population separately. Baseline disease characteristics will be evaluated descriptively and will be presented for the Recurrence population for each of the recurrence episode. Parameters are described in Section 2.1.1.

Demographic and baseline data, baseline characteristics, screening tests of pregnancy test and creatinine assessment, medical history, concomitant diseases, and ADAMTS13 activity will be listed. Separate listings will be presented for general medical history and for TTP history.

2.4.2 Concomitant medications

Concomitant medications will be presented for the ITO and recurrence populations.

Based on their start and stop date, prior and concomitant therapies will be reported in each analysis period during which they were applied. This implies that each therapy can be reported more than once.

For the ITO population, concomitant medication will be presented for the overall study period.

For the recurrence population, concomitant therapies will be tabulated by generic term and by phase, analysis period and subperiod. Multiple records of the same generic term for the same participant will be counted only once. The table will therefore present participants, not occurrences. The tables are sorted by decreasing frequency. 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 participants who received concomitant antithrombotic therapies (Anatomical therapeutic chemical classification system (ATC) codes starting with B01A) and the number and proportion of participants 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 for the recurrence population.

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 B or more details).

Prior and concomitant therapies will be listed including coding information. Plasma exchange will also be listed.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized within the recurrence population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and summarized for the recurrence population.

Duration of IMP exposure is defined as:

- Treatment duration (days) in a recurrence episode: date of last administration – date of first administration within the recurrence episode + 1 day.
- Total treatment duration (days): sum of the duration of treatment exposure.

Duration of IMP exposure will be summarized descriptively by analysis period and overall treatment period as a quantitative variable (number, mean, SD, median, minimum, and maximum).

Additionally, the number and percentage of participants with extension period in each recurrence episode will be provided.

Actual IMP exposure data, and derived data including total treatment duration, total number of study drug doses received, compliance, total corticosteroid treatment duration (days), and cumulative dose of corticosteroids by analysis period will be listed.

2.4.3.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Percentage of compliance for a participant will be defined as (number of study drug administrations received / number of study drug administration planned)*100 (%).

Treatment compliance will be summarized descriptively by analysis period and analysis subperiod as quantitative variables (number, mean, SD, median, minimum, and maximum) for the recurrence population.

Cases of overdose (see protocol for further details) will constitute AEs and will be listed as such.

2.4.4 Analyses of efficacy endpoints

All efficacy endpoints related to assessments on the Q6M FU visits will be analyzed using the ITO population. Summarization will be conducted on the total study population and by analysis group. For the group-wise analysis, the following groups will be considered:

- caplacizumab-treated: defined as subjects in the ITO population who have been randomized to caplacizumab in study ALX0681-C301, evaluated up to their first recurrence in the ALX0681-C302 trial;
- standard of care-treated, defined as subjects in the ITO population who have been randomized to placebo in study ALX0681-C301, evaluated up to their first recurrence in the ALX0681-C302 trial.

Subjects who had a recurrence during study ALX0681-C301 or between the Final (28 day) FU visit in study ALX0681-C301 and Screening/Baseline in study ALX0681-C302, will not be considered for the group-wise analyses.

All efficacy endpoints related to assessments during the recurrence period will be analyzed using the recurrence population. The effect of retreatment of caplacizumab on these endpoints will be evaluated. For the group-wise analysis the following groups are considered, unless otherwise specified:

- Treated with IMP: defined as subjects in the recurrence population who received caplacizumab in the ALX0681-C302 during a recurrence episode
- Not treated with IMP: defined as subjects in the recurrence population who did not received caplacizumab in the ALX0681-C302 during a recurrence episode.

Of note, depending on the recurrence episode, the same subject can appear in both analysis groups.

Select sensitivity analyses may be planned to assess the effect of heterogeneity in the timings of the baseline visit between subjects. Unless specified otherwise, no missing data imputation will be applied, and all efficacy endpoints will be analyzed as observed.

2.4.4.1 TTP-related events

The number and percentage of participants with TTP-related event as well as the number of such events, will be summarized. The total number and percentage of participants who have at least one of the TTP-related events will also be calculated.

For the ITO population, it will be after 12 months follow-up (M FU), 24M FU and 36M FU as well as a cumulative summary. For the Recurrence population, it will be during each recurrence period separately.

TTP-related events will be listed.

The time to the first TTP-related event will be summarized on the ITO population, using Kaplan-Meier (KM) estimates such as the median, 25% percentile and 75% percentile with associated 95% CIs, as well as the number of events and the number of censored observations. The KM estimates will also be presented graphically.

2.4.4.2 Major thromboembolic events

The number and percentage of participants with a major thromboembolic event as well as the number of such events, will be summarized. The total number and percentage of participants who have at least one of major thromboembolic event will also be calculated. Within the major thromboembolic events category, the frequency tabulation of PTs will also be summarized.

For the ITO population, it will be after 12M FU, 24M FU and 36M FU as well as a cumulative summary. For the Recurrence population, it will be during each recurrence period separately.

The time to the first major thromboembolic event will be summarized on the ITO population, using Kaplan-Meier (KM) estimates such as the median, 25% percentile and 75% percentile with associated 95% CIs, as well as the number of events and the number of censored observations. The KM estimates will also be presented graphically.

