## CLINICAL STUDY PROTOCOL

**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

<table>
<thead>
<tr>
<th>Short title:</th>
<th>A Phase III Trial with Caplacizumab in Patients with Acquired Thrombotic Thrombocytopenic Purpura</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigational product:</td>
<td>Caplacizumab (Sponsor code: ALX-0081)</td>
</tr>
<tr>
<td>EudraCT n°:</td>
<td>2015-001098-42</td>
</tr>
<tr>
<td>Sponsor protocol code:</td>
<td>ALX0681-C301</td>
</tr>
<tr>
<td>Sponsor:</td>
<td>Ablynx NV</td>
</tr>
<tr>
<td>Technologiepark 21</td>
<td></td>
</tr>
<tr>
<td>9052 Zwijnaarde, Belgium</td>
<td></td>
</tr>
<tr>
<td>Clinical Operations Contract Research Organisation:</td>
<td>Pharm-Olam Ltd.</td>
</tr>
<tr>
<td>The Brackens, London Road,</td>
<td></td>
</tr>
<tr>
<td>Ascot, Berkshire, SL5 8BJ, UK</td>
<td></td>
</tr>
<tr>
<td>Phase of Development:</td>
<td>Phase III</td>
</tr>
<tr>
<td>Indication:</td>
<td>Acquired Thrombotic Thrombocytopenic Purpura (TTP)</td>
</tr>
<tr>
<td>Study Center:</td>
<td>Multicenter</td>
</tr>
<tr>
<td>Protocol date:</td>
<td>July 20, 2016</td>
</tr>
<tr>
<td>Protocol version:</td>
<td>V3.0</td>
</tr>
<tr>
<td>Protocol Status:</td>
<td>Final</td>
</tr>
</tbody>
</table>

This study will be performed in compliance with the Clinical Trial Protocol, the principles of Good Clinical Practice (GCP), and the applicable regulatory requirement(s).
CONFIDENTIALITY STATEMENT

The information contained in this document, especially unpublished data, is the property of Ablynx NV (or under its control), and therefore provided to you in confidence as an Investigator, potential Investigator, or consultant, for review by you, your study staff, and applicable Independent Ethics Committee (IEC) /Institutional Review Board (IRB), and Competent Authorities (CA). It is understood that this information will not be disclosed to others without written authorization from Ablynx NV, except to the extent necessary to obtain informed consent from those persons to whom the study drug may be administered.
APPRAVAL OF CLINICAL STUDY PROTOCOL

The Sponsor and the Investigator(s) agree to conduct the study as outlined in this Clinical Study Protocol. Any modification of the Clinical Study Protocol must be agreed upon by the Sponsor and the Investigator(s), and must be documented in writing.

Sponsor:


Signature – Date: See signature page at the end of the document
Investigator:

I have read Clinical Study Protocol ALX0681-C301 and agree to personally conduct or supervise the clinical study in accordance with the Clinical Study Protocol.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

I confirm that the study team and I will not implement any deviations from the Clinical Study Protocol without agreement of Ablynx NV, except where necessary to eliminate an immediate hazard to the patients.

I confirm that I am thoroughly familiar with the appropriate use of the study drug, as described in the Clinical Study Protocol and any other information provided by Ablynx NV.

I confirm that I am aware of and will comply with ICH-GCP and applicable national and regional regulations/guidelines.

Hence, I agree to supply Ablynx NV with any necessary information regarding the ownership interest and financial ties, to promptly update this information if any relevant changes occur during the course of the study, and that Ablynx NV may disclose any available information about such ownership interest and financial ties to regulatory authorities.

Principal Investigator Name:

Site details/Address:

Signature – Date:
SERIOUS ADVERSE EVENT CONTACT INFORMATION

Serious adverse event contact information:

Contact details of the Sponsor and third parties are available in the "Investigator Site File".
TABLE OF CONTENTS

CONFIDENTIALITY STATEMENT .............................................................................. 2

APPROVAL OF CLINICAL STUDY PROTOCOL ........................................................... 3

SERIOUS ADVERSE EVENT CONTACT INFORMATION .............................................. 5

TABLE OF CONTENTS .............................................................................................. 6

LIST OF ABBREVIATIONS ....................................................................................... 9

CHANGES COMPARED TO PREVIOUS VERSION(S) .........................................................12

PROTOCOL SYNOPSIS ...........................................................................................15

SCHEDULES OF ASSESSMENTS ..............................................................................28

1. INTRODUCTION ...................................................................................................34
   1.1. THROMBOTIC THROMBOCYTOPENIC PURPURA ...........................................34
       1.1.1. Treatment of TTP ................................................................................ 37
   1.2. CAPLACIZUMAB ...........................................................................................38
       1.2.1. General Properties .............................................................................. 38
       1.2.2. Formulation ........................................................................................ 39
       1.2.3. Nonclinical Studies .............................................................................. 40
       1.2.4. Effects in Humans ............................................................................... 41
       1.2.5. Safety Profile and Risk Assessment .......................................................46

2. OBJECTIVES ........................................................................................................48

3. STUDY DESIGN ...................................................................................................49
   3.1. OVERALL STUDY DESIGN .............................................................................49
       3.1.1. Study Overview .................................................................................. 49
       3.1.2. Study Rationale .................................................................................. 53
       3.1.3. Blinding ............................................................................................. 57
   3.2. SELECTION OF STUDY POPULATION ................................................................59
       3.2.1. Inclusion Criteria ................................................................................ 59
       3.2.2. Exclusion Criteria ............................................................................... 59
       3.2.3. Removal of Subjects from Therapy or Assessment ...............................60
   3.3. TREATMENT OF SUBJECTS ...........................................................................63
       3.3.1. Randomization.................................................................................... 65
       3.3.2. Identity of Study Drug ......................................................................... 65
       3.3.3. Drug Accountability ............................................................................ 66
       3.3.4. Study Drug Handling .......................................................................... 67
       3.3.5. Study Drug Administration ...................................................................68
       3.3.6. Other Treatment/Medication Administered in the Study .......................70
       3.3.7. Concomitant Therapy .......................................................................... 71
3.4. ASSESSMENTS ............................................................................................. 73
3.4.1. Timing of Assessments ........................................................................ 73
3.4.2. Demographics and Medical History .................................................... 75
3.4.3. Assessments of Efficacy ..................................................................... 76
3.4.4. Pharmacokinetic Assessments ............................................................ 78
3.4.5. Pharmacodynamic Assessments .......................................................... 79
3.4.6. Assessment of Disease Related Markers ............................................. 79
3.4.7. Immunogenicity .................................................................................. 80
3.4.8. Assessments of Safety ........................................................................ 80
3.4.9. Other Assessments ............................................................................. 84
3.4.10. Total Blood Volume .......................................................................... 84
3.4.11. Appropriateness and Timing of Measurements .................................... 85
3.5. ADVERSE EVENT EVALUATION AND REPORTING ............................... 86
3.5.1. Adverse Events ................................................................................... 86
3.5.2. Serious Adverse Events ..................................................................... 88
3.5.3. Suspected Unexpected Serious Adverse Reactions .............................. 90
3.5.4. Reporting of Adverse Events ............................................................. 91
3.5.5. Follow-up of Adverse Events ............................................................. 91
3.5.6. Other Reportable Information ............................................................. 91
3.6. STATISTICS ............................................................................................... 93
3.6.1. Study Populations ............................................................................... 93
3.6.2. Statistical and Analytical Plan .............................................................. 93
3.6.3. Demographics and Baseline Characteristics ....................................... 93
3.6.4. Evaluation of Efficacy Parameters ...................................................... 93
3.6.5. Evaluation of Pharmacokinetic and Pharmacodynamic Parameters .... 97
3.6.6. Evaluation of Safety Parameters .......................................................... 98
3.7. DATA QUALITY ASSURANCE AND DIRECT ACCESS TO SOURCE DATA/DOCUMENTS ...................................................................................... 99
3.8. DATA PROTECTION .................................................................................. 100
4. ETHICS ........................................................................................................ 101
4.1. ETHICS COMMITTEES AND COMPETENT AUTHORITIES .................. 101
4.2. ETHICAL CONDUCT OF THE STUDY .................................................. 101
4.3. SUBJECT INFORMATION AND CONSENT .......................................... 102
4.4. PRIVACY ................................................................................................. 104
5. DATA HANDLING AND RECORD KEEPING .............................................. 105
5.1. DISTRIBUTION OF ACTIVITIES .......................................................... 105
5.2. DOCUMENTATION .................................................................................. 105
5.2.1. Case Report Form Completion ........................................................... 105
5.2.2. Source Documentation ....................................................................... 105
5.2.3. Record Retention .............................................................................. 106
5.2.4. Monitoring .......................................................................................... 107

6. FINANCING AND INSURANCE .................................................................... 108

7. USE OF INFORMATION AND PUBLICATION ............................................ 109

8. REFERENCES ............................................................................................... 110

9. APPENDICES .............................................................................................. 112
  9.1. GLASGOW COMA SCALE SCORE ....................................................... 112
LIST OF ABBREVIATIONS

aa  Amino acid
ADA  Anti-drug antibody
ADAMTS13 A disintegrin-like and metalloprotease with thrombospondin repeats 13
AE   Adverse event
AFA  Anti-factor VIII antibodies
aHUS Atypical Hemolytic Uremic Syndrome
ALP  Alkaline phosphatase
ALT  Alanine aminotransferase
AMI  Acute myocardial infarction
aPTT Activated partial thromboplastin time
AST  Aspartate aminotransferase
AUC  Area under the curve
BMI  Body mass index
BUN  Blood urea nitrogen
CA   Competent authority
CI   Confidence interval
Cmax Maximum concentration
CRO  Contract research organization
CRP  C-reactive protein
CTCAE Common terminology criteria for adverse events
CTD  Clinical Trial Directive
cTnI  Cardiac Troponin I
Da   Dalton
DNA  Deoxyribonucleic acid
DSMB Data and safety monitoring board
DVT  Deep venous thrombosis
EC   Ethics committee
ECG  Electrocardiogram
E. coli Escherichia Coli
eCRF Electronic case report form
EEG  electroencephalogram
ELISA Enzyme-linked immunosorbent assay
FU   Follow-up
PE  Plasma exchange
PK  Pharmacokinetics
p.o. Per orale
PP  Per-protocol
RICO Ristocetin cofactor activity
RIPA Ristocetin-induced platelet aggregation
RNA Ribonucleic acid
SAE Serious adverse event
SAP Statistical Analysis Plan
SAR Serious adverse reaction
s.c. Subcutaneous
SD  Standard deviation
SMMSE Standardized mini mental state examination
SMQ Standardized MedDRA Query
SUSAR Suspected and unexpected serious adverse reactions
$t_{1/2}$ Terminal half-life
TBT Template bleeding time
TE  Treatment-emergent
TEAE Treatment-emergent adverse event
TIMI Thrombolysis in Myocardial Infarction
TMA Thrombotic microangiopathy
$t_{\text{max}}$ Time to $C_{\text{max}}$
TnI Troponin I
TTP Thrombotic thrombocytopenic purpura
ULN Upper limit of normal
ULvWF Ultra-large vWF
US United States
vWF von Willebrand factor
vWF:Ag von Willebrand factor antigen
WFI Water for injection
**CHANGES COMPARED TO PREVIOUS VERSION(S)**

Version 2.0 (dated April 8, 2016) compared to Version 1.0 (dated June 5, 2015). This amendment is considered substantial due to a change in exclusion criteria (to exclude subjects who were previously enrolled in a clinical study with caplacizumab and received caplacizumab or for whom the assigned treatment arm is unknown) and removal of the planned interim analysis.

Version n° and date were adapted throughout the document (including headers and footers). The Table of Contents and List of Abbreviations was updated and the Section "Changes Compared to Previous Version(s)" was completed.

<table>
<thead>
<tr>
<th>Original section</th>
<th>Change/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval of Clinical Study Protocol</td>
<td>Due to an update of the Sponsor’s standard operating procedure on protocol writing, Clinical Study Protocols are no longer signed by the Chief Medical Officer but by the responsible Medical Lead.</td>
</tr>
<tr>
<td>Synopsis, Sections 2, 3.1.1., 3.1.3., 3.6.2. and 3.6.4.</td>
<td>Key and other secondary endpoints have been reworded and reordered in view of hierarchical statistical testing for the key secondary endpoints. In addition, the interim analysis of efficacy has been removed and the description of analysis of key secondary endpoints has been updated to reflect the hierarchical testing. The secondary objectives have been reworded to correspond to the rewording of the secondary endpoints.</td>
</tr>
<tr>
<td>Synopsis, Schedule of Assessments, Sections 3.1.1., 3.3.5. and 3.3.6.</td>
<td>For clarity, the statement &quot;(with)in the same day&quot;/&quot;within 1 day&quot; has been reworded to &quot;(with)in 24 hours&quot;.</td>
</tr>
<tr>
<td>Synopsis, Sections 1 and 8</td>
<td>Reference 1 has been replaced by a new reference as the original one is no longer applicable (due to the removal of the interim analysis).</td>
</tr>
<tr>
<td>Synopsis, Sections 3.1.1., 3.2.1, and 3.3.6.</td>
<td>Wording on PE treatment has been adapted to clarify that the PE treatment administered prior to randomization concerns a single PE treatment and that the maximum time allowed between the start of first PE (i.e., PE administered prior to randomization) and the start of the first PE after randomization (i.e., the first on-study PE) is 24 hours.</td>
</tr>
<tr>
<td>Synopsis, Sections 3.1.1. and 3.3.5.</td>
<td>For clarity, a definition of tapering has been added.</td>
</tr>
<tr>
<td>Synopsis, Sections 3.1.1., 3.3., and 3.3.5.</td>
<td>The time window allowed for study drug administration by i.v. bolus injection has been updated from within 2 hours to from 6 hours to 15 min prior to PE to allow more flexibility at the study sites. This time window has also been specified in additional sections to be consistent with the statement for the daily s.c. doses in the concerned sections.</td>
</tr>
<tr>
<td>Synopsis, Section 3.1.1.</td>
<td>For clarity, details have been added to the definition of exacerbation.</td>
</tr>
<tr>
<td>Synopsis, Section 3.2.2.</td>
<td>An extra exclusion criterion has been added to exclude subjects who were previously enrolled in a clinical study with caplacizumab and received caplacizumab or for whom the assigned treatment arm is unknown.</td>
</tr>
<tr>
<td>List of abbreviations, Synopsis, Schedule of Assessments, Sections 1.2.5., 3.1.2., 3.3., 3.3.2., 3.3.3., 3.3.5., 3.4.1.1., 3.4.3.5., 3.4.7.1., 3.4.8., 3.4.11., 3.7., 4.3., and 5.2.3.</td>
<td>Correction of typographical errors and rewording to ensure consistency or to avoid confusion.</td>
</tr>
<tr>
<td>Synopsis, Section 3.3.2.</td>
<td>The text on IMP strength has been updated to reflect that reconstitution of a vial containing 12.5 mg caplacizumab with the supplied kit components leads to a solution containing 11.1 mg/mL caplacizumab.</td>
</tr>
<tr>
<td>Synopsis, Schedule of Assessments and Sections 3.4.1.1. and 3.4.2.</td>
<td>Wording has been added to specify that the retrospective collection of data will include results of ADAMTS13 activity test performed per standard of care upon admission.</td>
</tr>
<tr>
<td>Section</td>
<td>Changes</td>
</tr>
<tr>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Synopsis, Section 3.4.1.1.</td>
<td>A footnote has been added to clarify that first administration of study drug can occur on Day 2 (due to allowed time windows).</td>
</tr>
<tr>
<td>Synopsis, Section 3.6.4.</td>
<td>As no ECG assessment is planned on Day 5, evaluation of cardiac ischemia and/or arrhythmia/conduction abnormalities on Day 5 has been removed from the concerned secondary endpoint.</td>
</tr>
<tr>
<td>Schedule of Assessments</td>
<td>Wording has been added to clarify what the bleeding assessment consists of, to emphasize that a blood sample needs to be taken in case of a severe and/or serious hypersensitivity reaction, and that no study drug is to be administered at Week 5 in case of no treatment extensions.</td>
</tr>
<tr>
<td>Schedule of Assessments, Section 3.4.8.2.</td>
<td>A specification has been added to clarify that pregnancy testing, screening samples for creatinine assessment and samples for platelet count will be analyzed by a local lab.</td>
</tr>
<tr>
<td>Schedule of Assessments, Sections 3.4.8.2. and 3.4.8.3.</td>
<td>A separate row has been created in the Schedule of Assessments for assessment of height and weight, as these are not to be assessed after 5 min in supine position. It is also clarified that these are to be assessed on Day 1 of the initial double-blind daily PE period only; this also applies for assessment of complement C5a and C5b-9.</td>
</tr>
<tr>
<td>Sections 3.1.3., 3.2.3.1. and 3.4.5.1.</td>
<td>To reduce the risk of unintentional unblinding, it has been clarified that analysis of RICO may only be done at the central laboratory. In addition, it has been emphasized that any event of unblinding should result in treatment discontinuation for the concerned subject.</td>
</tr>
<tr>
<td>Section 3.2.2.</td>
<td>Exclusion criterion 11 on concurrent participation in another clinical study has been reworded for clarification purposes.</td>
</tr>
<tr>
<td>Section 3.2.3.1.</td>
<td>For clarity, a criterion for temporary discontinuation of study drug stated in Section 3.3.5., is now also mentioned in the section on removal of subjects from therapy or assessments.</td>
</tr>
<tr>
<td>Section 3.3.3.</td>
<td>Wording has been added to clarify that unused returned IMP should no longer be used.</td>
</tr>
<tr>
<td>Sections 3.3.4. and 3.3.5.</td>
<td>A statement has been added to emphasize that subjects should not self-administer study drug prior to their visit to the study site on days a visit is planned.</td>
</tr>
<tr>
<td>Sections 3.3.4. and 3.4.9.1.</td>
<td>Wording has been adapted to clarify that product quality complaints should be communicated by completion of the IMP Notification Form. In addition, wording with regard to human factor engineering is deleted as this will not be part of this study.</td>
</tr>
<tr>
<td>Section 3.3.8.</td>
<td>A statement has been reworded to better reflect what is captured in the eCRF in case of a missed dose.</td>
</tr>
<tr>
<td>Section 3.4.3.6</td>
<td>Details on adjudication of major thromboembolic events and TTP-related death have been added.</td>
</tr>
<tr>
<td>Sections 3.4.4.1., 3.4.5.1., 3.4.6.1., and 3.4.7.1. and 3.4.10.</td>
<td>For clarity, text has been reworded to reflect total amount of blood to be taken by study duration and to correct the blood volume to be collected for some assessments. In addition, a statement has been added to allow remaining blood samples to be used for further exploratory work in the context of the development of caplacizumab.</td>
</tr>
<tr>
<td>Section 3.4.8.5.</td>
<td>For clarity, the body systems to be examined during physical examination have been added.</td>
</tr>
<tr>
<td>Section 3.5.1.3.</td>
<td>The word &quot;(specify)&quot; has been deleted with regard to causal relationship of any AE to PE or use of corticosteroids to avoid confusion on what is to be specified (AE, PE parameter or corticosteroid).</td>
</tr>
<tr>
<td>Section 3.5.6.1.</td>
<td>More details concerning pregnancy reporting have been added.</td>
</tr>
<tr>
<td>Sections 3.6.5. and 3.6.6.</td>
<td>Wording has been updated to better reflect the planned analysis approach.</td>
</tr>
<tr>
<td>Appendix 9.1</td>
<td>The appendix has been updated to reflect the latest version of the GCS.</td>
</tr>
</tbody>
</table>
**Version 3.0 (dated July 20, 2016) compared to Version 2.0 (dated April 8, 2016). This amendment is considered substantial due to a change in planned sample size.**

Version n° and date were adapted throughout the document (including headers and footers). The Table of Contents was updated and the Section "Changes Compared to Previous Version(s)" was completed.

<table>
<thead>
<tr>
<th>Original section</th>
<th>Change/Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synopsis, Sections 3.1.1. and 3.2.</td>
<td>The number of subjects planned to be included in the study has been increased from 92 to 132 to account for a change in the assumed treatment difference for the primary endpoint in the sample size calculation (to bring it in line with the results of the Phase II study), to account for drop-outs, and to increase the statistical power of the key secondary endpoint analyses.</td>
</tr>
<tr>
<td>Synopsis and Section 3.6.4.2.</td>
<td>Clarification to ensure consistency.</td>
</tr>
<tr>
<td>Schedule of Assessments and Section 3.4.9.1.</td>
<td>Assessment of usability of the IMP kit has been removed from the Schedule of Assessments as the reporting only occurs in case of issues with preparation and/or administration of the study drug by the subject (or the caregiver, if applicable).</td>
</tr>
</tbody>
</table>
PROTOCOL SYNOPSIS

Protocol title:
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.

Protocol short title:
A Phase III trial with caplacizumab in patients with acquired thrombotic thrombocytopenic purpura.

Investigational product:
Caplacizumab (Sponsor code: ALX-0081), an anti-von Willebrand Factor Nanobody

EudraCT n°:
2015-001098-42

Sponsor protocol code:
ALX0681-C301

Sponsor:
Ablynx NV
Technologiepark 21
9052 Zwijnaarde, Belgium

Phase of Development:
Phase III

Indication:
Treatment of acquired thrombotic thrombocytopenic purpura (TTP)

Study center:
Multicenter, global
Objectives:

- **Primary Objective:**
  - To evaluate efficacy of caplacizumab in more rapidly restoring normal platelet counts as measure of prevention of further microvascular thrombosis

- **Secondary Objectives:**
  - 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
  - to evaluate the effect of study drug on prevention of recurrence of TTP over the entire study period
  - to evaluate the effect of study drug on refractoriness to treatment
  - to evaluate the effect of study drug on biomarkers of organ damage: lactate dehydrogenase (LDH), cardiac troponin I (cTnI), and serum creatinine
  - to evaluate 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) markers: von Willebrand factor (vWF), coagulation factor VIII (FVIII), ristocetin cofactor activity (RICO)
  - pharmacokinetic (PK) parameters
  - immunogenicity (anti-drug antibodies [ADA])

Study design:

This is a phase III, double blind, placebo-controlled, randomized study to evaluate the efficacy and safety of caplacizumab treatment when administered in addition to standard of care treatment 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*, subjects 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

* Of note, the PE administered prior to randomization (PE of unrestricted intensity) may be given prior to signing ICF (as part of standard of care) and may be spread over 2 or more sessions in 24 hours as long as considered part of the 1 intense PE for the treatment of the presenting TTP episode. Note that the maximum time allowed between the start of first PE (i.e., PE administered prior to randomization) and the start of the first PE after randomization (i.e., the first on-study PE) is 24 hours.
neurological symptoms (Glasgow coma scale [GCS]).

**Standard of care treatment:**

- 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. Once the platelet count is ≥ 150 x 10⁹/L, daily PE should continue for at least 2 days. Tapering of PE after platelet count normalization, defined as reducing its frequency to less than once per day, is strongly discouraged and if considered, should be discussed with the Medical Monitor.

- Corticosteroid treatment should be initiated/continued with (methyl)prednisolone or (methyl)prednisone regimen of at least 1 mg/kg/day intravenous (i.v.) or per orale (p.o.) during the daily PE period and continued for the 1st week after end of daily PE. Afterwards corticosteroids may be tapered at the discretion of the Investigator, with the aim of being corticosteroid-free by Day 30 after cessation of daily PE as clinically indicated. At the Week 3 visit of the 30-day post-daily PE period, corticosteroid tapering should be reassessed based on ADAMTS13 activity data of the previous 2 visits and other clinical signs of underlying disease.

- Other immunosuppressive treatment: The use of other immunosuppressive treatment (e.g., rituximab) is allowed per standard site practice but should be considered in light of protocol required corticosteroid treatment.

**Study drug treatment:**

**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 the first PE done after randomization; an i.v. bolus of 10 mg will also be given prior to the 1st PE done for treatment of a first exacerbation or relapse.

- Daily subcutaneous (s.c.) dose: within 2 hours of completing each daily PE, a s.c. injection of 10 mg study drug will be administered daily throughout the full duration of PE treatment.

† Of note, the PE administered prior to randomization (PE of unrestricted intensity) may be given prior to signing ICF (as part of standard of care) and may be spread over 2 or more sessions in 24 hours as long as considered part of the 1 intense PE for the treatment of the presenting TTP episode. Note that the maximum time allowed between the start of first PE (i.e., PE administered prior to randomization) and the start of the first PE after randomization (i.e., the first on-study PE) is 24 hours.

‡ For logistical reasons, the Sponsor needs to be contacted if the daily PE period exceeds beyond 30 days.
It is expected that subjects are hospitalized for the duration of the daily PE period. Exceptions should be discussed with the Medical Monitor.

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. After discharge from hospital, subjects are allowed to self-administer (after learning how to prepare and s.c. inject the study drug).

Treatment extension period
Study drug treatment extension beyond these 30 days will be guided by a number of risk factors for relapse of the presenting TTP episode and must be accompanied by an optimization of the immunosuppressive treatment. The risk factors will include the ADAMTS13 activity profile (measured weekly), 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 study drug 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 for subjects with other clinical signs of underlying disease. In parallel, optimization of the immunosuppressive treatment should be considered starting at the Week 3 visit of the 30-day post-daily PE period and includes reversal of corticosteroid tapering through increase or re-initiation of corticosteroid treatment, or start/continuation of other immunosuppressive treatment such as rituximab (to be used as per standard site practice). Study drug treatment extension should be stopped when ADAMTS13 activity shows a sustained upward trend of >10% and at the latest on Day 28 of the study drug treatment extension.

Recurrence of TTP episode
- **Exacerbation** is defined as recurrent thrombocytopenia after initial recovery of platelet count (platelet count ≥ 150×10⁹/L with subsequent stop of daily PE within 5 days), requiring re-initiation of daily PE, occurring during the first 30-days post-daily PE period.
- **Relapse** is defined as recurrent thrombocytopenia after initial recovery of platelet count requiring re-initiation of daily PE, occurring after the 30-days post-daily PE period.

Based on the mechanism of action and the available efficacy and safety results from study ALX-0681-2.1/10 (Phase II TITAN trial) it is considered desirable from both a treatment and exposure perspective (to maximize the number of subjects exposed to caplacizumab), to allow for crossover to open-label caplacizumab for subjects who experience a recurrence of the TTP episode.

**Exacerbation**
In case of a first exacerbation of the presenting TTP episode, subjects will receive open label caplacizumab together with daily PE irrespective of what the initial treatment allocation was.
The blind will not be broken for the initial treatment allocation. Caplacizumab treatment and visit schedule will be the same as during the initial treatment period, covering i.v. bolus, daily PE (variable duration), 30-days post-daily PE and possible treatment extension. In case a subject has subsequent exacerbations, standard of care treatment of daily PE and appropriate immunosuppressive treatment should be initiated as per site practice. There will be no re-initiation of study drug administration for a second or further exacerbation.

**Relapse during the treatment extension period**

In case a subject has a first TTP recurrence while still receiving study drug in the treatment extension period, then daily PE should be started as part of standard of care treatment together with appropriate immunosuppressive treatment. Study drug treatment will crossover as open-label caplacizumab irrespective of what the initial treatment allocation was without breaking the blind of the initial treatment assignment. Caplacizumab treatment and visit schedule will be the same as during the initial treatment period, covering i.v. bolus, daily PE (variable duration), 30-days post-daily PE and possible treatment extension. In case a subject has subsequent relapses, standard of care treatment of daily PE and appropriate immunosuppressive treatment should be initiated as per site practice. There will be no re-initiation of study drug administration for a second or further relapse.

**Relapse during the 4-week follow-up (FU) period**

In case a subject has a first or subsequent TTP relapse after completing study drug treatment (i.e., in the FU period), standard of care treatment of daily PE and appropriate immunosuppressive treatment should be initiated as per site practice. There will be no re-initiation of study drug administration.

As stated above, there will be no re-initiation of study drug administration for subjects experiencing more than one exacerbation or relapse (or a relapse after an exacerbation or an exacerbation after a relapse).

**Study population:**

Adults with a clinical diagnosis of acquired TTP who require initiation of daily PE treatment.

**Number of subjects:**

132 adult subjects in 2 arms randomized in a 1:1 ratio, stratified by severity of neurological involvement prior to randomization (GCS score ≤ 12 vs. GCS score = 13 - 15).

Subjects who previously participated in this trial, cannot be re-enrolled.
Inclusion criteria:

The main criteria for inclusion include the following:

- Adult male or female ≥ 18 years of age at the time of signing the informed consent form (ICF)
- Clinical diagnosis of acquired TTP (initial or recurrent), which includes thrombocytopenia and microscopic evidence of red blood cell fragmentation (e.g., schistocytes)
- Requires initiation of daily PE treatment and has received 1 PE treatment§ prior to randomization

Exclusion criteria:

The main criteria for exclusion include the following:

- Platelet count ≥100×10^9/L
- Serum creatinine level >200 µmol/L in case platelet count is > 30×10^9/L (to exclude possible cases of atypical Hemolytic Uremic Syndrome [aHUS])
- Known other causes of thrombocytopenia including but not limited to:
  - Clinical evidence of enteric infection with E. coli 0157 or related organism
  - Atypical HUS
  - Hematopoietic stem cell, bone marrow or organ transplantation-associated thrombotic microangiopathy
  - Known or suspected sepsis
  - Diagnosis of disseminated intravascular coagulation
- Congenital TTP (known at the time of study entry)
- Pregnancy or breast-feeding
- Clinically significant active bleeding or high risk of bleeding (excluding thrombocytopenia)
- Known chronic treatment with anticoagulant treatment that cannot be stopped (interrupted) safely, including but not limited to:
  - vitamin K antagonists
  - heparin or low molecular weight heparin (LMWH)
  - non-acetyl salicylic acid non-steroidal anti-inflammatory molecules
- Malignant arterial hypertension
- Clinical condition other than that associated with TTP, with life expectancy < 6 months, such as end-stage malignancy

§ Of note, the PE administered prior to randomization (PE of unrestricted intensity) may be given prior to signing ICF (as part of standard of care) and may be spread over 2 or more sessions in 24 hours as long as considered part of the 1 intense PE for the treatment of the presenting TTP episode. Note that the maximum time allowed between the start of first PE (i.e., PE administered prior to randomization) and the start of the first PE after randomization (i.e., the first on-study PE) is 24 hours.
Subjects who were previously enrolled in a clinical study with caplacizumab and received caplacizumab or for whom the assigned treatment arm is unknown.

Study medication:

The study medication is provided in a kit containing the following components:

- One glass vial containing lyophilized powder for reconstitution (containing either caplacizumab or placebo – see details below).
- One prefilled glass syringe containing solvent for reconstitution (containing water for injection [WFI]).
- One “vial adapter” device to facilitate transfer of the solvent for reconstitution and subsequent recovery of the reconstituted drug.
- One safety needle for s.c. use (please note that a needle for the first i.v. bolus injection is not included in the kit).
- Two alcohol pads.

Further details on drug components:

- Caplacizumab 10 mg – lyophilized powder for solution for injection
  - Presented in ISO 2R glass vial with FluroTec® Butyl stopper filled with lyophilisate containing 12.5 mg caplacizumab and excipients (see below).
  - Active substance: caplacizumab (anti-vWF Nanobody).
  - Activity: caplacizumab is directed towards the A1 domain of vWF and specifically inhibits the interaction of (ultra-large)vWF ([UL]vWF) with the platelet Glycoprotein Ib (GPIb) receptor glycoprotein, thereby preventing (UL)vWF-mediated platelet aggregation.
  - Strength: One vial contains 12.5 mg of caplacizumab and comprises an overfill to compensate for losses during reconstitution and liquid transfer. After reconstitution using the supplied kit components, the resulting solution contains 11.1 mg/mL of caplacizumab (the total volume of the reconstituted solution is slightly more than 1 mL because the lyophilisate also takes up a certain volume). Taking into account losses during transfer from vial to syringe, the nominal administered dose is 10 mg when injecting the entire contents (nominally 0.9 mL) of the syringe.
  - Dosage form: powder for solution for injection; reconstitution with WFI yields solution for injection.
  - Route of administration: i.v. (first dose and prior to the first PE done after a first exacerbation or relapse), s.c. (all subsequent doses).

- Placebo - lyophilized powder for solution for injection:
  - Active substance: not applicable, the composition of placebo is the same as that of active IMP, without the active ingredient.
- Activity, strength: not applicable.
- Dosage form: powder for solution for injection; reconstitution with WFI yields solution for injection.
- Route of administration: i.v. (first dose and prior to the first PE done after a first exacerbation or relapse), s.c. (all subsequent doses).

**Study duration:**

The anticipated study duration per subject is approximately 2 months 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.

- **Screening period:**
  From signing of ICF until randomization

- **Study drug treatment period:**
  Covering daily PE period (variable duration) and 30-days post-daily PE period

- **Treatment extension period:**
  7-day extensions with maximum of 28 days, i.e., 4 x 7 days

- **Open-label:**
  In case an exacerbation during the 30 day treatment period or a relapse during the treatment extension period occurs (first exacerbation or relapse), subject will receive open label caplacizumab together with re-initiation of daily PE and optimized immunosuppressive treatment. Caplacizumab treatment schedule and visit schedule will be the same as for the initial study drug treatment period (covering daily PE [variable duration] and 30-days post-daily PE period) and the possible treatment extension period.

- **Follow-up period of 4 weeks:**
  A first FU visit 7 days and a final FU visit 28 days after the last day of study drug administration.

**Assessments:**

- **Screening**
  - Obtain informed consent
  - Review of eligibility criteria
  - Medical history, including TTP history (and ADAMTS-13 activity levels at admission, if available)
  - GCS
- Bleeding assessment
- Platelet count, blood smear, serum creatinine (local lab)
- Pregnancy test (urine or blood)
- Demographics
- Concomitant medication
- AEs

- Day 1
  - Randomization
  - Study drug administration** and PE + corticosteroids
  - Platelet count, blood smear
  - LDH, serum creatinine, cTnI, ADAMTS13 activity
  - Complement factors C5a and C5b-9
  - Assessment of the neurological system (including coma, stupor, seizures, disorientation/confusion, hemiparesis/-plegia, focal deficit, agitation, dysarthria)
  - Cognitive assessment (standardized mini mental state examination [SMMSE])
  - Clinically significant TTP event
  - AEs, safety laboratory parameters, physical examination, electrocardiogram (ECG), vital signs
  - Concomitant medication
  - Bleeding assessment
  - PK, PD parameters (vWF, FVIII and RICO)
  - Immunogenicity (ADA)

Study drug treatment period (including exacerbation during 30-day post daily PE period and relapse during treatment extension period), the possible treatment extension period and FU period - see Schedules of Assessments.