2.4.4.3 Recurrence of TTP

The number and percentage of participants with a recurrence of TTP as well as the number of such events, will be summarized over time for the ITO population (after 12M FU, 24M FU and 36M FU).

Time to the first recurrence of TTP will be summarized on the ITO population, using Kaplan-Meier (KM) estimates such as the median, 25% percentile and 75% percentile with associated 95% CIs, as well as the number of events and the number of censored observations. The KM estimates will also be presented graphically.

A subgroup analysis of incidence of recurrence of TTP to ADAMTS13 levels (≥10%, <10%) after end of previous TTP episode in the ALX0681-C301 trial will be performed on the ITO population.

2.4.4.4 TTP recurrence information.

TTP recurrence information will be summarized for the recurrence population.

2.4.4.4.1 Presenting symptoms

The number and percentage of participants with presenting symptoms at the recurrence visit will be summarized for each recurrence episode. The denominator for the percentage calculation is the number of assessable participants at each time point.

2.4.4.4.2 Duration of TTP (time to platelet count response)

The duration of TTP (platelet count response), will be summarized for each recurrence episode. The denominator for the percentage calculation is the number of assessable participants at each time point.

2.4.4.4.3 Outcome of recurrence episode

The outcome of the recurrence at the recurrence follow-up visit will be summarized for each recurrence episode. The denominator for the percentage calculation is the number of assessable participants at each time point.

2.4.4.5 Treatment outcome

2.4.4.5.1 Time to platelet count ≥ 150×10^{9}/L

Time to platelet count ≥ 150×10^{9}/L will be summarized using Kaplan-Meier (KM) estimates such as the median, 25% percentile and 75% percentile with associated 95% CIs, as well as the number of events and the number of censored observations. The KM estimates will also be presented graphically.

2.4.4.5.2 Duration of Daily PE

The duration of daily PE will be summarized descriptively per recurrence period.

2.4.4.5.3 Hospitalization/Intensive Care Unit

The number of days of hospitalization as well as the number of days intensive care unit will be summarized by recurrence period.

2.4.4.6 Cognitive assessment

Actual and change from screening/baseline RBANS score will be summarized descriptively for the ITO population. There will be a descriptive comparison of RBANS with the reference population.

2.4.4.7 Quality of life

Actual and change from screening/baseline SF-36 at the Q6M follow-up visits will be summarized descriptively for the ITO population. The actual SF-36 at the end of the recurrence follow-up visit will be summarized for the recurrence population at each recurrence episode.

2.4.4.8 Multiplicity issues

There are no multiplicity issues because no formal statistical test will be performed.

2.4.4.9 Additional efficacy analysis

2.4.4.9.1 Subgroup Analysis

The following endpoints will be summarized for participants with ADAMTS13 activity at the end of the previous TTP (end of the treatment period of the last recurrence episode in the ALX0681C301 trial) < 10% / ≥ 10% on the ITO population. Subgroup analysis will only be conducted for each subgroup category if at least 5 participants are available.

- Incidence of recurrence of aTTP

Furthermore, the same analysis will be performed by number of recurrences in the ALX0681-C301 trial (1 recurrence, more than 1 recurrence).

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group. For the ITO population, the treatment groups are:

- Caplacizumab total: Subjects who received caplacizumab during the ALX0681-C301 study (during the double blind or the open-label periods).
- Not treated: Subjects who never received Caplacizumab during the ALX0681-C301 trial

For the recurrence population, adverse events will be presented for:

- Treated with IMP: patients treated with caplacizumab in the ALX0681-C302 study
- Not Treated with IMP: patients not treated with caplacizumab in the ALX0681-C302 study during the trial

General common rules

All safety analyses will be performed on the ITO and recurrence populations as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- For analysis related to the Q6M FU visits, the baseline value is defined as screening/baseline value visit. For analysis related to the recurrence period, the baseline value is defined as the recurrence visit value and will be calculated for each recurrence period separately
- For assessments with multiple parameters per participant (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.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit.
- The analysis of the safety variables will be essentially descriptive, and no systematic testing is planned.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pretreatment and posttreatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment,

treatment-emergent, or posttreatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment or posttreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse events (AEs) will be placed into analysis periods according to their start date (time). The AE will only be presented in the analysis period during which it started, ie, period start date (time) ≤ AE start date (time) ≤ period stop date (time). There will be no imputation of other missing date (time) fields, nor of the missing parts of other partially known date (time) fields. When needed (e.g., an incomplete date (time) leads to a double phase allocation), the following rules will be applied: adverse events will be allocated on all analysis levels (ie, for analysis periods and subperiods, see Section 2.5.4) according to their start date (time). In case the adverse event (AE) start date(time) is incomplete, the allocation will be done according to the available parts of the AE start date(time) and taking into account the AE end date(time) (ie, the AE start date(time) cannot be later than the AE end date(time):

- When, due to missing date (part) an allocation needs to be made to an analysis period, the AE will be allocated to the treatment phase and not off-treatment phase (worst-case allocation).
- When an allocation needs to be made to a specific recurrence period, the AE will be allocated to the first recurrence period.
- When an allocation needs to be made within a recurrence period, the event will be allocated to the daily PE subperiod.