Statistics:

Endpoints
Primary:
Time to platelet count response defined as initial platelet count ≥ 150×10⁹/L with subsequent stop of daily PE within 5 days.

** Note that study drug administration can occur on Day 2 as a time window of 24 hours is permitted between the start of first PE (i.e., PE administered prior to randomization) and the start of the first PE after randomization (i.e., the first on-study PE), resulting in a possible time window between randomization and first study drug administration.
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 (e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism or deep venous thrombosis [DVT]; also see section 3.4.3.6) during the study drug treatment period (including extensions).

2. Proportion of subjects with a recurrence of TTP in the overall study period (including 4-week FU period).

3. Proportion of subjects with refractory TTP, defined as absence of platelet count doubling after 4 days of standard treatment, and LDH >ULN

4. Time to normalization of all 3 of the following organ damage marker levels:
   - Time to LDH ≤ 1 x upper limit of normal (ULN), and cTnI ≤ 1 x ULN, and serum creatinine ≤ 1 x ULN

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 (see section 3.4.3.2), as well as the number of such events in the overall study period (including 4-week FU period)
- Area under the curve (AUC) of platelet count until Day 5, truncated at 150×10⁹/L if platelet count is 150×10⁹/L or above
- Mortality rate during 4 time periods: initial daily PE period, full study drug treatment period, FU period (of 4 weeks after stop of study treatment) and overall study period
- Organ damage markers: Time to LDH ≤ 1 x ULN
- Organ damage markers: Time to cTnI ≤ 1 x ULN
- Organ damage markers: Time to serum creatinine ≤ 1 x ULN
- Proportion of subjects with increases in organ damage markers (cTnI and serum creatinine) above 1 x ULN in 4 time periods: initial daily PE period, full study drug treatment period, FU period (of 4 weeks after stop of study treatment) and overall study period
- Proportion of subjects with neurological symptoms based on neurological assessment on Day 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
- Change from baseline in 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
- 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 the 30-day post-daily PE treatment period, and the first and final FU visit
- Proportion of subjects who have a platelet count ≥ 150×10⁹/L on Day 1, 2, 3, 4, 5 and Day 10 and end of study drug treatment (i.e., last weekly visit during the study drug treatment period)
• Time to stop of daily PE
• Bleeding events
• Proportion of subjects with at least one treatment-emergent thromboembolic event (based on the Standardized MedDRA Query [SMQ] Embolic and thrombotic events [arterial, venous, and vessel type unspecified and mixed arterial and venous]).
• (S)AEs
• PE parameters: number of days and total volume (absolute and normalized) in 2 time periods: initial daily PE period and full study drug treatment period
• Number of days in ICU and in hospital in 4 time periods: initial daily PE period, full study drug treatment period, in the FU period (of 4 weeks after stop of study treatment) and overall study period
• PD parameters: vWF, FVIII, RICO
• PK parameters
• Immunogenicity (ADA)

Note: The components of composite key secondary endpoints will also be analyzed separately as ‘other secondary endpoint’.

**Statistical Methods**

**Sample size:**
The 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 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 an incidence of 30% and 10% in the placebo and caplacizumab arms, respectively.

**Randomization:**
Subjects will be randomized to one of the 2 arms in a 1:1 ratio. Randomization will be stratified by severity of neurological involvement (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.

**Analysis of primary endpoint:**
Time to platelet count response in the caplacizumab arm and placebo arm will be compared by conducting a two-sided stratified Log-rank test (significance level of 5%) based on a Kaplan-Meier (KM) analysis, with severity of neurological involvement as stratification factor. 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). The censoring plan will be detailed in the statistical analysis plan (SAP). The analysis will be performed on the modified intent-to-treat (mITT) population (ICH E9 guidance), which comprises all randomized subjects who have received at least one study drug dose. Subjects will be analyzed according to the treatment to which they were assigned. Crossover of subjects who experience a recurrence of TTP during the study to open-label caplacizumab will not affect the primary efficacy endpoint analysis as an exacerbation can only occur after the primary endpoint has been reached.

**Analysis of secondary endpoints:**

**Key secondary endpoints**
Confirmatory hypothesis testing will be conducted 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 DVT) during the study drug treatment period (including extensions): Cochran-Mantel-Haenszel test with adjustment for severity of neurological involvement (stratification factor used in randomization). Subjects who have crossed over from placebo to caplacizumab will be evaluated in the initial treatment arm (placebo) only.
2. Proportion of subjects with a recurrence of TTP in the overall study period (including 4-week FU period): Cochran-Mantel-Haenszel test with adjustment for severity of
neurological involvement (stratification factor used in randomization). Subjects who have crossed over from placebo to caplacizumab will be evaluated in the initial treatment arm (placebo) only.

3. Proportion of subjects with refractory TTP, defined as absence of platelet count doubling after 4 days of standard treatment, and LDH >ULN: Cochran-Mantel-Haenszel test with adjustment for severity of neurological involvement (stratification factor used in randomization). Subjects who have crossed over from placebo to caplacizumab will be evaluated in the initial treatment arm (placebo) only.

4. Time to normalization of all three organ damage marker levels: stratified Log-rank test based on a KM analysis with adjustment for severity of neurological involvement 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. Subjects who have crossed over from placebo to caplacizumab before having reached the endpoint will be censored at time of crossover.

Other secondary endpoints
All other endpoints will be summarized using standard statistics such as number of observations, means, standard deviations, and proportions, as appropriate.

Overview of the study design

[Diagram of study design with stages and timelines]
## SCHEDULES OF ASSESSMENTS

### Table 1: Time and events schedule: screening

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

^a 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.

^b To be assessed within 2 hours prior to randomization.

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

^d Only for women of childbearing potential. Pregnancy test (urine or blood) will be assessed locally.

^e 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).
Table 2: Time and events schedule: Daily PE period

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

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 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.

All assessments to be done on Day 8, 15,... include assessments done on daily basis plus extra weekly assessments.

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.
d 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.

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

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 that will be assessed by a local laboratory.

k Organ damage markers include LDH, Troponin I, creatinine.

l PD parameters include RICO, vWF:Ag, and FVIII:C.

m 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.
### Table 3: Time and events schedule: 30-day post-daily PE period, early termination and follow-up period

<table>
<thead>
<tr>
<th>Study Period</th>
<th>30-Day Post-Daily PE Period</th>
<th>Early Termination Visit</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Visit</strong></td>
<td><strong>Week 1</strong></td>
<td><strong>Week 2</strong></td>
<td><strong>Week 3</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Day 1</strong></td>
<td><strong>Day 8</strong></td>
<td><strong>Day 15</strong></td>
</tr>
<tr>
<td></td>
<td><strong>(1 day after last daily PE)</strong></td>
<td><strong>(8 days after last daily PE)</strong></td>
<td><strong>(15 days after last daily PE)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>(± 1 day)</strong></td>
<td><strong>(± 1 day)</strong></td>
<td><strong>(± 1 day)</strong></td>
</tr>
<tr>
<td>Study drug administration (daily)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Review of patient diary</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Neurologic assessments c</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>SMMSE</td>
<td></td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Clinically significant TTP event</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Bleeding assessment g</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Physical examination</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Vital signs e</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>12-lead ECG f</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count h</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Clinical laboratory analyses g</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Organ damage markers i</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>ADAMTS13 Activity</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>PK</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>PD parameters j</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Immunogenicity (ADA) k</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

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.

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.

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

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

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

To be performed after 5 min in supine position.

Clinical laboratory analyses include blood chemistry, hematology and blood coagulation parameters.

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

Organ damage markers include LDH, Troponin I, creatinine.

PD parameters include RICO, vWF:Ag, and FVIII:C.
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.
Table 4: Time and events schedule: Treatment extension period

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

* 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.

* Also see section 3.1.1

* 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.

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

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

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

* Organ damage markers include LDH, Troponin I, creatinine.

* PD parameters include RICO, vWF:Ag, and FVIII:C.

* 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.
1. INTRODUCTION

Caplacizumab (Sponsor code: ALX-0081) is intended to inhibit the interaction between von Willebrand factor (vWF) and platelets, by targeting the A1 domain of vWF. Caplacizumab selectively prevents thrombus formation in high-shear blood vessels, blocks ultra-large (UL) vWF mediated platelet interactions, and is expected not to interact with hemostasis in normal, healthy blood vessels.

Currently, caplacizumab is being developed for treatment of acquired thrombotic thrombocytopenic purpura (TTP) [1]. 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.

1.1. THROMBOTIC THROMBOCYTOPENIC PURPURA

Acquired TTP is a rare, potentially life-threatening, (sub)acute onset thrombotic microangiopathy that leads to microvascular occlusions and variable organ ischemia throughout the body including brain, heart and to lesser extent kidneys. It is characterized by thrombocytopenia, hemolytic anemia and signs and symptoms of tissue ischemia, resulting from ULvWF forming platelet aggregates in the microvasculature. The ischemic damage may result in both acute complications as well as in poorer longer term outcomes [2, 3]. Next to this acute phase, exacerbations of the presenting TTP episode occur in approximately 30% of subjects.

In TTP patients, the processing of ULvWF multimers by a disintegrin-like and metalloprotease with thrombospondin repeats 13 (ADAMTS13) is impaired, resulting in the persistence of ULvWF with constitutively active A1 domain. This A1 domain readily interacts with the Glycoprotein Ib (GPIb)-IX-V receptor on platelets, resulting in ULvWF mediated platelet string formation and subsequent thrombocytopenia, microvascular thromboembolism and erythrocyte fragmentation (schistocytes) (also see section 1.2.1). Impaired processing of ULvWF in TTP is often caused by inhibitory auto-antibodies to ADAMTS13 (idiopathic acquired TTP), or due to mutation(s) in the ADAMTS13 gene (congenital form of TTP). Although ADAMTS13 deficiency is the primary molecular mechanism for TTP, it is not mandatory for the clinical diagnosis of acquired TTP, but may help to confirm it.
Acute myocardial infarction (AMI) has been reported as an early complication of TTP based both on clinical diagnosis of AMI [4] and autopsy findings [5]. Post-mortem evaluation of 25 patients with TTP who died within 5 – 126 days of the TTP diagnosis (23 of whom died in 1995 or before, when plasma exchange (PE) was not the standard of care treatment [for treatment of TTP, also see section 1.1.1]), revealed clear involvement of myocardial arteries and more variable vascular involvement in the brain, kidney, pancreas and adrenal glands [5].

The use of PE treatment has greatly improved survival, however the ischemic damage remains a cause of concern: in a retrospective review of 74 patients with thrombotic microangiopathies (TMA) it was demonstrated that patients with clinically suspected TTP are at high risk to develop AMI, based on high serum lactate dehydrogenase (LDH) and troponin I (TnI) elevations. At presentation there were 14 subjects in whom a diagnosis of AMI was made (TnI > 1 ng/mL with at least one further criterion for AMI). Thirty-two patients of the 74 TMA patients were assessed as having TTP. Thirteen of these TTP patients (41%) had an AMI indicating that among TMA patients, those with TTP are more susceptible [4]. In another retrospective study in 41 TTP patients, raised troponin T levels >0.01 µg/L were linked with mortality and acute morbidity. 27/41 subjects had troponin T levels above normal range (>0.01 µg/L) and 22/41 had levels ≥0.05 µg/L. Half of the subjects with troponin T ≥0.05 µg/L (12/22) had clinical cardiac symptoms (including chest pain, syncope, dyspnea and palpitations). Moreover, subjects that died (5/41) had higher troponin T levels (median: 0.305 µg/L), while there were no deaths in the group of normal troponin T levels (<0.1 µg/L). Histology confirmed widespread myocardial microvascular thrombosis in the 5 subjects that died [6].

In another, prospective cohort study of 133 TTP patients with severe ADAMTS13 deficiency (ADAMTS13 activity < 10%) for whom frozen samples on diagnosis were available for cardiac TnI (cTnI) measurement, 78 patients (59%) had cTnI > 0.1 µg/mL. Thirty-three patients (25%) in this cohort died and 19 patients (17%) were assessed with refractory disease (absence of platelet count doubling after 4 days of standard of care treatment with persistently high LDH levels). A cut off value for cTnI predicting death was determined as 0.25 µg/mL. Patients with cTnI at baseline > 0.25 µg/mL showed more cerebral and cardiac involvement and experienced a more severe outcome with a higher death rate: 3-fold increase in risk of death or refractory disease [7]. These results suggest that more rapidly reducing further microvascular cardiac ischemia, e.g. measured by troponin, of the presenting TTP episode could be expected to have a clinical benefit. Other retrospective reports found similar results on acute and long-term cardiac involvement in TTP patients including myocardial infarctions [8] and other cardiac events like infarctions, arrhythmias, cardiogenic shock and sudden cardiac death [9].

In addition to the cardiac manifestations, neurological involvement is considered to be one of the differentiating factors for TTP. It is observed in more than half of patients presenting
with TTP: reported proportions vary from 50% in the Oklahoma TTP registry (patients with ADAMTS13 <10%) [10] to 68% in the French cohort study [7]. Longer term consequences of the acute ischemia and/or recurrent episodes have been reported as cognitive deficits based on a selection of 24 patients from the Oklahoma Registry with documented ADAMTS13 deficiency at the time of initial TTP episode and who were functioning independently in their normal work and daily activities at the time of the study. Twenty-four patients were included and underwent a variety of tests assessing 11 domains of cognitive function. Results of these tests were compared to the United States (US) normative population (16th percentile) and the group performance for these 24 subjects was worse than the US population norms for neurologically normal subjects. Eighteen (75%) of the TTP patients performed below expectations in one or more of the following domains: complex attention and sequencing, manual dexterity, rapid language generation and list learning [11]. In addition, a health-related quality of life survey in patients from the Oklahoma TTP Registry (using a standardized questionnaire, the Short Form-36, covering eight different domains of physical/mental health and general health) also revealed that patients with TTP have worse daily functioning and well-being compared to the US normative population [12].

Another report from the Oklahoma Registry based on the annual follow-up through 2012 of 57 patients in the registry who had recovered from TTP associated with acquired, severe ADAMTS13 deficiency, concluded that TTP survivors have a greater risk for poor health and premature death. Hypertension and diabetes were not significantly different in prevalence at the time of TTP diagnosis. However, at the time of the report the prevalence of hypertension was greater than expected (40% vs. expected value of 23%, p = 0.011) but not that of diabetes (14% vs. expected 10%, p = 0.439). Depression was more prevalent in 2012 for these patients than expected (prevalence of 19% vs. expected 6%, p = 0.005 for major depression) – none of the patients with major depression had a relapse TTP episode. For the 57 patients evaluated over a median of 7.8 years, there was a higher than expected mortality rate of 19% and the 11 patients who died all did before their expected age of death [2]. Contributory factors to the poorer outcomes noted by the authors were: age, race, gender and body mass index (BMI), and the small number of patients with TTP precluded determination of TTP as an independent factor.

More recently, longer term outcomes were reported from a single center retrospective analysis of 100 patients diagnosed with TTP and followed for a median of 59 months (range 1 – 117 months). In the 91 patients who survived there was a higher prevalence of hypertension (61.5 % vs. 24%), depression (26% vs. 12%), chronic kidney disease (26% vs. 15%), stroke (12% vs. 6%) and diabetes (7% vs. 4%) when comparing the follow-up (FU) period to the prevalence at diagnosis [13].

A fast normalization of LDH as marker for hemolysis and ischemic organ damage may potentially also be beneficial for long term clinical outcome. In a retrospective study of 282 subjects, high levels of LDH at presentation were linked with a worse long term
outcome (mortality), reflective of a severe multiple organ involvement [14]. Moreover, a persistent elevation of LDH after the initiation of PE (2 or more sessions of PE) predicts mortality in acquired TTP subjects [15]. Similarly, a retrospective analysis of 30 patients with TMA/TTP showed that a more pronounced decline of LDH (i.e., LDH ratio of < 0.6; calculated as the LDH levels before the third PE session / LDH level at baseline) was linked with a more favorable outcome [16]. In addition, TMA patients with an LDH ratio > 0.6 prior to the third PE were reported to have a significantly higher risk for AMI [4]. These results suggest that a faster normalization of LDH levels would be linked to a better clinical outcome.

1.1.1. TREATMENT OF TTP

Plasma exchange therapy is the standard of care treatment for acquired TTP. It replenishes ADAMTS13, partially normalizing vWF processing, and removes pathogenic auto antibodies when present. Immunosuppressive treatment, most commonly corticosteroids, is started together with the PE therapy. Daily PE therapy is stopped (or tapered) when the platelet count has normalized for at least 48 hours. An “exacerbation” occurs in approximately 30% of patients [17]. Despite prompt initiation of daily PE and immunosuppressive treatment, acquired TTP still has an associated mortality of 10 to 20%. Severe ADAMTS13 deficiency (<10%) has been recognized as a potential biomarker for the management and follow-up relating to risk of relapse of acquired TTP patients [18, 19]. Although different thresholds for defining a severe deficiency in ADAMTS13 activity have been described, recent guidance papers have proposed a cut-off level of <10% to define a severe ADAMTS13 deficiency. ADAMTS13 levels below 10% during remission may predict an increased risk for relapse [20-22] and may be used as marker for active underlying disease [23].

In spite of recent advances in understanding the disease, there are no approved pharmacological therapies for acquired TTP. Caplacizumab represents a novel approach to the treatment microvascular thrombosis inherent in TTP and may provide significant benefit in terms of efficacy, safety and quality of life for subjects with TTP. Caplacizumab is being developed with the aim of preventing platelet consumption and formation of further microthrombi thereby reducing the duration of tissue ischemia and protecting the patient from the manifestations of the disease while the underlying process resolves.
1.2. **CAPLACIZUMAB**

The following paragraphs provide summary information on caplacizumab; for more detailed background information, please refer to the Investigator’s Brochure.

1.2.1. **GENERAL PROPERTIES**

Caplacizumab is a Nanobody developed by Ablynx NV. Nanobodies are therapeutic proteins that are derived from the smallest functional fragments of heavy chain only antibodies, which occur naturally in the Camelidae family. They have a high degree of homology (in terms of sequence and structure) to human immunoglobulin heavy chain variable region domains, and can be further engineered and expressed by a variety of expression systems.

Caplacizumab is a humanized bivalent Nanobody which is produced in *E. coli* and consists of two identical humanized anti-vWF building blocks, genetically linked by a 3-alanine linker (Figure 1).

![Schematic structure of caplacizumab](image)

(aa: amino acid; MW: molecular weight; Da: Dalton)

**Figure 1: Schematic structure of caplacizumab**

The target of caplacizumab, vWF, is a key protein in hemostasis. vWF is expressed by endothelial cells and secreted into the systemic circulation as ULvWF. The A1 domain in ULvWF is activated and is able to interact spontaneously, in circulation, with the platelet receptor GPIb-IX-V.

In healthy subjects, ULvWF multimers are immediately cleaved into smaller, regular-sized multimers by the vWF-cleaving protease ADAMTS13. In TTP patients, processing of ULvWF
multimers by ADAMTS13 is impaired, resulting in the persistence of the constitutively active A1 domain. This domain readily interacts with the GPIb-IX-V platelet receptor, resulting in the characteristic microvascular blood clots reported in the TTP patient population. Caplacizumab is able to interact with vWF in both its active (i.e., functional interaction with GPIb-IX-V as ULvWF multimers) and its inactive form (i.e., multimers prior to conformational change of A1 domain), thereby blocking the activation and interaction stages of vWF with the GPIb-IX-V platelet receptor. As such, this Nanobody prevents the characteristic platelet string formation that would otherwise lead to platelet agglutination in the microvasculature, local ischemia and platelet consumption (see Figure 2).

![Figure 2: Mechanism of action of caplacizumab in TTP.](image)

The interaction of caplacizumab with vWF is highly specific, and binding of the Nanobody to the vWF A1 domain does not affect the capacity of vWF to interact with coagulation factor VIII (FVIII), for which vWF has a carrier function (preventing the degradation of FVIII while in its inactive state in circulation). Similarly, the selective binding of caplacizumab does not affect the capacity of vWF to interact with fibrillar collagens or collagen type VI. The Nanobody also does not cross react with human blood cells or platelets, and does not affect the activity of the vWF cleaving protease ADAMTS13. Due to this high specificity, off-target effects are not expected and have not been observed in the clinical trials to date.

### 1.2.2. FORMULATION

Caplacizumab 10 mg is provided as a lyophilized powder for solution for injection. The lyophilized powder is to be reconstituted with sterile water for injection (WFI).

Details on the manufacture and pharmaceutical properties of caplacizumab are included in the Investigator’s Brochure.
1.2.3. NONCLINICAL STUDIES

All relevant nonclinical studies conducted with caplacizumab are described in the Investigator’s Brochure.

- Pharmacology: The pharmacodynamic (PD) properties of caplacizumab were studied in in vitro and in vivo studies.
  Caplacizumab was shown to:
  - Bind to the A1 domain of vWF in normal and ultra large multimers.
  - Inhibit concentration-dependently and completely the interaction of (UL)vWF with platelets.
  - Inhibit in vitro and in vivo arterial thrombus formation.
  - Prevent in vitro platelet string formation with ULvWF.
  - Inhibit completely ristocetin-induced platelet aggregation (RIPA) and ristocetin cofactor activity (RICO) in vitro and in vivo.
  - Decrease dose-dependently and saturably FVIII activity and von Willebrand factor antigen (vWF:Ag) levels with recovery after treatment stop.
  - Not increase surgical bleeding in vivo.
  - Prevent and treat thrombocytopenia and schistocytic hemolytic anemia in a baboon model of acquired TTP.

- Pharmacokinetics: The pharmacokinetic (PK) properties of caplacizumab were analyzed in 4 cross-reactive species (baboon, farm pig, cynomolgus monkey and guinea pig). Different routes of administration were assessed, namely intravenously (i.v.), subcutaneously (s.c.) and intramuscularly (i.m.). The terminal half-life (t1/2) of caplacizumab - more precisely caplacizumab bound to vWF - ranges between 5-36 hours across the relevant species. The complex of caplacizumab and vWF is eliminated hepatically, possibly via a target specific pathway and the excess of unbound drug is rapidly cleared via renal filtration [24]. Consequently, after i.v., s.c. or i.m. administration, non-linear kinetics were observed: exposure does not increase proportionally to the dose. This PK behavior limits the potential for overdosing. The absolute bioavailability of caplacizumab after s.c. administration, in cynomolgus monkey, ranged from 82% to 97% [25].

- Toxicology: Toxicity studies include:
  - Single dose toxicity studies in cynomolgus monkey and guinea pig after i.v. and s.c. administration,
  - 2-week repeated dose toxicity studies in cynomolgus monkey after i.v. and s.c. administration,
- 13-week repeated dose toxicity studies in cynomolgus monkey and guinea pig after s.c. administration and
- A 26-week chronic dose toxicity study in cynomolgus monkey after s.c. administration.

The toxicology data revealed:
- Neutralization of vWF activity throughout dosing period (as measured through RICO).
- Mild bleeding events such as epistaxis and menorrhagia.
- One case of marked and persistent anemia, signs of inflammation, an increased bleeding tendency and low FVIII clotting activity (FVIII:C), concurrent with the presence of inhibitory anti-FVIII antibodies (AFA) in one cynomolgus monkey, with unclear assignment to study drug (high dose group, 26-week toxicity study in cynomolgus monkey).
- One case of profound but reversible decrease of platelet counts in cynomolgus monkey (high dose group, 26-week toxicity study).
- No immune response-induced adverse events (AEs) were reported in any of the toxicity studies.
- Development of AFA without clinical correlates in 4 animals (2 out of 32 verum-treated animals from 13-week toxicity study in cynomolgus monkey and 2 out of 40 verum-treated animals from 26-week toxicity study).
- In the 26-week repeated dose toxicity study, the no observed adverse effect level (NOAEL) was established at 4 mg/kg/day based on morbidity of one high-dose animal and the absence of findings in the 4 mg/kg/day group. The observation of AFA positivity across dose groups, was not used to determine the NOAEL as immune-mediated processes are known not to be dose-related.

1.2.4. EFFECTS IN HUMANS

**Phase I studies**

Up to now, the following Phase I studies have been completed in healthy volunteers and in patients:
- Study ALX-0081-01/06 was a Phase Ia double-blind, placebo-controlled, randomized parallel group, single ascending i.v. dose study conducted in healthy male subjects to investigate the safety, tolerability and pharmacokinetics of caplacizumab administered i.v. as single ascending doses.
- Study ALX-0681-1.1/08 (Phase I) examined the safety, tolerability, pharmacokinetics and pharmacodynamics of caplacizumab (ALX-0081) in healthy volunteers after single or multiple s.c. administrations.
- Study ALX-0081-1.2/08 was performed mono-centric with stages A and B as a double-blind, placebo-controlled, randomized, dose-escalation Phase Ib study to evaluate the safety of ascending doses of caplacizumab in stable angina patients undergoing percutaneous coronary intervention (PCI). An open label extension (OLE) stage (Stage C)
was added to this study to evaluate administration of caplacizumab as an i.v. bolus injection and to obtain additional information on the target pharmacological effect and the overall biological and clinical response.

- Study ALX0681-C102 was a Phase I, single center, open-label, randomized, single dose, 2-way 2-period cross-over study in healthy male subjects to evaluate the PK characteristics and demonstrate bioequivalence of a reconstituted new lyophilized formulation of caplacizumab for s.c. injection as compared to an equal nominal s.c. dose of the reference liquid formulation. In addition, the safety and tolerability, and the PD parameters of the new formulation were compared with those of the reference formulation.

Based on the clinical data, single administrations of caplacizumab (up to 12 mg for i.v. administrations and up to 10 mg for s.c. administrations) and multiple administrations of caplacizumab (6+4+4+4 mg q6h i.v.) were well tolerated in healthy volunteers and PCI patients. In general, incidence of treatment-related AEs was low after single dose administration and administration did not result in clinically significant signs of bleeding. After multiple dose treatment (7 and 14 days), more treatment-related AEs were observed including an increase in the number of bruises and bleeding, all being of mild intensity.

In the Phase I studies, no treatment-emergent (TE) anti-drug antibodies (ADA) have been observed after single or multiple administrations of caplacizumab.

The PK profile is determined by target-mediated drug disposition since only drug bound to the target vWF is retained in circulation with a half-life (90% confidence interval [CI]) of 10-30 hours, and excess drug is rapidly cleared renally due to its small size (28 kDa). Consequently, after i.v. and s.c. administration, non-linear kinetics were observed: exposure does not increase proportionally to the dose and an increase in clearance can be noted. This PK behavior is expected to translate into a low overdosing potential for caplacizumab.

In the study evaluating bioequivalence of s.c. administration of the reconstituted new lyophilized formulation and the reference liquid formulation of caplacizumab (study ALX0681-C102), the geometric mean for $C_{\text{max,D}}$, $AUC_{0-\text{last,D}}$ and $AUC_{0-\infty,D}$ were similar following of 10 mg reconstituted lyophilized solution and 10 mg of the reference liquid formulation. The formal statistical analysis confirmed that these PK parameters were bioequivalent at the 10% significance level. Also the median $t_{\text{max}}$ and $t_{1/2}$ was similar for both formulations.

The PD properties of caplacizumab are:
- Inhibition of vWF mediated platelet activation assessed via complete inhibition of ristocetin induced platelet aggregation (RIPA and RICO).
• Transient, clinically insignificant and fully reversible reduction of vWF:Ag and FVIII:C levels and fully reversible prolongation of Template Bleeding Time (TBT).

**Phase II studies**

One Phase II study has been completed in the development of caplacizumab for the treatment of acquired TTP. An additional Phase II study was completed in an additional development path for acute coronary syndrome (which is no longer being pursued for strategic reasons):

• Study ALX-0681-2.1/10 was a Phase II, single-blind, randomized, placebo-controlled multicenter trial to study the efficacy and safety of anti-von Willebrand factor Nanobody caplacizumab (ALX-0081) administered as adjunctive treatment to plasma exchange to patients with acquired TTP.

• ALX-0081-2.1/09, a Phase II trial was conducted to compare caplacizumab and abciximab (ReoPro®) in high risk PCI patients.

**Study ALX-0681-2.1/10 (TITAN trial) in acquired TTP**

The efficacy and safety of caplacizumab in the treatment of acquired TTP have been evaluated in trial ALX-0681-2.1/10 comparing it to placebo when added to daily PE and in the 30-day post-daily PE period. The trial was terminated early due to recruitment challenges, with a total of 75 subjects enrolled and included in the intent-to-treat (ITT) analysis, but nonetheless demonstrated a statistically significant treatment effect as evidenced by the primary endpoint “time to confirmed platelet count normalization”, with a hazard rate ratio (95% CI) for the caplacizumab versus placebo groups of 2.2 (1.3, 3.8), p-value for the stratified log-rank test of p=0.0048. This corresponded to a reduction in median time to confirmed platelet count normalization from 4.8 (3.6, 5.9) days in the placebo treatment group to 3.0 (2.8, 3.9) days in the caplacizumab treatment group.

The secondary endpoints illustrate the potential protective effect of caplacizumab treatment in the acute phase of TTP:

• Complete remission following initial daily PE was observed in a much higher number and proportion of subjects who received caplacizumab compared with the placebo group (29 [80.6%] subjects versus 18 [46.2%] subjects, respectively).

• A lower proportion of subjects with an exacerbation during treatment of 8% (n = 3) for caplacizumab compared to 28% (n = 11) for placebo.

• When the 1-month FU is also considered, a similar number and proportion of subjects had an exacerbation of TTP and/or a relapse of TTP (10 [27.8%] subjects in the caplacizumab treatment group and 11 [28.2%] subjects in the placebo treatment group). This suggests that in a number of subjects, the underlying auto-immune activity had not sufficiently resolved. Immunosuppressive treatment was not standardized and the shorter duration of PE in the caplacizumab arm may also have impacted the timing of the resolution of the underlying auto-immune disorder.
The mean number of PE days during the initial daily PE period was lower in the caplacizumab group compared with the placebo group (5.9 versus 7.9, respectively), as was the mean total volume of PE administered (19923 mL versus 28307 mL, respectively).

Results from the caplacizumab arm suggest that ADAMTS13 activity data could identify subjects who were at risk for early relapse. In 7 of 8 subjects with a relapse in the first month, it occurred within 4-10 days after stopping caplacizumab. All 7 subjects had ADAMTS13 activity values <10% at baseline, during and near the end of the treatment period, indicating unresolved underlying disease activity. In the 8th subject, the relapse event occurred at 30 days after stopping caplacizumab treatment. This subject had normalization of ADAMTS13 activity during and near the end of the treatment period. However at the time of the relapse, ADAMTS13 activity was again suppressed <10%, which suggests a de novo TTP event. Conversely, 22 caplacizumab-treated subjects did not have an exacerbation or relapse, with ADAMTS13 activity data available near the end of the treatment period for 16/22 patients. In 13 of 16 subjects without exacerbation or relapse, ADAMTS13 activity had returned to values ≥10% near the end of the treatment. ADAMTS13 activity results from the placebo treated subjects supported the potential predictive value of the marker: for 14 of 16 placebo subjects without exacerbation or relapse (ADAMTS13 data available for 16/23 placebo subjects), ADAMTS13 activity values were ≥10% near the end of the placebo treatment period. A total of 11 placebo subjects had an exacerbation during the treatment period, and ADAMTS13 activity data were available for 8 of them. Seven of 8 placebo subjects with an exacerbation had ADAMTS13 activity <10% around the time of the exacerbation, while the 8th subject had a borderline ADAMTS13 activity value of 11%. In summary, the data support ADAMTS13 activity as a potential marker to identify patients at risk for exacerbation or relapse, specifically patients with signs of ongoing active disease during the treatment period who are at risk of relapse early after stopping caplacizumab treatment.

No significant unanticipated safety concerns were raised for treatment with caplacizumab in this study. The results were as expected for the population of patients with acquired TTP. The overall duration of exposure to study drug was similar in the two treatment arms. No subjects in the caplacizumab treatment group died during the study. Two subjects in the placebo treatment group died between the end of study treatment up to and including 1 month FU: one subject had a treatment emergent adverse event (TEAE) of cerebral hemorrhage which was assessed as related to TTP; the other placebo subject died from the serious TEAE of refractory TTP.

A total of 574 TEAEs were reported in 34 (97.1%) subjects in the caplacizumab treatment group compared with 545 TEAEs in 37 (100%) subjects in the placebo treatment group. A comparable number of subjects was also observed between the two treatment arms with regard to serious adverse events (SAEs), 57.1% of subjects in the caplacizumab treatment
group and 51.4% of subjects in the placebo treatment group. The number of subjects with any TEAE leading to discontinuation of study drug was low in both treatment groups (4 and 2 in the caplacizumab and placebo groups, respectively).

The proportion of subjects with any bleeding-related TEAE was higher in the caplacizumab treatment group (54.3% of subjects) than in the placebo treatment group (37.8% of subjects); most bleeding-related TEAEs were mild (83% of events) or moderate (14% of events) in severity. Amongst the bleeding-related TEAE, epistaxis was the most common Preferred Term (31% of subjects for ALX-0081 and 11% of subjects for placebo (all mild or moderate). Two subjects in each treatment arm experienced serious bleeding related TEAEs. The TE bleeding AEs did not lead to emergency measures. Furthermore, no vWF or Factor VIII supplementation was administered during the trial.

Treatment-emergent ADA were detected in 9% of the subjects in the ALX-0081 treated group and in no placebo treated subjects. These had no apparent influence on PK and PD parameters. There was also no association found between the ADAs and safety findings.

Study ALX-0081-2.1/09
This study evaluated caplacizumab in patients undergoing a percutaneous coronary intervention. Caplacizumab was given as a 6 mg i.v. injection prior to the intervention and with 4 mg i.v. injections every 6 hours afterwards for 3 doses. The primary endpoint of the study was a composite of all bleeding events according to the Thrombolysis in Myocardial Infarction (TIMI) classification and was designed to detect a relative risk reduction of 0.4 (caplacizumab versus abciximab [ReoPro®]). Both caplacizumab and abciximab showed comparable bleeding profiles: 36 (19.9%) patients in the caplacizumab treatment group and 28 (15.3%) patients in the abciximab treatment group reported bleeding events. Only 3 (1.7%) caplacizumab treated patients and 2 (1.1%) abciximab treated patients showed a major bleeding event during the 30 day period following the PCI procedure. The safety profile of caplacizumab and abciximab was similar in this study. There were no notable differences in the AE profile between the treatment groups. The proportion of SAEs was low in both treatment groups and the number of deaths was low at Day 30 with only 1 patient in the abciximab group. At 1 year FU, the number of deaths was even at 5 in each treatment arm. All but one of the deaths were considered to be unlikely/not related to the study drug. This other death in the caplacizumab treatment group was considered as possibly related.

In this Phase II study, treatment-emergent antibodies were detected in 10.9% of the caplacizumab-treated subjects. No neutralizing antibodies were detected.