Tables on the recurrence population will include only adverse events that occurred during the recurrence period, treatment-emergent (for patients who received the IMP) and non-treatment emergent (for patients who did not received the IMP).

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

AE onset day and AE duration are defined as follows:

- AE onset day
  - AE start date – reference date + 1 day (when the AE start date is completely known)
  - Missing (when the AE start date is incomplete or unknown).
  - Two different onset days will be calculated: one with the reference date being the screening/baseline visit; and the other, for adverse events occurring during the recurrence period, with reference date being the recurrence visit.
- 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.

AE incidence tables will present by SOC and PT, sorted by decreasing frequency of SOC and PTs within SOCs, the number (n) and percentage (%) of participants experiencing an adverse event. The denominator for computation of percentages is the population within each treatment group.

The following analysis periods will be considered for all TEAEs tables on the recurrence population:

- Treatment daily PE period
- Treatment post-daily PE period
- Overall treatment period
- Follow-up period
- Overall recurrence period

The following analysis periods will be considered for AE occurring in the recurrence periods for patients not treated with the IMP:

- Daily PE period
- Post Daily PE period
- Overall recurrence period

The following analysis period will be considered for the adverse events observed during the study for the ITO population:

- Overall study period

Analysis of all adverse events

The following adverse event summaries will be generated by analysis period for the patients not treated in the recurrence population and for the ITO population.

- Overview of adverse events, summarizing number (%) of participants, the number of events, and the incidence per 100 person months, which will be calculated as: 100 x (Number of participants with AE)/(Total number of months observed within analysis period, summed for all participants) with any
  - Participants with at least one AE
  - Participants with at least one serious AE

- Participants with at least one AE leading to death
- Participants with at least one PE-related AE (only for the recurrence population)
- Participants with at least one serious PE-related AE (only for the recurrence population)
- Participants with at least one bleeding event, i.e. an event documented as event indicating an increased bleeding tendency
- Participants with at least one bleeding event, based on the Standardized MedDRA Query (SMQ) "Haemorrhage" with exclusion of the PT "TTP"
- Participants with at least one thromboembolic event, based on the SMQ "Embolic and thrombotic events" (arterial, venous, and vessel type unspecified and mixed arterial and venous) with exclusion of the PT "TTP"

- All AE by primary SOC and PT, showing the number (%) of participants with at least 1 AE. The number of events and the number and percentage of participants having an event will be presented.
- AEs will be summarized by SOC, PT and severity. This will be done for each analysis period. The number and percentage of participants having an event will be presented for the worst severity reported for each event.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated by analysis period for the recurrence population.

- Overview of treatment-emergent adverse events, summarizing number (%) of participants, the number of events, and the incidence per 100 person months, which will be calculated as: 100 x (Number of participants with AE)/(Total number of months observed within analysis period, summed for all participants) with any
  - Participants with at least one TEAE
  - Participants with at least one serious TEAE
  - Participants with at least one TEAE leading to death
  - Participants with at least one TEAE for which the study drug was interrupted
  - Participants with at least one TEAE for which the study drug was withdrawn
  - Participants with at least one TEAE that was considered treatment-related by the investigator
  - Participants with at least one serious TEAE that was considered treatment-related by the investigator
  - Participants with at least one PE-related TEAE
  - Participants with at least one serious PE-related TEAE
  - Participants with at least one bleeding event, i.e. an event documented as event indicating an increased bleeding tendency

- Participants with at least one bleeding event, based on the Standardized MedDRA Query (SMQ) "Haemorrhage" with exclusion of the PT "TTP"
- Participants with at least one thromboembolic event, based on the SMQ "Embolic and thrombotic events" (arterial, venous, and vessel type unspecified and mixed arterial and venous) with exclusion of the PT "TTP"
- Participants with at least one hypersensitivity reaction, based on the SMQs "Hypersensitivity" (Narrow), "Anaphylactic reaction" (Narrow) and "Angioedema" (Narrow)
- Participants with at least one hypersensitivity reaction, based on the SMQs "Hypersensitivity" (Narrow), "Anaphylactic reaction" (Narrow) and "Angioedema" (Narrow), considered treatment-related by the investigator.

- All TEAE by primary SOC and PT, showing the number (%) of participants with at least 1 TEAE. The number of events and the number and percentage of participants having an event will be presented.
- TEAEs will be summarized by SOC, PT and severity. This will be done for each analysis period. The number and percentage of participants having an event will be presented for the worst severity reported for each event.
- TEAEs considered treatment-related by the investigator will be summarized by SOC and PT. This will be done for each analysis period. The number of events and the number and percentage of participants having an event will be presented.

Analysis of all (treatment emergent) serious adverse event(s)

- Serious (TE)AEs and non-serious (TE)AEs will be summarized by SOC and PT. This will be done for each analysis period. The number of events and the number and percentage of participants having an event will be presented.
- Serious (TE)AEs will be summarized by SOC, PT and severity. This will be done for each analysis period. The number and percentage of participants having an event will be presented for the worst severity reported for each event.
- Serious (TE)AEs considered treatment-related by the investigator will be summarized by SOC and PT. This will be done for each analysis period. The number of events and the number and percentage of participants having an event will be presented.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- TEAEs leading to discontinuation will summarized separately and combined by SOC and PT. This will be done for each analysis period. The number of events and the number and percentage of participants having an event will be presented.