The PD assessments showed an immediate drop in RICO activity 5 to 10 minutes after the caplacizumab bolus injection. Clinically relevant RICO inhibition (< 20%) was maintained for 24 hours post-bolus in the caplacizumab group which was accompanied by an expected transient and mild decrease in vWF antigen and FVIII activity.
1.2.5. SAFETY PROFILE AND RISK ASSESSMENT

The benefit and risk assessment for administration of caplacizumab, as detailed in the Investigator’s Brochure, supports initiation of the proposed clinical trial.

Overall, the TITAN 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) and reducing the incidence of exacerbation during treatment. These findings are expected to be predictive of tangible clinical benefits in terms of reduced mortality/morbidity. The higher incidence of relapse soon after discontinuation of caplacizumab appeared to be associated with persistent low ADAMTS13 activity (<10%), suggesting unresolved underlying auto-immune activity. The current study will evaluate whether such patients would benefit from continuing treatment with caplacizumab for a longer period after discontinuation of PE.

The safety results in study ALX-0681-2.1/10 revealed no unexpected findings in relation to adverse events. The main safety finding associated with caplacizumab treatment was an increase in bleeding-related adverse events, which was consistent with findings in previous studies and is an expected consequence of the pharmacological activity of the drug. Notwithstanding this, the majority of bleeding events in the study were mild to moderate in severity, and an equal number of subjects in each treatment arm (2 subjects per arm) had a serious bleeding related TEAE. Hence, bleeding risk appears to be acceptable in the context of the anticipated clinical benefits of caplacizumab in the TTP indication. Nonetheless, vWF can be used as antidote for caplacizumab if needed. vWF and FVIII preparations as combination products are commercially available.

With regard to immunogenicity, taking into account patient, product and disease related factors, caplacizumab was assigned a low risk class designation. In the TITAN trial, drug induced TE antibodies were detected in 9% of caplacizumab treated subjects. No immunogenicity related safety findings were reported.

Regarding the Reference Safety Information to be considered for ICH E2A, E2B, E2F reporting obligations relative to Pharmacovigilance guidelines, the AEs that would be considered as “Expected” include mild bleeding (very common), as well as decreases of Factor VIII and/or vWF not requiring supplementation with exogenous factor VIII and/or vWF (very common). As such, all other AEs fulfilling the conditions for Serious Adverse Reactions (SAR) are to be considered as unexpected, and therefore reported as Suspected Unexpected Serious Adverse Reaction (SUSAR) according to the guidelines stated above.

Subjects with acquired TTP may have a treatment benefit with caplacizumab in the form of a faster normalization of platelet count, potentially leading to shorter duration of tissue
ischemia and consequent TTP-associated morbidity. In addition they may experience fewer exacerbations while on treatment.

The current overall risk benefit balance is therefore considered to be positive.
2. OBJECTIVES

- Primary Objective:
  - To evaluate efficacy of caplacizumab in more rapidly restoring normal platelet counts as measure of prevention of further microvascular thrombosis

- Secondary Objectives:
  - 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
  - To evaluate the effect of study drug on prevention of recurrence of TTP over the entire study period.
  - To evaluate the effect of study drug on refractoriness to treatment
  - To evaluate the effect of study drug on biomarkers of organ damage: LDH, cTnI, and serum creatinine
  - To evaluate the effect of study drug on PE parameters (days of PE and volume), days in intensive care unit (ICU), days in hospital
  - AEs
  - PD parameters: vWF, FVIII, RICO
  - PK parameters
  - Immunogenicity (ADA)

For information concerning study endpoints, please refer to section 3.6.4.
3. STUDY DESIGN

3.1. OVERALL STUDY DESIGN

3.1.1. STUDY OVERVIEW

This is a Phase III double blind, placebo-controlled, randomized study to evaluate the efficacy and safety of caplacizumab treatment in addition to standard of care treatment (daily PE + corticosteroid treatment) 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 subjects with a clinical diagnosis of acquired TTP 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 symptoms (Glasgow coma scale [GCS] ≤ 12 vs. GCS = 13 - 15).

Standard of care treatment:

- 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). Once the platelet count is ≥ 150 x 10⁹/L, daily PE should continue for at least 2 days. Tapering of PE after platelet count normalization, defined as reducing its frequency to less than once per day, is strongly discouraged and if considered, should be discussed with the Medical Monitor.

- Corticosteroid treatment should be initiated/continued with (methyl)prednisolone or (methyl)prednisone regimen of at least 1 mg/kg/day i.v. or per orale (p.o.) during the daily PE period and continued for the 1st week after end of daily PE. Afterwards corticosteroids may be tapered at the discretion of the Investigator, with the aim of being

†† Of note, the PE administered prior to randomization (PE of unrestricted intensity) may be given prior to signing ICF (as part of standard of care) and may be spread over 2 or more sessions in 24 hours as long as considered part of the 1 intense PE for the treatment of the presenting TTP episode. Note that the maximum time allowed between the start of first PE (i.e., PE administered prior to randomization) and the start of the first PE after randomization (i.e., the first on-study PE) is 24 hours.
corticosteroid-free by Day 30 after cessation of daily PE as clinically indicated. At the Week 3 visit of the 30-days post-daily PE period, corticosteroid tapering should be reassessed based on ADAMTS13 activity data of the previous 2 visits and other clinical signs of underlying disease.

- Other immunosuppressive treatment: The use of other immunosuppressive treatment (e.g., rituximab) is allowed per standard site practice but should be considered in light of protocol required corticosteroid treatment.

**Study drug treatment:** see section 3.3 for details

*Daily PE period***‡‡

- Loading i.v. dose: subjects will receive a single loading dose of study drug by i.v. bolus injection from 6 hours to 15 minutes prior to the first PE done after randomization;
- Daily s.c. dose: a s.c. injection of study drug will be administered daily after completing the daily PE session.

It is expected that subjects are hospitalized for the duration of the daily PE period. Exceptions should be discussed with the Medical Monitor.

*30-day post-daily PE period*

Daily s.c. administration of 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. After discharge from hospital, subjects are allowed to self-administer.

*Treatment extension period*

Study drug treatment extension beyond these 30 days for additional 7-day periods with a maximum of 28 days, will be guided by a number of risk factors for relapse of the presenting TTP episode and must be accompanied by an optimization of the immunosuppressive treatment. The risk factors will include the ADAMTS13 activity profile (measured weekly), 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.

*Recurrence of TTP episode*

- **Exacerbation** is defined as recurrent thrombocytopenia after initial recovery of platelet count (platelet count ≥ 150×10^9/L with subsequent stop of daily PE within 5 days), requiring re-initiation of daily PE, occurring during the first 30-days post-daily PE period.
- **Relapse** is defined as recurrent thrombocytopenia after initial recovery of platelet count requiring re-initiation of daily PE, occurring after the 30-days post-daily PE period.

***‡‡ For logistical reasons, the Sponsor needs to be contacted if the daily PE period exceeds beyond 30 days.
Based on the mechanism of action and the available efficacy and safety results from study ALX-0681-2.1/10 (Phase II TITAN trial) it is considered desirable from both a treatment and exposure perspective (to maximize the number of subjects exposed to caplacizumab), to allow for crossover to open-label caplacizumab for subjects who experience an exacerbation of the TTP episode.

**Exacerbation**
In case of a first exacerbation of the presenting TTP episode, subjects will receive open label caplacizumab together with daily PE irrespective of what the initial treatment allocation was. The blind will not be broken for the initial treatment allocation. Caplacizumab treatment and visit schedule will be the same as during the initial treatment period. In case a subject has subsequent exacerbations, standard of care treatment of daily PE and appropriate immunosuppressive treatment should be initiated as per site practice. There will be no re-initiation of study drug administration for a second or further exacerbation.

**Relapse during the treatment extension period**
In case a subject has a first TTP recurrence while still receiving study drug in the treatment extension period, then daily PE should be started as part of standard of care treatment together with appropriate immunosuppressive treatment. Study drug treatment will crossover as open-label caplacizumab irrespective of what the initial treatment allocation was, without breaking the blind of the initial treatment assignment. In case a subject has subsequent relapse, standard of care treatment of daily PE and appropriate immunosuppressive treatment should be initiated as per site practice. There will be no re-initiation of study drug administration for a second or further relapse.

**Relapse during the 4-week FU period**
In case a subject has a first or subsequent TTP relapse after completing study drug treatment in the FU period, standard of care treatment of daily PE and appropriate immunosuppressive treatment should be initiated as per site practice. There will be no re-initiation of study drug administration.

As stated above, there will be no re-initiation of study drug administration for subjects experiencing more than one exacerbation or relapse (or an exacerbation after a relapse or a relapse after an exacerbation).
**Figure 3: Overview of the study design**

**Estimated Study Duration**
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.

**Determination of Sample Size**
The 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 ≥ 150×10^9/L with subsequent stop of daily PE within 5 days). The required sample size is 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 an incidence of 30\% and 10\% in the placebo and caplacizumab arms, respectively.

**Independent Data and Safety Monitoring Board (DSMB)**

The sponsor will appoint a DSMB consisting of an independent group of clinical experts, who are not participating in the study. They will be supplemented by an independent statistician. The objective of the DSMB will be to review unblinded safety data on SAEs with a focus on mortality rate. Acquired TTP is still associated with a mortality rate of 10 – 20\% and an efficacious treatment may reduce this. The first DSMB meeting will be convened as of 5 deaths, or after 24 subjects have completed the study drug treatment period, whichever occurs earlier. This is to review the SAE and mortality information (including the overall number of subjects treated up to that point, rates, and subject-level details) and determine if there is an imbalance in the treatment arms with respect to these events, based on clinical judgment of the DSMB. Subsequent meetings will be determined by the DSMB based on the recruitment rate into the study, and incidence of SAEs, particularly death. The DSMB will advise the sponsor concerning continuation, modification or termination of the study after every meeting.

The composition, objectives, and role and responsibilities of the independent DSMB will be described in a DSMB charter, agreed with the DSMB members and Sponsor. The DSMB charter will also define and document the content of the safety summaries, and general procedures (including communications).

**3.1.2. STUDY RATIONALE**

Preclinical studies demonstrate that (i) caplacizumab is able to immediately halt ULvWF platelet string formation in *in vitro* flow chamber experiments and (ii) caplacizumab prevents the progressing formation of platelet aggregates as demonstrated through histological measurement of vessel occlusion in a baboon model of acquired TTP [26]. These results provide evidence for the prevention of further microthrombi formation upon administration of caplacizumab. Given the pathophysiology of acquired TTP whereby ULvWF strings consume platelets in the formation of microthrombi, it is reasonable to infer that the recovery of platelet counts is an indirect measure of prevention of further microthrombi formation. The morbidity and the acute mortality associated with acquired TTP is a result of
these microthrombi. Although the mechanism of action of caplacizumab is not expected to have an effect on the underlying trigger of the disease, i.e., formation of auto-antibodies against the ADAMTS13 enzyme, through its protective effect on platelets, it is expected to be able to reduce the morbidity and potentially the acute mortality rate. The presenting signs and symptoms of TTP are very heterogeneous with respect to both the organ systems involved and the extent of involvement.

**Rationale for choice of primary endpoint**
Platelet count is considered to be a valid measure of (potential) morbidity caused by microvascular thrombosis in the absence of a direct and/or feasible measure of the latter. Thrombocytopenia is present in all patients by definition. Platelet count normalization is the primary factor in the decision to stop daily PE treatment [19, 27]. The increase in platelet counts is also an important measure for the responsiveness to standard of care treatment. The diagnosis of a patient as having primary refractory TTP is based on an ‘inadequate platelet response’ over a variable observation period (e.g., 4 – 10 days) which depends on local clinical practice [28]. For example, a single center retrospective review of 64 patients with a clinical diagnosis of TTP identified a platelet count response rate of 5 x 10⁹/L per 24 hours over the first 3 days of PE treatment to be a predictor of sustained remission after PE and of survival [29]. The results of the TITAN trial demonstrated a more rapid return to normal platelet counts when caplacizumab was given in conjunction to daily PE, compared to placebo plus daily PE (approx. 40% improvement in time to confirmed platelet normalization) as noted in section 1.2.4.

Clinical endpoints related to disease presentation such as neurological impairment or myocardial ischemia are not suitable as a primary endpoint since they are not sufficiently characteristic of TTP. Patients present with a very variable set of signs and symptoms. There is also no standardized set of criteria or scoring system to measure the clinical severity of the disease presentation on which a clinical endpoint could be based. Biomarkers of tissue ischemia are similarly also variable in TTP patients: LDH may be seen as an overall marker of tissue ischemia, serum creatinine of renal impairment and cardiac troponin levels for cardiac ischemia but not all patients will have each biomarker elevated, further reducing the patient population if this were to become an eligibility criterion. These elements are nonetheless all important in understanding the overall treatment effect and are therefore included as secondary endpoints.

This also highlights the challenges of conducting a clinical trial in a very rare condition which is further complicated by the emergency care setting and the urgency of initiating appropriate treatment. Previous randomized trials in TTP were terminated prematurely due to low recruitment rates, including the TITAN trial which was terminated early for this after enrolling 75 subjects out of a planned 110, at 32 of 56 approved sites in 13 countries worldwide over a period of 3 years. The STAR study enrolled 3 patients of the planned 220 from April 2009 to February 2010 after which it was terminated due to low recruitment at
the 17 participating sites [30]; and the ARC1779 trial which enrolled 9 subjects of the planned 100 subjects.

_Dose Selection Rationale_

The pharmacology of caplacizumab is two-fold. Caplacizumab affects the functionality of vWF, leading to inability of vWF to bind to platelets. It also affects the disposition of vWF, leading to transient reductions of total vWF:Ag levels during treatment.

A population PK/PD model was developed using total vWF:Ag levels as PD endpoint on data pooled from the different clinical trials performed in healthy volunteers and in patients. This model adequately describes the PK and PD observations in the TITAN trial. _In vitro_ experiments identified a correlation between target inhibition and target occupancy, which is similar across a wide range of vWF:Ag levels. These _in vitro_ results support that a population PK/PD approach which assesses the effect of caplacizumab on free and total levels of vWF is suited to define adequate dose levels in acquired TTP patients.

The dose of 10 mg used in the TITAN trial was proposed based on the information available on the suppression of vWF by s.c. administration of caplacizumab in healthy volunteers as measured _ex vivo_ (ALX-0681-1.1/08).

The efficacy and safety results from the TITAN trial confirm the appropriateness of the 10 mg dose. The 10 mg i.v. loading dose in the TITAN trial ensured caplacizumab exposure was detectable already 5-10 minutes after administration allowing a rapid attainment of the desired drug concentration, while the 10 mg s.c. daily dose assures sufficient daily exposure to maintain the pharmacological effect. The effect on target neutralization was measured through the RICO assay and this demonstrated the desired sustained suppression of RICO activity to < 20% throughout the treatment period.

A PK/PD model was additionally used to evaluate the expected exposure and corresponding effect on total, free and complexed vWF levels for different dosing scenarios in a virtual TTP patient population, through simulations. A virtual population of TTP patients (n=500), with characteristics based on the population from the TITAN study, was created by sampling the truncated distributions of body weights (mean 81.9 kg ± 22.6 standard deviation [SD], range 47.5-150 kg) and model-estimated baseline vWF in the TTP population of the TITAN trial as well as gender distribution (M:F 40:60).

Simulated scenarios included an initial 8 days daily PE procedure with a concomitant s.c. daily administration of caplacizumab 1h after the termination of each PE at doses of 2.5, 5, 10, 20 mg (period 1). Subsequently, caplacizumab was assumed to be administered at the same dose levels/regimen for additional 30 days in absence of any other PE procedure (period 2).
The % change of the free vWF from baseline increases with the dose, but less than dose-proportional. A large inter-individual variability, mainly related to the large variability of target expression (vWF) at study entry, is predicted at all the dose levels. The two lower doses (2.5 and 5 mg once daily) lead to a sub-optimal target inhibition, whereas a higher daily dose of caplacizumab than the one tested in the TITAN study (20 mg) does not substantially benefit the overall simulated TTP population. Figure 4 shows the model-predicted % decrease from baseline of free vWF:Ag levels at the end of period 2 as a function of the dose level, including patients treated with placebo.

**Figure 4: vWF levels in TTP patients**

Model-predicted % decrease from baseline of free vWF levels at the end of period 2 as a function of the daily dose level, including patients treated with placebo. Median, 25th and 75th percentiles are indicated.

The simulated plasma profiles of the drug, free, complex and total vWF levels for a 10 mg once daily dose are illustrated in Figure 5.
Figure 5: PK/PD-Model of caplacizumab and free, total and complexed vWF

(A) Model-predicted caplacizumab concentration profiles after daily s.c. administration during period 1 and period 2 (with and without concomitant daily PE). (B) Model-predicted free vWF levels during a daily 10 mg s.c. administration of caplacizumab and after the treatment period. (C) Estimated complex caplacizumab-vWF levels during a daily 10 mg s.c. administration of caplacizumab and after the treatment period. (D) Model-predicted total vWF levels during a daily 10 mg s.c. administration of caplacizumab and after the treatment period. Median profiles, 5th and 95th percentiles are shown.

Next to change in levels of the free vWF as marker for target neutralization, the change in levels of total vWF as marker for bleeding risk was evaluated. A threshold of 0.4 IU/mL (or 16 nM) was used, observed in von Willebrand’s disease type I [31]. Panel D shows that total vWF levels for the proposed dose of 10 mg once daily would remain above this threshold considered for risk of bleeding events [31].

Based on the previous in vitro study results and model-predicted levels of biomarkers for efficacy (free vWF) and safety (total vWF), the dosing regimen used in the TITAN trial and proposed for this study (10 mg daily) is considered as adequate for reaching the desired suppression of the platelet-binding capacity of (UL)vWF in TTP patients.

3.1.3. BLINDING

In order to protect the integrity of the data, caplacizumab treatment assignment will be kept blinded for investigative sites, subjects, site monitors, and other members of the study
team, until the final database lock when the last subject has completed the final FU visit and all data is considered clean.

Note that all subjects experiencing a first exacerbation during the 30-days post daily PE period (without a prior relapse) or a first relapse during the treatment extension period (without a prior exacerbation) will subsequently receive caplacizumab in an open-label design irrespective of initial treatment allocation but the blind will not be broken for the initial treatment allocation.

**Emergency unblinding procedure**

Code-breaking and unblinding in the event of medical emergencies can be done by the Investigator via the Interactive web/voice response system (IWRS/IVRS), which will be accessible 24 hours per day/7 days per week.

Unblinding by the Investigator should occur only in the event of AE for which it is necessary to know the study treatment to determine an appropriate course of therapy for the subject. The Investigator should first discuss options with the Medical Monitor if possible with due consideration of the safety of the subject. If the Investigator must identify the treatment assignment of an individual subject, the Principal Investigator/Subinvestigator is to contact the IWRS/IVRS.

Subjects for whom unblinding has occurred, will have to discontinue treatment and all efforts must be made to conduct the Early Termination Visit and first and final FU visits.
3.2. SELECTION OF STUDY POPULATION

Approximately 132 adults with a clinical diagnosis of acquired TTP who require initiation of daily PE treatment are planned to be included in the study. Subjects who previously participated in this trial, cannot be re-enrolled.

3.2.1. INCLUSION CRITERIA

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

1. Adult male or female ≥ 18 years of age at the time of signing the informed consent form (ICF)
2. Clinical diagnosis of acquired TTP (initial or recurrent), which includes thrombocytopenia and microscopic evidence of red blood cell fragmentation (e.g. schistocytes)
3. Requires initiation of daily PE treatment and has received 1 PE treatment §§ prior to randomization
4. Female subjects of childbearing potential (excluding postmenopausal women, sterilized, ovariectomized and hysterectomized women) must have a negative pregnancy test and must agree to use a generally accepted adequate contraceptive method from screening until at least 2 months after last dosing
5. Subjects have provided informed consent prior to initiation of any study specific activity/procedure. In case the subject is unconscious or if their ability to give (written) informed consent is compromised due to the neurological impairment or severity of TTP symptoms, a subject’s legal acceptable representative or independent physician (as per local law and Ethics Committee [EC]/Institutional Review Board [IRB] approval) has provided informed consent prior to any study specific activity/procedure.

3.2.2. EXCLUSION CRITERIA

Subjects meeting any of the following criteria may not be enrolled in the study:

1. Platelet count \( \geq 100 \times 10^9/L \)
2. Serum creatinine level \( > 200 \mu mol/L \) in case platelet count is \( > 30 \times 10^9/L \) (to exclude possible cases of atypical Hemolytic Uremic Syndrome [aHUS])

---

§§ Of note, the PE administered prior to randomization (PE of unrestricted intensity) may be given prior to signing ICF (as part of standard of care) and may be spread over 2 or more sessions in 24 hours as long as considered part of the 1 intense PE for the treatment of the presenting TTP episode. Note that the maximum time allowed between the start of first PE (i.e., PE administered prior to randomization) and the start of the first PE after randomization (i.e., the first on-study PE) is 24 hours.
3. Known other causes of thrombocytopenia such as (including but not limited to):
   a. Clinical evidence of enteric infection with *E. coli* 0157 or related organism
   b. Atypical HUS
   c. Hematopoietic stem cell, bone marrow or organ transplantation-associated thrombotic microangiopathy
   d. Known or suspected sepsis
   e. Diagnosis of disseminated intravascular coagulation
4. Congenital TTP (known at the time of study entry)
5. Pregnancy or breast-feeding
6. Clinically significant active bleeding or high risk of bleeding (excluding thrombocytopenia)
7. Known chronic treatment with anticoagulant treatment that cannot be stopped (interrupted) safely, including but not limited to:
   a. vitamin K antagonists
   b. heparin or low molecular weight heparin (LMWH)
   c. non-acetyl salicylic acid non-steroidal anti-inflammatory molecules
8. Malignant arterial hypertension
9. Clinical condition other than that associated with TTP, with life expectancy < 6 months, such as end-stage malignancy
10. Have a known hypersensitivity to the active product or any excipient of the study drug.
11. Subjects currently or less than 28 days prior to enrollment in this study, enrolled in a clinical study with another investigational drug or device.
12. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.
13. Subjects who were previously enrolled in a clinical study with caplacizumab and received caplacizumab or for whom the assigned treatment arm is unknown.

3.2.3. REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

3.2.3.1. CRITERIA FOR STUDY DRUG TREATMENT DISCONTINUATION

Temporary discontinuation of study drug should be considered in case the subject develops a severe or serious bleeding. All subjects in the study experiencing bleeding should be treated for the bleeding by the standard medical and/or surgical intervention (also see section 3.3.5). Treatment with study drug should only be restarted when the bleeding has stopped.

*** The exclusion criteria 13 through 16 are assigned in the German-specific ALX0681-C301 protocol version and cannot be re-used in this global ALX0681-C301 protocol version for administrative reasons.
Permanent discontinuation of study drug should be considered in case the subject develops:

- a severe hypersensitivity reaction, as discussed with Sponsor/Medical Monitor
- a severe (including life-threatening) bleeding requiring urgent medical and/or surgical intervention which is accompanied by significantly low vWF and/or FVIII levels which are slow to respond to study drug interruption and replacement therapy

Study drug must be permanently discontinued if any of the following occurs:

- Subjects on study drug treatment experiencing a second exacerbation or a second relapse, or a relapse after an exacerbation, or an exacerbation after a relapse must be discontinued from study drug treatment
- Withdrawal of consent
- Diagnosis of aHUS as confirmed by start of treatment with eculizumab
- Pregnancy or pregnancy planned within the study period
- If unblinding has occurred
- If the Investigator deems it is in the subject’s best interest

Subjects who have to discontinue study drug but are not withdrawing consent for post-treatment FU, should return for an early termination visit and the first and final FU visits to undergo the assessments as specified in the Schedules of Assessments. Subjects on treatment experiencing a second exacerbation or a second relapse, or a relapse after an exacerbation, or an exacerbation after a relapse should return for a “second or subsequent recurrence visit” at the time of initiating the daily PE and the final FU visit to undergo the assessments as specified in the Schedules of Assessments.

For all subjects, every effort should be made to contact the medical monitor prior to discontinuing study drug, where medically feasible. Subjects who are withdrawn will not be replaced, except for subjects who did not receive any administration of study drug.

3.2.3.2. CRITERIA FOR WITHDRAWAL OF SUBJECTS FROM STUDY

Participation in the study is strictly voluntary. A subject has the right to withdraw from the study at any time, for any reason.

Subjects who terminate study participation for reasons of lost to follow-up, informed consent withdrawal, or death will not have any FU assessments.

In the event a subject is discontinued from the study, the medical monitor will be informed.
3.2.3.3. STUDY TERMINATION

If the Sponsor abandons the study prior to commencement of any protocol activities, and/or after IEC/IRB and Competent Authority (CA) approvals have been received, the Investigator or Sponsor must notify the IEC/IRB and CA by letter outlining the reasons for abandonment of the study, as required per national regulations.

At any time during the study, the Sponsor may suspend or terminate the study or part of the study for any reason. If the Investigator plans to suspend or terminate participation in the study, the Investigator will promptly inform the Sponsor and the IEC/IRB and provide them with a detailed written explanation.

Upon study completion, the Sponsor will provide the Investigator, IEC/IRB, and CA with final reports and summaries as required by regulations.

In case of suspension or halt due to safety reasons, the CA and IEC/IRB will be notified immediately and at the latest within the number of days as specified by local regulations after the study is halted, clearly explaining the reasons, and describe follow-up measures, if any, taken for safety reasons.
3.3. TREATMENT OF SUBJECTS

Study drug treatment:

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 the first PE done after randomization; also i.v. bolus of 10 mg caplacizumab (open label) will be given prior to the 1st PE for treatment of a first exacerbation during the 30-day post daily PE period or a first relapse during the treatment extension period (without a prior exacerbation).
- Daily s.c. dose: within 2 hours of completing each daily PE, a s.c. injection of 10 mg study drug will be administered daily throughout the full duration of PE treatment.

For more details on the study drug administration, please refer to section 3.3.5.

It is expected that subjects are hospitalized for the duration of the daily PE period. Exceptions should be discussed with the Medical Monitor.

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. Study drug should be administered at approximately the same time each day. Towards the end of the daily PE period and when hospital discharge is foreseen, subjects (or caregiver) should be trained in the s.c. self-administration of the study drug under the supervision of the Investigator or designee to allow for self-administration when at home. After discharge from hospital, subjects or caregiver will need to be able to self-administer s.c. study drug. For more details, please refer to section 3.3.5.

Treatment extension period
Study drug treatment extension beyond the 30 days will be guided by a number of risk factors for relapse of the presenting TTP episode and must be accompanied by an optimization of the immunosuppressive treatment. Study drug treatment should be extended for subjects who in the opinion of the Investigator have persistent active underlying disease for additional 7-day periods with a maximum of 28 days. In parallel, optimization of the immunosuppressive treatment should be considered at least at the Week 3 visit of the 30-day post-daily PE period and may include reversal of corticosteroid tapering through increase or re-initiation of corticosteroid treatment, or start/continuation of other immunosuppressive treatment such as rituximab (to be used as per standard site practice).

Decision on treatment extension
The decision to extend treatment with additional 7-day periods should be made by the Investigator based on 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. ADAMTS13 activity will be measured weekly and results of these analyses will be communicated to the clinical sites upon availability.

Study drug treatment extension should be stopped when ADAMTS13 activity shows a sustained upward trend of >10% or is stable and there are no other signs and symptoms of disease activity, and at the latest on Day 28 of the study drug treatment extension.

The reason for each weekly extension must be recorded in the electronic Case Report Form (eCRF).

**Exacerbation**

In case of a first exacerbation of the presenting TTP episode, subjects will receive open label caplacizumab together with daily PE irrespective of what the initial treatment allocation was. The blind will not be broken for the initial treatment allocation. Caplacizumab treatment and visit schedule will be the same as during the initial treatment period. In case a subject has subsequent exacerbations, standard of care treatment of daily PE and appropriate immunosuppressive treatment should be initiated as per site practice. There will be no re-initiation of study drug administration for a second or further exacerbation.

**Relapse during the treatment extension period**

In case a subject has a TTP recurrence while still receiving study drug in the treatment extension period and has not had a prior exacerbation, then daily PE should be started as part of standard of care treatment together with appropriate immunosuppressive treatment. Study drug treatment will crossover as open-label caplacizumab irrespective of what the initial treatment allocation was without breaking the blind of the initial treatment assignment. Caplacizumab treatment and visit schedule will be the same as during the initial treatment period, covering i.v. bolus, daily PE (variable duration), 30-days post-daily PE and possible treatment extension. This will apply only for the first relapse. In case of further exacerbation or relapse in the subsequent treatment period, study drug will be discontinued. In case a subject has subsequent relapses, standard of care treatment of daily PE and appropriate immunosuppressive treatment should be initiated as per site practice. There will be no re-initiation of study drug administration for a second or further relapse.

**Relapse during the 4-week FU period**

In case a subject has a first or subsequent TTP relapse in the FU period after completing study drug treatment, standard of care treatment of daily PE and appropriate immunosuppressive treatment should be initiated as per site practice. There will be no re-initiation of study drug administration.
As stated above, there will be no re-initiation of study drug administration for subjects experiencing more than one exacerbation or relapse (or an exacerbation after a relapse or a relapse after an exacerbation).

Subjects on treatment experiencing a second exacerbation or a second relapse, or a relapse after an exacerbation, or an exacerbation after a relapse should return for a “second or subsequent recurrence visit” at the time of initiating the daily PE and the final FU visit to undergo the assessments as specified in the Schedules of Assessments.

### 3.3.1. RANDOMIZATION

After obtaining oral and written informed consent, subjects will be screened according to the inclusion and exclusion criteria and will receive a unique subject identification (ID) number, assigned by IWRS/IVRS.

At randomization, subjects will be randomized to a caplacizumab or placebo arm in a 1:1 ratio, and will receive a randomization number just prior to study drug administration according to the randomization scheme.

Randomization will be stratified by severity of neurological involvement (GSC ≤ 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.

### 3.3.2. IDENTIFY OF STUDY DRUG

The study medication is provided in a kit containing the following components:

- One glass vial containing lyophilized powder for reconstitution (containing either caplacizumab or placebo – see details below).
- One prefilled glass syringe containing solvent for reconstitution (containing WFI).
- One “vial adapter” device to facilitate transfer of the solvent for reconstitution and subsequent recovery of the reconstituted drug.
- One safety needle for s.c. use (please note that a needle for the first i.v. bolus injection is not included in the kit).
- Two alcohol pads.

Further details on drug components:

- Caplacizumab 10 mg – lyophilized powder for solution for injection
  - Presented in ISO 2R glass vial with FluroTec® Butyl stopper filled with lyophilisate containing 12.5 mg caplacizumab and excipients (see below).
  - Active substance: caplacizumab (anti-vWF Nanobody).
- Activity: caplacizumab is directed towards the A1 domain of vWF and specifically inhibits the interaction of (UL)vWF with the platelet GPIb receptor glycoprotein, thereby preventing (UL)vWF-mediated platelet aggregation.
- Strength: One vial contains 12.5 mg of caplacizumab and comprises an overfill to compensate for losses during reconstitution and liquid transfer. After reconstitution using the supplied kit components, the resulting solution contains 11.1 mg/mL of caplacizumab (the total volume of the reconstituted solution is slightly more than 1 mL because the lyophilisate also takes up a certain volume). Taking into account losses during transfer from vial to syringe, the nominal administered dose is 10 mg when injecting the entire contents (nominally 0.9 mL) of the syringe.
- Dosage form: powder for solution for injection; reconstitution with WFI yields solution for injection.
- Route of administration: i.v. (first dose and prior to the first PE done after a first exacerbation or relapse), s.c. (all subsequent doses).

• Placebo - lyophilized powder for solution for injection:
  - Active substance: not applicable, the composition of placebo is the same as that of active IMP, without the active ingredient.
  - Activity, strength: not applicable.
  - Dosage form: powder for solution for injection; reconstitution with WFI yields solution for injection.
  - Route of administration: i.v. (first dose and prior to the first PE done after a first exacerbation or relapse), s.c. (all subsequent doses).

3.3.3. DRUG ACCOUNTABILITY

The Pharmacist or his/her designee is responsible for acknowledge receipt of each shipment of study drug and will verify the condition and quantity of the study drug.

At study site, the study drug will be kept in a locked and secured storage facility accessible only to those authorized by the Investigator to dispense the study drug. The responsible person will keep an inventory. This will include the quantity of study drug received for the study and a record of the materials that are dispensed, to whom (subject number) and when.

At all ambulatory study drug administrations, the subject will note information with regard to the study drug administration (e.g., the timing, kit number, injection location) in the patient diary. All used and unused vials and syringes should be returned to the site at the...
following clinic visit. These should not be used for future administrations (including administrations at the study site). The subject must bring his/her patient diary to all study visits. At each visit, site personnel will review the patient diary. At each visit, site personnel will record the new information in the eCRF (also see section 3.3.5), and return the diary to the subject. Subjects will be instructed to return the completed diary at the latest at their final visit.

The pharmacist, the Investigator and/or designated personnel will conduct a final inventory of the study drug supply and will record the results of this inventory in the Drug Accountability Form. Upon Sponsor approval, all study drug supplies will be returned to the depot, or will be locally destroyed according to local regulations and site procedures.

Instructions for drug accountability are available in the manual concerning study drug.

### 3.3.4. STUDY DRUG HANDLING

Instructions for study drug receipt, handling, storage and administration are available in the manuals concerning study drug and IWRS/IVRS.

**Packaging and Labeling**

The study drug will be labeled with at least study number, storage conditions, dosing instructions, Sponsor’s name, address and telephone number in accordance with Annex 13 of EudraLex Volume 4 requirements and local regulations.

One IMP kit contains 1 vial of study drug (1 syringe with water for injection, 1 vial adapter, 1 safety needle for s.c. injection and 2 alcohol pads). Note that a needle for the first i.v. bolus injection is not included in the kit and an appropriate i.v. needle available at the site should be used.

**Storage**

The IMP kit will be provided under refrigerated conditions and must be stored in a secure, limited-access location under the storage conditions specified by the Sponsor.

The IMP kit must be refrigerated at 2°C to 8°C (35.6 °F to 46.4 °F) and should be stored in the secondary packaging until administration. It should not be frozen or shaken.

Site storage conditions should be monitored by the site personnel and reviewed by the monitor during site visits. Deviations from the storage requirements must be documented and reported to the Sponsor, according to the instructions provided in the manual concerning study drug.
Verbal and written instructions for proper storage, handling, and administration of the study drug will be given to the subject, and will include instructions to contact the study site immediately if they experience problems with the study drug and/or administration.

**Dispensing**

The Investigator or qualified designee(s) will dispense (via IWRS/IVRS) study drug to subjects who have met the entry criteria. Clinical supplies may not be used for any purpose other than that which is stated in this protocol.