Thromboembolic events

- Thromboembolic events (treatment-emergent or not), based on the SMQ "Embolic and thrombotic events" (arterial, venous, and vessel type unspecified and mixed arterial and venous) with exclusion of the PT "TTP", will be summarized by SOC and PT. This will be

done for each analysis period and population. The number of events and the number and percentage of participants having an event will be presented.

Bleeding events

- Bleeding events and serious bleeding events (treatment-emergent or not) will be summarized by SOC and PT. This will be done for each analysis period. The number of events and the number and percentage of participants having an event will be presented based on eCRF and SMQ.
- Treatment-emergent bleeding events based on SMQ and bleeding events considered treatment-related by the investigator based on eCRF will be summarized by SOC, PT and severity. This will be done for each analysis period. The number of events and the number and percentage of participants having an event will be presented for the worst severity reported for each event based on the eCRF and SMQ separately.

Hypersensitivity reactions

- Hypersensitivity reactions (including anaphylaxis and angioedema) will be summarized by SOC and PT. This will be done for each analysis period. The number of events and the number and percentage of participants having an event will be presented. This analysis will be repeated for hypersensitivity reactions considered treatment-related by the investigator.

Listings

- Listings will be provided for all AE, SAE, TEAE leading to treatment discontinuation, bleeding events, severe/serious hypersensitivity AE.

2.4.5.2 Deaths

AEs leading to death will be listed.

2.4.5.3 Analyses of laboratory variables

Laboratory analyses will be performed on the ITO and recurrence populations using the corresponding baseline visits.

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 standard international (SI) units.

Values will be scored as abnormal low (L), normal (N) or abnormal high (H). A value is classified as abnormal low when the value < lower limit of the normal (LLN) range. A value is classified as abnormal high when the value > upper limit of the normal (ULN) 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 abnormal low (L). An original value like ">X" where X equals the upper limit of the normal range will be classified as abnormal high (H).

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 = abnormal high: at least one post-dose measurement is above the normal range, and there are no values below the normal range.
- L = abnormal low: at least one post-dose measurement is below the normal range, and there are no values above the normal range.
- H+L = abnormal 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.

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all laboratory variables (actual values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point) by treatment group.

A shift table will be created per laboratory parameter. The table will present the shift in abnormality (L/N/H) at each post-baseline time point versus the baseline abnormality (L/N/H). Laboratory parameters without normal ranges will not be presented in this table. In addition, the tables that present the shift in abnormality (L/N/H/L+H) at the worst post-baseline time point versus the baseline abnormality (L/N/H) will also be created.

Laboratory variables will be listed. All data scored as out-of-normal-range or clinically significant will also be listed.

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all vital sign variables (actual values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point) by treatment group.

Vital signs values will be listed.

2.4.5.5 Analyses of immunogenicity

Immunogenicity assessments on serum samples will be performed at Ablynx GLP using 4 validated methods. The results of the analysis will be transferred to SGS Secure Data Office in Excel format. Results will be reported as log10 (titer).

2.4.5.5.1 Available data

The available parameters per sample are:

- Anti-drug antibody (ADA) log10(titer) (no data imputation). Titers <log10 are considered ADA negative.
- Modified anti-drug antibody (mADA) assay log10(titer) (for subset of subjects only, no data imputation)
- Neutralizing antibody (NAb) log10(titer) (for subset of samples only, data imputation required for ADA negative samples)
- NECA log10(titer) (for subset of samples only, data imputation required for ADA negative samples)

Based on the above listed data per subject, a subject classification will be attributed for each assay, resulting in the following reported data per subject:

- ADA subject classification (all subjects)
- mADA subject classification (for subset of subjects)
- Overall subject classification (based on ADA and mADA analysis)
- NAb subject classification (all subjects)
- NECA subject classification (all subjects)

2.4.5.5.2 ADA and mADA analysis

ADA

Immunogenicity samples will be evaluated in a three-tiered homogenous bridging ADA assay (screen/confirmatory/titer tiers). All samples confirmed positive in the ADA assay will be titrated. The log10 (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 log10 (titer) is reported as < log10 (Minimal required dilution [MRD]) with MRD = 96, i.e. log10 (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:

1. ADA negative: no positive ADA samples at any of the sampling time points
2. ADA positive: positive ADA samples at one or more sampling time points
3. Inconclusive: no positive ADA samples and drug is present at levels higher than the drug tolerance characteristics of the assay. Drug tolerance limit is 10µg/mL.
4. Missing: missing will only be used if samples were taken but no reportable result could be obtained for that subject.

Based on these ADA results, no statement can 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 subject and/or (ii) pre-Ab might be diluted during PE treatment. PE is part of the standard of care and no ADA pre-PE sample will be available to determine the pre-Ab status of the subject.

mADA

All confirmed positive ADA samples will be further evaluated in a mADA assay. This assay employs a modified caplacizumab molecule as detection reagent in the bridging format, ie, 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 is not detected. In other words, drug-induced TE ADA will score positive in the mADA assay. All samples confirmed positive in the mADA assay will be titrated and reported as log10 (titer). Samples scoring negative in the mADA assay are not titrated and the respective log10 (titer) is reported as < log10 ([MRD) with MRD = 96, ie, log10 (titer) < 1.98. The latter are not included in descriptive statistics on titers.