For ambulatory study drug administrations, enough IMP until the next visit will be provided for the subjects to take home. Note: On days a visit to the study site is planned, subjects should not self-administer study drug prior to their visit. Study drug administration will be done after all visit assessments have been performed.

**Product Quality Complaint**

Any malfunctioning has to be communicated by completion of the Sponsor’s IMP Notification Form and the malfunctioning IMP kit has to be returned to the Sponsor or its designee upon Sponsor’s request.

### 3.3.5. STUDY DRUG ADMINISTRATION

Detailed instructions for study drug administration are available in the manual concerning study drug.

**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 PE (i.e., prior to the first session in case PE is given over multiple sessions within 24 hours) by a health professional; also i.v. bolus of 10 mg caplacizumab (open label) will be given prior to the 1st PE for treatment of a first exacerbation during the 30-day post daily PE period or a first relapse during the treatment extension period (without a prior exacerbation).
- Daily s.c. dose: From Day 1 and throughout the daily PE period, study drug is to be administered daily s.c. within 2 hours after end of PE (i.e., after the last session in case PE is given over multiple sessions within 24 hours). In case of tapering, study drug should be administered as specified above on days PE is done and at approximately the same time as on the day before on days when there is no PE. Tapering of PE after platelet count normalization, defined as reducing its frequency to less than once per day, is strongly discouraged and if considered, should be discussed with the Medical Monitor.

It is expected that subjects are hospitalized for the duration of the daily PE period. Exceptions should be discussed with the Medical Monitor.

At the clinical site, subjects will be observed in order to assess adverse reactions.
30-day post-daily PE period
After subjects are discharged from hospital, subjects should self-administer study drug (training will be given during hospitalization on how to prepare and s.c. inject the study drug). Subjects will be instructed to administer study drug at approximately the same time during the day and will be requested to be accompanied by a second person during administration and for a period of 30 minutes afterwards. In case the subject is unable or unwilling to self-administer, study drug may be administered by a caregiver who has been trained at the site.

For all study drug injections, study drug administrations should occur approximately 24 hours apart with a minimum of 12 hours apart.

Note: On days a visit to the study site is planned, subjects should not self-administer study drug prior to their visit. Study drug administration will be done after all visit assessments have been performed.

Subcutaneous injections are to be performed in the abdominal region. As injections are to be performed daily, injections need to be performed in a different quadrant than the quadrant in which study drug was injected the previous days. Also note that the area of administration needs to be evaluable for local skin reaction. The location used for the administrations will be noted as a guide/memory aid for the site and for the subject for appropriate rotation of next dose administration.

In case of an injection site reaction, it should be followed-up and documented in which exact quadrant the skin reaction appears.

Information with regard to study drug administration to be recorded in the eCRF will include: time of administration, kit number, route of administration.

Of note, subjects will be provided with an “In case of emergency card”, which will contain at least following information: study number, indication of study drug as “anti-vWF agent”, Investigator name and Investigator/site emergency contact details.

Missed Doses
For missed doses during hospitalization, study drug should be administered as soon as possible after the protocol-defined time window and separated by at least 12 hours of the next administration. If the next administration is due within the next 12 hours, then the missed dose should not be given. The next administration should be given at the usual time.

If a subject misses an ambulatory dose, a new injection should be performed as soon as the subject remembers during that day and separated by at least 12 hours of the next
administration. If the next administration is due within the next 12 hours, then the missed
dose should not be given. The next administration should be given at the usual time.

**Management of Overdose**

Given the rapid clearance by the kidney of unbound study drug due to its relatively small
size (28 kDa), the risk of overdose is considered (partially) self-limiting. In case of
overdose, there is a potential for increased risk of bleeding based on the pharmacological
action of study drug. Subjects should be monitored closely for signs and symptoms of
clinically relevant bleeding in case of actual or suspected overdose. In case of clinically
relevant bleeding associated with (suspected) overdose, appropriate treatment for bleeding
according to standard practice should be initiated and treatment with study drug must be
interrupted. In addition, plasma levels of vWF:Ag and FVIII:C may be determined locally to
assess possible need for treatment with FVIII or FVIII/vWF concentrates. Treatment with
study drug should only be restarted when the bleeding has stopped. The PE treatment, if
applicable, should continue as clinically indicated.

In case of (suspected) overdose with no clinically relevant bleeding observed, study drug
administration may continue after the next PE or next daily dose as applicable.

Note that permanent discontinuation of study drug should be considered for subjects who
develop a severe bleeding requiring urgent medical and/or surgical intervention which is
accompanied by significantly low vWF:Ag and/or FVIII:C levels which are slow to respond to
study drug interruption and replacement therapy (also see section 3.2.3).

### 3.3.6. OTHER TREATMENT/MEDICATION ADMINISTERED IN THE STUDY

**Standard of care treatment:**

- 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. PE
[see section 3.1.1] should have been started prior to randomization with volume and
intensity at the discretion of the Investigator. PE duration and whether desired volume is
exchanged in one or more sessions within 24 hours is at the discretion of the
Investigator, according to standard site practice. Note that the maximum time allowed
between the start of first PE (i.e., PE administered prior to randomization) and the start
of the first PE after randomization (i.e., the first on-study PE) is 24 hours.
- Once the platelet count is ≥ 150 x 10⁹/L, daily PE should continue for at least 2 days.
- Tapering of PE after platelet count normalization is strongly discouraged and if
considered, should be discussed with the Medical Monitor.

Information with regard to PE to be recorded in the eCRF will include: start time and end
time of that day’s PE, number of sessions for the desired plasma volume, plasma volume (in L and in multiple of total plasma volume), plasma product name, plasma exchange technique, and specification with regard to single or pooled donor.

**Corticosteroid treatment:**
Corticosteroid treatment should be initiated/continued with (methyl)prednisolone or (methyl)prednisone regimen of at least 1 mg/kg/day i.v. or p.o. during the daily PE period and continued for the 1st week after end of daily PE. Afterwards corticosteroids may be tapered at the discretion of the Investigator, with the aim of being corticosteroid-free by Day 30 after cessation of daily PE as clinically indicated. At the Week 3 visit of the 30-day post-daily PE period, corticosteroid tapering should be reassessed based on ADAMTS13 activity data of the previous 2 visits and other clinical signs of underlying disease.

**Other immunosuppressive treatment:**
The use of other immunosuppressive treatment (e.g., rituximab) is allowed per standard site practice but should be considered in light of protocol required corticosteroid treatment.

### 3.3.7. CONCOMITANT THERAPY

**Disallowed medication:** desmopressin promotes the release of vWF and is not indicated in patients with TTP as it may worsen the condition.

Throughout the study, the Investigator may prescribe any concomitant medication needed as supportive care, except for desmopressin. Medications associated with the occurrence of TTP such as but not limited to clopidogrel and ticlopidine should be avoided during this study but may be used at the discretion of the Investigator, and should be used with caution.

Note that existing use of anticoagulant treatment (such as vitamin K antagonists, heparin or LMWH, or non-acetyl salicylic acid non-steroidal anti-inflammatory molecules) needs to be stopped prior to the subject’s inclusion in the study but if needed can be re-started at the discretion of the Investigator and should be used with caution (due to an increased bleeding risk).

Any concomitant medication taken during the study (i.e., from signing of ICF until the subject’s last visit) must be recorded in the eCRF. Items to be recorded concerning concomitant medication include: dose and units of dose, start and end date, administration frequency, route of administration, therapeutic indication, brand name (or generic name if brand name is not available).
Contraceptives
Female subjects of childbearing potential (excluding postmenopausal women, sterilized, ovariectomized, and hysterectomized women) must agree to use a generally accepted adequate contraceptive method or should agree upon continuous abstinence from heterosexual contact from screening until at least 2 months after last study drug administration.
No additional contraceptive method is needed in case of surgical sterilization (at least 3 months prior to screening), hysterectomy, or a partner who has been vasectomized (at least 3 months prior to screening).

Male subjects are not obliged to use a contraceptive method specifically for this study. The influence of caplacizumab treatment on male reproductive organs has been studied in non-human primates and no influence was seen on parameters tested including histopathology and sperm quality. Caplacizumab is a biotherapeutic and is not expected to pass the blood-sperm barrier or enter cells, therefore a risk to genetic material (genotoxicity) can be excluded.

If additional local regulations apply, contraceptives should be used consistent with these.

3.3.8. TREATMENT COMPLIANCE

To ensure treatment compliance, study drug will be administered by a health care professional (or under supervision of a health care professional in case of training for self-administration) during the hospital stay, except for ambulatory study drug administration.

For study drug administrations at the clinical site, the exact times of study drug administration will be recorded in the eCRF. If a dose is missed, the reason for the not-dosed IMP should be recorded in the eCRF. Compliance will be further confirmed by bioanalytical assessment of caplacizumab in plasma samples.

For ambulatory study drug administration, each subject will be provided with a patient diary to collect information (e.g., the timing, kit number, location of injection) of each study drug administration. For more information on the study patient diary, please refer to section 3.3.3.
3.4. ASSESSMENTS

3.4.1. TIMING OF ASSESSMENTS

Study related procedures will be done after (informed) consent has been obtained after which each subject will be assigned a unique subject ID number.

AEs and concomitant medications will be recorded from the study inclusion date (ICF signed) to the subject’s last visit.

3.4.1.1. ELIGIBILITY PROCEDURES

A signed and dated ICF, must be obtained before any study-specific procedures are performed. The ICF will foresee retrospective collection of certain data related to the diagnosis of the TTP episode for which subject is included in the study (including results of ADAMTS13 activity tests performed as per standard of care upon admission). These observations will have preceded the ICF signing.

The screening process begins when the subject or his/her representative signs the ICF and continues until randomization.

At screening, subjects will be screened according to the inclusion and exclusion criteria (section 3.2) and have other assessments performed as specified in the Schedules of Assessments. The results from the screening procedures needed to evaluate eligibility must be available prior to randomization. Results from standard of care procedures performed before signing of the ICF may be used for screening.

Subjects discontinuing, for any reason, without completing all screening evaluations successfully and all subjects completing all screening evaluations successfully but who discontinue prior to randomization, will be considered “screen failures”.

Data of all subjects screened will be collected in the eCRF in order to assess the numbers and characteristics of the excluded subjects, and the reasons for their exclusion.

For details with regard to randomization, please refer to section 3.3.1.

Assessments and procedures should be performed as outlined in the Schedules of Assessments.

Screening and baseline can be on the same day as long as the above applies.
Screening
- Obtain informed consent
- Review of eligibility criteria
- Medical history, including TTP history (and ADAMTS-13 activity levels at admission, if available)
- GCS
- Bleeding assessment
- Platelet count, blood smear, serum creatinine (local lab)
- Pregnancy test (urine or blood)
- Demographics
- Concomitant medication
- AEs

Day 1
- Randomization
- Study drug administration††† and PE + corticosteroids
- Platelet count, blood smear
- LDH, serum creatinine, cTnI, ADAMTS13 activity
- Complement factors C5a and C5b-9
- Assessment of the neurological system (including coma, stupor, seizures, disorientation/confusion, hemiparesis/-plegia, focal deficit, agitation, dysarthria)
- Cognitive assessment (standardized mini mental state examination [SMMSE])
- Clinically significant TTP event
- AEs, safety laboratory parameters, physical examination, electrocardiogram (ECG), vital signs
- Concomitant medication
- Bleeding assessment
- PK, PD parameters (vWF, FVIII and RICO)
- Immunogenicity (ADA)

3.4.1.2. ASSESSMENT PERIOD

During the daily PE period, assessments should be performed at approximately the same time with frequency as detailed in the Schedule of Assessments.

††† Note that study drug administration can occur on Day 2 as a time window of 24 hours is permitted between the start of first PE (i.e., PE administered prior to randomization) and the start of the first PE after randomization (i.e., the first on-study PE), resulting in a possible time window between randomization and first study drug administration.
After the end of daily PE, subjects will return for ambulatory visits planned once weekly. All weekly visits should occur at the indicated week ± 1 day. Of note, as tapering of PE after platelet count normalization is strongly discouraged, visits in the 30-day post-daily PE period are linked to end of daily PE (not taking into account possible tapering).

All assessments will be performed as specified in the Schedules of Assessments.

Unscheduled visits may be planned to assess, confirm, and follow up on clinically relevant AEs or laboratory abnormalities. Findings made during these unscheduled visits should be reported in the designated sections of the eCRF.

**Missed visits:**
All attempts should be made to follow the original visit schedule. If a subject misses a visit, he/she should come to the site as soon as possible after the planned missed visit.

### 3.4.1.3. FOLLOW-UP

Subjects who have received all study medication through the end of fixed treatment visit of the 30-day post-daily PE period and those with study drug treatment extensions of 1 to maximum 4 weeks should return for FU visits 7 and 28 days after last study drug administration.

**Discontinuation of Study Drug Administration**
Subjects who have to discontinue study drug but are not withdrawing consent for post-treatment FU, should return for an early termination visit and the first and final FU visits to undergo the assessments as specified in the Schedules of Assessments.

**Termination of Study Participation**
Subjects who terminate study participation for reasons of lost to follow-up, informed consent withdrawal, or death are not expected to return for any FU visit.

### 3.4.2. DEMOGRAPHICS AND MEDICAL HISTORY

Demographic and medical history data will be collected at screening.

Demographic data will include (but are not limited to): year of birth, date of ICF signed, gender, race (if allowed), and ethnicity (if allowed).

Both general and TTP-specific medical history, including ADAMTS-13 activity levels at admission (if available), will be collected.
### 3.4.3. ASSESSMENTS OF EFFICACY

#### 3.4.3.1. ASSESSMENT OF PLATELETS AND BLOOD SMEAR

Blood samples for assessment of platelets and blood smear will be collected at the time points indicated in the Schedules of Assessments.

In general, blood samples will be collected via an indwelling i.v. catheter or by direct venipuncture. Details on method, sampling and processing procedures will be provided in a separate Lab Manual. Samples for platelet counts and blood smear will be assessed by the local laboratory.

#### 3.4.3.2. CLINICALLY SIGNIFICANT TTP EVENT

Clinically significant TTP events will be assessed at the time points indicated in the Schedules of Assessments.

Date of onset, severity, and outcome of following parameters will be collected:

- Neurological
- 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)

#### 3.4.3.3. NEUROLOGICAL ASSESSMENT

At screening, the neurologic status of the subjects will be assessed using the GCS, a neurological scale that measures the conscious state of the subject. The GCS is to be assessed within 2 hours prior to randomization. The best eye, verbal and motor responses will be scored according to the scale, and the separate scores added up to obtain the final
score, ranging from 3 to 15. An example of the Glasgow Coma Scale is provided in Appendix 9.1.

At all other time points defined in the Schedules of Assessments, the neurological status of the subjects will also be assessed by examination of the neurological system and presence (including severity) or not of the following: coma, stupor, seizures, disorientation/confusion, hemiparesis/-plegia, focal deficit, agitation, and dysarthria (primarily physical examination and as per standard of care: electroencephalogram [EEG], magnetic resonance imaging [MRI], ...).

In case coma or stupor are present, the GCS needs to be completed.

The Investigator will determine whether the observed abnormality is to be considered as a clinically significant TTP event.

3.4.3.4. COGNITIVE ASSESSMENT

The cognitive status of the subjects will be assessed using the SMMSE [32] according to the time points defined in the Schedules of Assessments.

The SMMSE is a validated test used to examine the cognitive mental status of a subject. It can be used to screen for cognitive impairment, to estimate the severity of cognitive impairment at a given point in time and to follow the course of cognitive changes in an individual over time. 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 (write a sentence, construct a diagram and follow a three-step verbal command). The SMMSE is a brief 30-point questionnaire which can be completed in approximately 10 minutes. Scores between 26-30 are considered normal in the general population; subjects with scores between 20-25 may have mild cognitive impairment; those who score between 10-20 have moderate cognitive impairment; scores between 0-9 denote severe cognitive impairment. Age and level of education affect the SMMSE. Therefore, the normal value is corrected for degree of schooling and age (patient-specific norms on the basis of age and educational level are available). If the subject is unable to complete the test due to a physical handicap (e.g. blindness), the value of the questions which cannot be completed is subtracted from 30, and the resulting number is used as the denominator for the test score. If a denominator of less than 30 is used, the nature of the physical handicap should be indicated on the form. If a subject is unconscious, the score is 0/30.
3.4.3.5. **ASSESSMENT OF CARDIAC ISCHEMIA AND ARRHYTHMIA/ CONDUCTION ABNORMALITY**

Cardiac ischemia/infarction (cardiac troponin and/or ECG) and arrhythmia/conduction abnormality on ECG. The Investigator will determine whether the observed abnormality is to be considered as a clinically significant TTP event.

For information on ECG, please refer to section 3.4.8.4.

3.4.3.6. **ADJUDICATION OF MAJOR THROMBOEMBOLIC EVENTS AND TTP-RELATED DEATH**

If a potential major thromboembolic event (e.g., cerebrovascular accident, myocardial infarction, pulmonary embolism or deep venous thrombosis [DVT]) or TTP-related death occurs in a subject, the Investigator will be requested to provide additional information (e.g., onset and duration of symptoms, physical examination findings, reports of magnetic resonance imaging and/or computerized tomography scans, ECGs, laboratory results, lung ventilation/perfusion scans, Doppler ultrasonography, post-mortem report) for adjudication by a blinded independent committee. As this reporting only occurs in cases where additional information is needed, it is not included in the Schedule of Assessments.