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

1. Pre-Ab positive ‑ Drug-induced TE ADA negative: all ADA positive samples analyzed in the mADA assay score negative (i)
2. Pre-Ab negative ‑ Drug-induced TE ADA positive: all ADA positive samples analyzed in the mADA assay score positive (ii)
3. Pre-Ab positive ‑ Drug-induced TE ADA positive: from the ADA positive samples analyzed in the mADA assay, some score positive and some score negative (ii)
4. Inconclusive: no positive ADA samples in the mADA assay and drug is present at levels higher than the drug tolerance characteristics of the assay. Drug tolerance limit is 10 µg/mL.
5. Missing: Relevant samples are missing.

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

(ii) Subjects will be classified "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.

Overall subject classification

For the overall subject classification, subjects will be classified as follows based on the ADA and /or mADA assay results:

1. Pre-Ab negative ‑ Drug-induced TE ADA negative: no positive ADA samples
2. Pre-Ab positive ‑ Drug-induced TE ADA negative: all ADA positive samples analyzed in the mADA assay score negative

3. Pre-Ab negative ‑ Drug-induced TE ADA positive: all ADA positive samples analyzed in the mADA assay are positive
4. 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
5. Inconclusive: no positive ADA samples or positive mADA samples and drug is present at levels higher than the drug tolerance characteristics of the assay. Drug tolerance limit is 10µg/mL.
6. Missing: Relevant samples are missing.

Subjects classified "ADA negative" based on ADA assay results will per default be classified as "Pre-Ab negative- Drug-induced TE ADA negative" for the overall subject classification (#1). No results will be reported for samples not evaluated in the mADA assay (#6).

2.4.5.5.3 NAb

The neutralizing antibody (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 (i.e. baseline visit), recurrence visit day 1 (if applicable) and wash out samples (follow-up samples) will be analyzed. All samples confirmed positive in the ADA assay at these time points will be analyzed in the NAb assay. Samples scoring negative in the NAb assay will be reported as <log10 (MRD) with MRD = 2.30 i.e. log10 (titer) < 0.36. The latter are not included in descriptive statistics on titers. Samples scoring positive will be reported as >= 0.36. These positive samples should be plotted as log (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:

1. Pre-dose negative,- TE negative: no NAb positive samples
2. Pre-dose negative,- TE positive: ADA or NAb negative at baseline visit and one or more NAb positive samples post-dose
3. Pre-dose positive,- TE negative: NAb positive at baseline visit and all post-dose samples score NAb negative
4. Pre-dose positive,- TE positive: NAb positive at baseline visit and at least 1 NAb positive post-dose sample
5. Missing: Relevant samples are missing.

Subjects with no positive ADA samples will be classified as NAb pre-dose negative, TE negative (data imputation). 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.

2.4.5.5.4 NECA (neutralizing antibody epitope characterization assay; null variant assay; alternative NAb): ADA with neutralizing potential

To detect ADA with potential neutralizing activity under treatment, an alternative NAb assay will be used, consisting of the homogenous 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 von Willebrand factor [vWF]) will be dependent on affinity and titer level and should be related to PK, PD, safety and efficacy read-outs.

All samples confirmed positive in the ADA assay, will be analyzed in this alternative NAb assay. Samples scoring positive in the alternative NAb assay are titrated. The titer per sample is reported as log10 (titer). Samples scoring negative in the alternative NAb assay are not titrated and the respective titer is reported as < log10 (MRD) with MRD = 96, i.e. log10 (titer) < 1.98. The latter are not included in descriptive statistics on titers.

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:

1. Pre-dose negative, - TE negative: no alternative NAb positive samples
2. Pre-dose negative, - TE positive: ADA or alternative NAb negative at baseline visit and one or more alternative NAb positive samples post-dose.
3. Pre-dose positive, - TE negative: alternative NAb positive at baseline visit and no titer increase post-dose or all samples scoring alternative NAb negative post-dose
4. Pre-dose positive, - TE positive: alternative NAb positive at baseline visit and titer increase post-dose. If a positive pre-dose titer is reported, the titer is considered to be significantly increased post-dose, if the highest post-dose titer compared to the pre-dose titer is higher than the minimum significant ratio [MSR] value: the increase of the log10 titer post versus pre-dose should be > log10 (MSR). The MSR value was determined in Ablynx GLP and is 1.89.
5. Inconclusive: no alternative NAb positive samples and drug is present at levels higher than the drug tolerance characteristics of the assay. Drug tolerance limit is 10µg/mL.
6. Missing: Relevant samples are missing.

Subjects with no positive ADA sample will be classified as “pre-dose negative- TE negative” (#1) in the alternative NAb assay (data imputation). 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.

2.4.5.5.5 Analysis

Immunogenicity will be assessed through summary tables, figures, and listing of individual results by subject. All immunogenicity data related to assessments on the Q6M FU visits will be analyzed using the ITO population on the following analysis groups:

- Caplacizumab total: Subjects who received caplacizumab during the ALX0681-C301 study (during the double blind or the open-label periods).
- Not treated: Subjects who never received Caplacizumab during the ALX0681-C301 trial

All immunogenicity data related to assessments during the recurrence periods will be analyzed using the recurrence population with the following analysis groups:

- Treated with IMP: patients treated with caplacizumab in the ALX0681-C302 study for the specific recurrence episode
- Not Treated with IMP: patients not treated with caplacizumab in the ALX0681-C302 study for a specific recurrence episode

ADA assay results

The number and percentage of subjects per ADA subject category will be summarized.

Incidence of positive ADA samples by visit.

Spaghetti plot of ADA log10 (titer) vs. time. Negative values for ADA (reported as log10 (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 log10 (titer) = 1.98.

mADA assay results

The number and percentage of subjects per mADA subject category will be summarized. This tabulation and analysis will be performed on a subset of the population, consisting of subjects who were classified as ADA positive based on ADA data.

- Each mADA subject category
- Classified as TE ADA within the pre-Ab negative and within the pre-Ab positive population
- Classified as pre-Ab negative, pre-Ab positive, drug-induced TE negative and drug-induced TE positive

Incidence of positive mADA samples by visit.

Spaghetti plot of mADA log10 (titer) vs. time. Negative values for mADA (reported as log10 (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 log10 (titer) = 1.98.

ADA/mADA assay results (overall subject classification)

The number and percentage of subjects will be summarized by group using following categorization.

- Each overall subject category
- Classified as TE ADA within the pre-Ab negative and within the pre-Ab positive population
- The number and percentage of subjects classified as pre-Ab negative, pre-Ab positive, drug-induced TE negative and drug-induced TE positive

NAb assay result

The number and percentage of subjects will be summarized using following categorization. This analysis will be performed on subset of the population , consisting of subjects who were classified as ADA positive based on ADA data.

- Each NAb subject category
- Classified as pre-dose negative, pre-dose positive, TE negative and TE positive

Alternative NAb (null variant) assay result

The number and percentage of subjects will be summarized using following categorization.

- Each alternative NAb subject category
- Classified as pre-dose negative, pre-dose positive, TE negative and TE positive

Incidence of positive alternative NAb samples by visit.

Spaghetti plot of alternative NAb log10 (titer) vs. time. Negative values for alternative NAb (reported as log10 (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 log10 (titer) = 1.98.

Individual line plots of ADA log10 (titer), mADA log10 (titer), NAb log10 (titer), alternative NAb log10 (titer), PK, RICO activity, vWF:Ag concentration, over time with indication of PE treatment days and treatment with rituximab. PE and rituximab treatment days should be visualized on the plot. For ADA, mADA, and alternative NAb titer plotting, negative values (reported as log10 (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 log10 (titer) = 1.98. Negative values for NAb assay (reported as log10 (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 log10 (titer) = 0.36. Different responses can be plotted against separate Y-axes above each other, but scale of time-axis should be identical for each plotted response.

Listing of all immunogenicity parameters (ADA log10 (titer), mADA log10(titer), NAb result log10(titer), alternative NAb result log10(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.

Scatter plot of drug concentration (logarithmic) by subject category based on the ADA, mADA, NECA and Nab results. Connect means per group to visualize mean drug concentrations per subject category.

Scatter plot of % change from baseline vWF:Ag concentrations (logarithmic) by subject category based on the ADA, mADA, NECA and Nab results. Connect means per group to visualize mean % change from baseline vWF:Ag concentrations per subject category.

Scatter plot of RICO activity (logarithmic) by subject category based on the ADA, mADA, NECA and Nab results. Connect means per group to visualize mean RICO activity per subject category.

Km plot time to platelet count response by subject category based on the ADA, mADA, NECA and Nab results.

Subgroup analysis by hypersensitivity analysis (no or at least one hypersensitivity reaction) based on ADA/mADA results (overall subject classification) and based on NAb results

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

2.4.6.1 Analysis of pharmacokinetic

Determination of caplacizumab concentrations in plasma will be done by a validated enzyme-linked immunosorbent assay (ELISA)-based method according to the bioanalytical methodology and procedures described in a separate Bioanalytical Analysis Plan.

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 analysis period and scheduled sampling time using descriptive statistics and will be listed and summarized in tabular and graphical form.

Spaghetti plot of individual drug concentrations over time will be provided. Nominal sampling times are used. Plots will be created with both linear and semi-logarithmic PK profiles.

Line plot of the mean drug concentrations vs. scheduled sampling time, including SE bars, will be provided for all participants from the recurrence visit up to recurrence follow-up visit or study completion/discontinuation (if earlier). Plots will be created with both linear and semi-logarithmic PK profiles.

Line plot of the geometric mean drug concentrations vs. scheduled sampling time, including geometric SD bars, will also be provided for all participants from start of the study up to recurrence of aTTP or study completion/discontinuation (if earlier). Plots will be created with both linear and semi-logarithmic PK profiles.

All analyses will be run on patients treated with the IMP in the recurrence 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.

2.4.6.2 Analysis of Pharmacodynamics

RICO activity and vWF:Ag concentration will be summarized using descriptive statistics by analysis period and will be listed and summarized in tabular and graphical form.

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

Line plots (Mean ±SE) of RICO activity and vWF:Ag concentrations vs. time points for all participants from start of the study up to recurrence of aTTP or study completion/discontinuation (if earlier) will be provided.

Analyses of RICO activity will be run on the patients treated with IMP in the recurrence population. Analyses of vWF:Ag concentration will be run on the ITO and recurrence population. Pharmacodynamic concentrations or activity and their descriptive statistics will be reported to 3 significant digits.

2.4.7 Analysis of disease-related markers

Troponin I and ADAMTS13 activity will be summarized using descriptive statistics for each time point on the recurrence and ITO populations. Line plot of the mean ADAMTS13 activity, including SE bars, will be provided.

Furthermore, for subjects experiencing a recurrence, time to sustained ADAMTS13 activity ≥ 10% will be summarized using KM estimates such as the median, 25% percentile and 75% percentile with associated 95% CIs, as well as the number of events and the number of censored observations. The KM estimates will also be presented graphically.

Troponin I and ADAMTS13 activity will also be listed.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

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 (eg, 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 geomean), 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).

Rounding of calculated parameters

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

The following formulas will be used for computation of parameters.

2.5.2 Data handling conventions efficacy variables

Data handling conventions are described in Section 2.1.3.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment case report form page. If this date is missing, the exposure duration should be left as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. 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:

- 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.

Handling of adverse events with missing or partial date/time of onset

For missing or partial date/time of onset, data handling is described in Section 2.4.5.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

In case of recurrence with treatment with the IMP, when the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of the recurrence visit until the end of the recurrence episode should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose intake should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

In case of a recurrence with treatment with the IMP, if the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity of adverse events

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

Handling of missing data due to COVID-19 pandemic

Due to COVID-19 pandemic, some patients may have missing or delayed visits. The visit windows have been extended to allow patients to attend their visit. Missing visits due to COVID will be reported.

2.5.4 Windows for time points

The following analysis periods and phase are defined for this study for the Q6M FU visits and the recurrence period.

Table 1 – Analysis phases and periods for the recurrence period- Caplacizumab treated patients

Phase	Period	Subperiod	Start date	End date
Recurrence episode x	Treatment	Daily PE	Recurrence visit date of the recurrence episode	End date of the daily plasma exchange in the recurrence episode
		Post-daily PE	End date of daily plasma exchange in the recurrence episode + 1 day	End date of the treatment period in the recurrence episode
	Follow-up		End date of treatment period + 1 day	Recurrence follow-up visit date

Table 2 – Analysis phases periods for the recurrence period – non-treated patients

Phase	Period	Subperiod	Start date	End date
Recurrence episode x	No-treatment	Daily PE	Recurrence visit date in the recurrence episode	End date of daily plasma exchange in the recurrence episode
	Follow-up		End of daily plasma exchange in the recurrence episode + 1 day	Recurrence follow-up visit date

Table 3 – Analysis phases and periods for the Q6M FU visits

Phase	Period	Subperiod	Start period	End period
Observation			Screening/baseline visit	End of participation to the trial

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

2.5.5 Unscheduled visits

For the assessment of the Q6M FU visits, the closest visit to the planned Q6M FU visit date will be used for summary statistics.

Unscheduled measurements will be taken into account for derivation of time to event parameters. They will also be used if there is a worst-case determination or abnormality over a period of time.

All values will be listed.

2.5.6 Pooling of centers for statistical analyses

Not applicable.

2.5.7 Statistical technical issues

There are no statistical technical issues.

3 INTERIM ANALYSIS

Not applicable.

4 DATABASE LOCK

The database lock is planned for December 2020.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

6 REFERENCES

1. Scully, M. et al. Consensus on the standardization of terminology in thrombotic thrombocytopenic purpura and related thrombotic microangiopathies. J Thromb Haemost 2017, DOI: 10.1111/jth.13571.

2. Levey, A. et al. A new equation to estimate glomerular filtration rate. Ann intern Med 2009, DOI: 10.7326/0003-4819-150-9-200905050-00006.

3. Dixon JS. Second-line Agents in the Treatment of Rheumatic Diseases. Informa Health Care 1991. p.456.

7 LIST OF APPENDICES

Appendix A Schedule of assessment

Table 4 Schedule of assessments for twice yearly visits

Study Period	Screening/Baseline and Assessment Period (Months)						
Study Visit	**Screening/ Baseline[a]**	**6M FU visit (±1 month)**	**12M FU visit (±1 month)**	**18M FU visit (±1 month)**	**24M FU visit (±1 month)**	**30M FU visit (±1 month)**	**36M FU visit (±1 month)/ Early termination visit**
Written informed consent	X						
Review of eligibility criteria	X						
Medical history[b] and demographics	X						
Concomitant medication	→	→	→	→	→	→	→
Adverse events	→	→	→	→	→	→	→
Supine heart rate & blood pressure[c]	X	X	X	X	X	X	X
Physical examination	X	X	X	X	X	X	X
Body weight	X	X	X	X	X	X	X
Height	X						
SF-36	X	X	X	X	X	X	X
RBANS[d]	X						X
HIT-6™	X	X	X	X	X	X	X
Clinical laboratory analyses + urinalysis [e]	X	X	X	X	X	X	X
Organ damage markers: TnI	X	X	X	X	X	X	X
ADAMTS13 activity	X	X	X	X	X	X	X
PD parameter : vWF:Ag	X	X	X	X	X	X	X
Immunogenicity (ADA panel)	X	X	X	X	X	X	X

a The Screening/Baseline Visit will coincide with or is to be scheduled to take place within 1 month after the Final (28 day) FU visit in the preceding Study ALX0681-C301 (HERCULES). Note: for subjects for whom the Final (28 day) FU visit occurred prior to local approval and site activation for this study, a time window of + 1 month after site activation is permitted to complete the screening/baseline visit.

b Medical history, including general and TTP-related medical history (TTP episodes and major thromboembolic events, e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism, deep venous thrombosis, transient ischemic attack, heart failure, unstable angina, coronary revascularization), and history of hypersensitivity to IMP in Study ALX0681-C301.

c Heart rate and blood pressure to be assessed after 5 min in supine position.

d Only in those countries where RBANS is available in the local language(s).

e Clinical laboratory analyses include hematology (Hb, Hct, RBC, WBC, platelets); chemistry (AST, ALT, LDH, creatinine, protein, cholesterol and CRP). Urinalysis includes assessment of albumin.

Table 5 Schedule of assessments in case of TTP recurrence and administration of IMP

Study Period	Recurrence Period				
	Caplacizumab Treatment Period				Recurrence FU visit
Study Visit	Recurrence Visit	Day 3 visit Treatment Day 3	Week 1 visit Post-daily PE Day 1 (1 day after last daily PE)	Weekly visits till end of treatment with caplacizumab Post-daily PE Day 8, 15, 22, and 29 (±1 day)	7 (±1) days after end of treatment with caplacizumab
Review of caplacizumab treatment criteria	X				
Pregnancy test[a]	X				
TTP recurrence information[b]	X		X		X
Study drug administration	→	→	→	→	
PE information			X		
Concomitant medication	→	→	→	→	→
Adverse events	→	→	→	→	→
Supine heart rate & blood pressure[c]	X	X	X	X[d]	X
Physical examination	X	X	X	X[d]	X
SF-36					X
Clinical laboratory analyses + urinalysis[e]	X	X	X	X	X
Organ damage markers: TnI[f]	X	X	X	X	X
ADAMTS13 activity[f]	X	X	X	X	X
Immunogenicity (ADA panel) [f,g]	X	X	X	X	X
PK[f]	X	X	X	X	X
PD parameters[f,h]	X	X	X	X	X

a Pregnancy test (urine or blood) for female subjects of childbearing potential will be assessed per local laboratory.

b TTP recurrence information includes presenting symptoms (assessed at recurrence visit), duration (assessed at the Week 1 visit) and outcome (assessed at the recurrence FU visit).

c Heart rate and blood pressure to be assessed after 5 min in supine position.

d To be assessed at the post-daily PE Day 29 only.

e Clinical laboratory analyses include hematology (Hb, Hct, RBC, WBC, platelets); chemistry (AST, ALT, LDH, creatinine, protein, cholesterol and CRP). Urinalysis includes assessment of albumin. The results of assessment of platelet count and LDH levels performed as per standard of care (by a local laboratory) at any time during the recurrence period will be collected in the eCRF, if available.

f At the recurrence visit and the Treatment Day 3 visit, samples need to be collected prior to start of the PE treatment and/or study drug administration (whatever comes first). At all subsequent visits, blood samples need to be taken prior to study drug administration.

g 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.

h PD parameters include RICO and vWF:Ag.

Table 6 Schedule of Assessments in Case of TTP Recurrence (in Case Treatment with Caplacizumab is not Initiated)

Study Period	Recurrence Period (no caplacizumab)	
Study Visit	**Recurrence Visit** **Recurrence Day 1**	**Recurrence FU visit** **30 days after end of daily PE**
TTP recurrence information[a]	X	X
PE information		X
Concomitant medication	→	→
Adverse events	→	→
Supine heart rate & blood pressure[b]	X	X
Physical examination	X	X
SF-36		X
Clinical laboratory analyses + urinalysis[c]	X	X
Organ damage markers: TnI[d]	X	X
ADAMTS13 activity [d]	X	X
Immunogenicity (ADA panel) [d]	X	
PD parameter : vWF:Ag [d]	X	X

a TTP recurrence information includes presenting symptoms (assessed at recurrence visit), duration and outcome (assessed at the recurrence FU visit).

b Heart rate and blood pressure to be assessed after 5 min in supine position.

c Clinical laboratory analyses include hematology (Hb, Hct, RBC, WBC, platelets); chemistry (AST, ALT, LDH, creatinine, protein, cholesterol and CRP). Urinalysis includes assessment of albumin. The results of assessment of platelet count and LDH levels performed as per standard of care (by a local laboratory) at any time during the recurrence period will be collected in the eCRF, if available.

d Samples need to be collected prior to start of the first PE treatment.

Appendix B Prednisolone equivalent dose chart

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

* Based on Prednisolone dose of 5 mg/day. (3)

Signature Page

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