3.4.4. **PHARMACOKINETIC ASSESSMENTS**

3.4.4.1. **SAMPLE COLLECTION AND HANDLING**

Throughout the study, blood samples of approximately 2.0 mL will be taken for analysis of caplacizumab concentrations, according to the time points defined in the Schedules of Assessments.

The blood samples will be collected via an indwelling i.v. catheter or by direct venipuncture. For further details on sample collection, shipment, storage and processing, please refer to a separate Lab Manual.

3.4.4.2. **BIOANALYSIS**

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.
3.4.5. PHARMACODYNAMIC ASSESSMENTS

3.4.5.1. SAMPLE COLLECTION AND HANDLING

Throughout the study, separate blood samples of approximately 3.5 mL will be taken for analysis of RICO, vWF:Ag, and FVIII:C levels, according to the time points defined in the Schedules of Assessments.

All PD blood samples will be taken via an indwelling i.v. catheter or by direct venipuncture. For further details on sample collection, shipment, storage and processing, please refer to a separate Lab Manual.

Note that analysis of RICO is to be performed by the central lab. In order to maintain the blind, it may not be performed locally.

3.4.5.2. BIOANALYSIS

Determination of RICO, vWF:Ag, and FVIII:C levels in plasma will be done by a validated method. Bioanalytical procedures will be described in a separate Bioanalytical plan.

3.4.6. ASSESSMENT OF DISEASE RELATED MARKERS

3.4.6.1. SAMPLE COLLECTION AND HANDLING

Throughout the study, separate blood samples will be taken for analysis of ADAMTS13 activity and following biomarkers for organ damage: LDH, Troponin I, and serum creatinine, according to the time points defined in the Schedules of Assessments:

- for analysis of ADAMTS13 activity, a sample of approximately 4.5 mL.
- for analysis of LDH, and serum creatinine, a sample of approximately 2.5 mL.
- for analysis of Troponin, a sample of approximately 2.5 mL.

All blood samples for disease-related markers will be taken via an indwelling i.v. catheter or by direct venipuncture. For further details on sample collection, shipment, storage and processing, please refer to a separate Lab Manual.
3.4.6.2. **BIOANALYSIS**

Determination of ADAMTS13 activity, LDH, Troponin I, and serum creatinine will be done by a validated method. Bioanalytical procedures will be described in a separate Bioanalytical plan.

3.4.7. **IMMUNOGENICITY**

3.4.7.1. **SAMPLE COLLECTION AND HANDLING**

To assess systemic immunogenicity of caplacizumab, blood samples of approximately 5 mL will be collected at the time points defined in the Schedules of Assessments for the determination of ADA.

All immunogenicity blood samples will be taken via an indwelling i.v. catheter or by direct venipuncture. For further details on sample collection, shipment, storage and processing, please refer to a separate Lab Manual.

In case of a severe and/or serious hypersensitivity reaction, an additional blood sample should be collected as soon as possible after the start of the event (blood volume: 8 mL) to characterize the reaction. No human DNA or RNA analysis will be performed. The sample will be shipped to the central laboratory.

3.4.7.2. **BIOANALYSIS**

Determination of ADA will be done using a validated screening, confirmation and titration ADA bridging assay, with further characterization by modified ADA (mADA) assay and potentially with a neutralizing Antibody (nAb) assay. The immunogenicity data will be processed according to a dedicated Bioanalytical Analysis plan.

3.4.8. **ASSESSMENTS OF SAFETY**

Safety and tolerability assessments consist of AEs (including serious adverse events, hypersensitivity reactions, AEs of interest [bleeding-related events]), as well as laboratory assessments, vital signs, physical examinations, and ECGs. The time points are defined in the Schedules of Assessments.

As indicated above, in case of a severe and/or serious hypersensitivity reaction, an additional blood sample should be collected as soon as possible after the start of the event to characterize the reaction.
3.4.8.1. ADVERSE EVENTS

General information on evaluation and reporting of AEs is provided in section 3.5.

All AEs occurring between the time a signed and dated ICF is obtained until completion of the subject’s last visit must be documented in the source documents and the eCRF. For adverse events related to injection site reactions, documentation must also include the location of the event.

Criteria for determining whether an abnormal objective test finding (e.g., laboratory, vital signs), a complication of a protocol mandated procedure (e.g., blood draw, injection of study drug), or a change in physical examination findings should be reported as an AE are as follows, but not limited to:

1. Result/finding is associated with accompanying clinical signs and symptoms (new onset or aggravated in severity of frequency from baseline condition), and/or
2. Result/finding requires extra diagnostic testing (other than diagnostic exclusion tests) or medical/surgical intervention, and/or
3. Result/finding would require a change in study drug dosing or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
4. Result/finding leads to any of the outcomes included in the definition of an SAE, and/or
5. Result/finding is considered to be an AE by the Investigator.

Any abnormal test result that is determined to be an error and merely repeating an abnormal test does not require reporting as an AE.

Adverse Event of Interest
In the AE record, the Investigator will need to indicate whether the AE is considered an event indicative of an increased bleeding tendency, manifesting as e.g., overt bleeding, bruising, petechiae, etc.

Exacerbations/Relapses
All exacerbations and relapses must be considered covered by the “another medically important serious event” criterion and must be reported as SAE.
3.4.8.2. LABORATORY ASSESSMENTS

Blood samples for clinical laboratory analyses will be collected at the time points indicated in the Schedules of Assessments.

All samples will be analyzed by a central laboratory, except for pregnancy testing, screening samples for creatinine assessment, and samples for platelet count.

In general, blood samples will be collected via an indwelling i.v. catheter or by direct venipuncture. Details on method, sampling and processing procedures will be provided in a separate Lab Manual.

The following tests will be included in the clinical laboratory analysis:

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

In female subjects of childbearing potential, a pregnancy test will be performed at screening.

Complement C5a and C5b-9 levels will be evaluated on Day 1 of the initial daily PE period only.

Laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the Investigator, except for values of samples for complement assessment.

All clinically significant laboratory findings will be recorded as AEs in the eCRF (also see section 3.4.8.1).

In the event of unexplained or unexpected clinical laboratory test values, the test(s) will be repeated and followed up until the results have returned to the normal range and/or an adequate explanation for the abnormality is found.
3.4.8.3. **VITAL SIGNS**

Vital signs parameters (assessed after 5 min in supine position) will be measured at the time points indicated in the Schedules of Assessments. All parameters will be recorded in the eCRF.

The following vital signs parameters will be assessed: blood pressure, pulse, and temperature.

Height and weight will be assessed on Day 1 of the initial daily PE period only.

Clinically relevant abnormalities emerging during the study should be recorded as AE in the eCRF.

3.4.8.4. **ELECTROCARDIOGRAM**

12-lead ECGs assessed after 5 min in supine position will be recorded at the time points indicated in the Schedules of Assessments.

ECG assessment will include the Investigator’s conclusion on the ECG profile (including diagnosis and indicated as “normal”, “abnormal, not clinically significant”, or “abnormal, clinically significant”).

Clinically significant abnormalities emerging during the study should be recorded as AE in the eCRF. The Investigator will also determine whether the observed abnormality is to be considered as a clinically significant TTP event.

3.4.8.5. **PHYSICAL EXAMINATION**

A complete physical examination will be performed at the time points indicated in the Schedules of Assessments. Of note, additional physical examinations may be performed upon the discretion of the Investigator (e.g., in case of AEs).

Physical examination should include at least the following body systems:

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

Physical examination will be recorded as “normal”, “abnormal, not clinically significant” or “abnormal, clinically significant” at every assessment. A new finding or a change of a finding that is judged as an undesirable medical event (including all findings recorded as “abnormal, clinically significant”) shall be reported as an AE.

3.4.9. OTHER ASSESSMENTS

3.4.9.1. IMP KIT USABILITY

On a weekly basis, the study staff will ask the patient if he/she (or the caregiver, if applicable) encountered any issues with preparation and/or administration of the study drug using the different components. In case of issues, information will be gathered via the IMP Notification Form that should be faxed/emailed to the sponsor.

3.4.9.2. HOSPITALIZATION

Following information on hospitalization is to be collected:
- date of admission and discharge of hospitalization
- date of admission and discharge to ICU (if applicable)
- date of diagnosis

3.4.10. TOTAL BLOOD VOLUME

At every study visit, approximately 35 mL of blood will be collected. The total amount of blood taken during the study will vary depending on the study duration (determined by the course of the presenting TTP episode and the occurrence of exacerbations and/or relapses).

The anticipated study duration is approximately 2 months up to maximum 6 months (in case of treatment extension and exacerbation or relapse). The total volume of blood taken during the study will be approximately 320 mL for a subject with a 2 month study duration and 600 mL for a subject with the maximum study duration of 6 months.

If necessary, in order to obtain additional information to ensure safety to the subject, additional blood (and urine) samples may be taken at the discretion of the Investigator. Due to this possibility, the blood volumes presented in the following tables are provided as best estimations.
Samples that remain, after protocol-specific assessments have been performed, may be used by the Sponsor for further exploratory work in the context of the development of caplacizumab or evaluation of TTP (only if permitted per local regulations). These samples may be kept for up to 5 years after the end of the study. No human DNA or RNA analysis will be performed.

### 3.4.11. Appropriateness and timing of measurements

The assessments which will be made in this study are standard and generally recognized as reliable, accurate, and relevant.

The timing of all assessments is detailed in the [Schedules of Assessments](#).

During the daily PE period, samples for PK, PD, disease-related markers and safety will be obtained on the day itself and prior to PE (for Day 1, i.e., prior to the i.v. dose administration).

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) 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 all other assessments have been performed (and during the daily PE period, s.c. study drug should be dosed after end of the day’s PE).
3.5. ADVERSE EVENT EVALUATION AND REPORTING

3.5.1. ADVERSE EVENTS

AE definitions will be followed as stated in the “Note for Guidance on clinical safety data management: definitions and standards for expedited reporting” (International Conference on Harmonization [ICH] topic E2A).

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not considered related to that medicinal (investigational or non-investigational) product.

This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities.

In differentiating between medical history and AEs, the following points will be considered:

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present up to the timing of signing of informed consent are recorded as medical history (e.g., seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, but with unchanged severity, are recorded as medical history (e.g., allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as AEs.

All AEs will be reported from the time a signed and dated ICF is obtained until completion of the subject’s last visit.

A TEAE is any AE temporally associated with the use of study drug, whether considered related to the study drug or not. TEAEs are recorded from the start of study drug administration, until completion of the subject’s last visit.

It is the responsibility of the Investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation, and by routine
open questioning (e.g., "How have you felt since I saw you last?"; "Is there anything new that you wish to discuss").

All AEs will be assessed by the Investigator and recorded in the patient medical records and on the AE eCRF page. AE entry should indicate time of onset and end time and rating of the seriousness (see section 3.5.2), severity (see section 3.5.1.1), and outcome (see section 3.5.1.2) of the AEs, relationship to study drug, PE, and corticosteroids (see section 3.5.1.3), action taken regarding study drug (see section 3.5.1.4), and concomitant therapy taken for the AE.

The Investigator will judge upon the severity of the AEs and relation to study drug and study procedures.

### 3.5.1.1. AE SEVERITY

The severity of AEs will be rated on a 3-point scale:
- Mild: discomfort noticed but no disruption of normal daily activity
- Moderate: discomfort sufficient to reduce or affect normal daily activity
- Severe: incapacitating with inability to work or perform normal daily activity

It is emphasized that the term severe is a measure of intensity: a severe AE is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

Please refer to the Common Terminology Criteria for Adverse Events (CTCAE v4.0) as guidance for assessment of severity of laboratory abnormalities.

### 3.5.1.2. OUTCOME

The outcome of the AE is to be documented as follows:
- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown
3.5.1.3. RELATION TO DRUG OR STUDY PROCEDURES

The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the eCRF.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question. Possible answers are:

- Unlikely/Not related
- Possibly related
- Related
- Not applicable

Note that only AEs starting after administration of study drug can be assigned a causal relationship between the AE and study drug administration. For AEs starting prior to study drug administration, causal relationship between the AE and study drug should be not applicable.

Assessment of causal relationship of any AE to PE or use of corticosteroids can be completed with:

- Yes
- No

3.5.1.4. ACTION TAKEN REGARDING STUDY DRUG

Any action taken regarding the study drug is to be documented using following categories:

- Dose not changed
- Drug interrupted
- Drug withdrawn
- Not applicable
- Unknown

3.5.2. SERIOUS ADVERSE EVENTS

An SAE is any untoward medical occurrence that at any dose meets any of the following conditions:

- Results in death.
• Is life-threatening: the subject is at risk of death at the time of the event. It does not refer to an event that hypothetically might cause death if it were more severe.

• Requires in-patient hospitalization or prolongation of existing hospitalization; an AE associated with a hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:
  - The admission results in a hospital stay of less than 12 hours.
  - The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study).
  - The admission is not associated with an AE (e.g., social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of “medically important” and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

• Results in persistent or significant disability/incapacity. Disability means a substantial disruption of a person’s ability to conduct normal life’s functions.

• Results in a congenital anomaly/birth defect.

• Is another medically important serious event as judged by the Investigator, or is defined as requiring intervention to prevent one of the outcomes listed in the definition above (including suspected transmission of an infectious agent by a medicinal product should be reported as an SAE). Other examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. Any AE is considered an SAE if it is associated with clinical signs or symptoms judged by the Investigator to have a significant clinical impact.

All exacerbations and relapses must be considered covered by the “another medically important serious event” criterion and must be reported as SAE.

A treatment-emergent SAE is any SAE temporally associated with the use of study drug, whether considered related to the study drug or not.

The Investigator or clinical site personnel should notify the contract research organization (CRO) of all SAEs, regardless of relationship to the study drug, within 24 hours of clinical site personnel becoming aware of the event (see Investigator Site File). The Investigator will provide the initial notification by faxing a completed “SAE Notification Form”, which must include the Investigator’s assessment of the relationship of the event to study drug, and must be signed by the Investigator.
The first report of an SAE may also be made by telephone. The Reporter must provide the minimal information: i.e., reporter identification, study number, year of birth, medication code number, period of intake, nature of the AE, and relation to study drug.

This report of an SAE by telephone must always be confirmed by a written, more detailed report (the SAE Form) to be completed and signed by the Investigator.

Follow-up information, or new information regarding an ongoing SAE, must be provided promptly to the contacts provided in the Investigator Site File.

The SAE should also be recorded in the eCRF. Any medications necessary for the treatment of the SAE must be recorded on the concomitant medication section of the eCRF.

SAEs that begin after the subject’s participation in the study is complete, but that the Investigator considers to be related to study drug, should be reported to the CRO/Sponsor at any time.

### 3.5.3. SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTIONS

Unexpected adverse reactions are adverse reactions of which the nature or severity is not consistent with the applicable product information (as described in the Reference Safety Information, provided in the Investigator’s Brochure).

The CRO will report expedited the following SUSARs to the IEC/IRB on behalf of the Sponsor:

- SUSARs that have arisen in the current clinical study that was assessed by the IEC/IRB.
- SUSARs that have arisen in other clinical studies of the same Sponsor and with the same study drug and that could have consequences for the safety of the subjects involved in the current clinical study that was assessed by the IEC/IRB.

The CRO will report expedited all SUSARs to the relevant CA on behalf of the Sponsor.

The Sponsor (or the CRO on behalf of the Sponsor) will also report to all concerned Investigators all SAEs that are unlisted (unexpected) and associated with the use of the drug.

The expedited reporting will occur no later than 15 calendar days after the Sponsor (or the CRO on behalf of the Sponsor) has first knowledge of the adverse reactions.

For fatal or life-threatening cases the term will be maximal 7 calendar days for a preliminary report with another 8 days for completion of the report.
3.5.4. REPORTING OF ADVERSE EVENTS

AEs reporting, including SUSARs, will be carried out in accordance with applicable local regulations. For reported deaths, the Investigator should supply the Sponsor and the IEC/IRB with any additional requested information (e.g., autopsy reports and terminal medical reports).

After termination of the clinical study (last subject last visit in the study), any unexpected safety issue that changes the risks benefit analysis and is likely to have an impact on the subjects who have participated in it, will be reported by the Sponsor as soon as possible to the competent authority(ies) concerned together with proposed actions.

3.5.5. FOLLOW-UP OF ADVERSE EVENTS

AEs will be handled according to common clinical practice. If necessary, in order to obtain additional information to ensure safety to the subject, additional blood and urine samples may be taken at the discretion of the Investigator. Information relative to other means of investigational diagnostics used in relation to the AE will also be communicated.

AEs are recorded from signing the ICF until completion of the subject’s last visit. TEAEs are recorded from the start of study drug administration, until the subject’s last visit.

All AEs occurring at any time during the study (including the FU period) will be followed until stable outcome.

3.5.6. OTHER REPORTABLE INFORMATION

3.5.6.1. PREGNANCY

The Investigator must report to the Sponsor any pregnancy occurring in a study subject, or in his partner, during the subject’s participation in this study and within 2 months after final study drug dose.

All pregnancies will be documented on the Pregnancy Report provided to the Investigator. The report should be submitted within the same timelines as an SAE, although a pregnancy per se is not considered an SAE. The progression of the pregnancy and the eventual birth (if applicable) must be followed-up using the Pregnancy Report in which the Investigator has to report on the health of the mother and of the child. The health of the child must be followed for 30 days after birth for any significant medical issues.
A pregnancy becomes an SAE in the following circumstances: miscarriage, abortion, or anomaly/birth defect of the child. Those SAEs must be additionally reported using the Investigator SAE Report form.

Note that as indicated in section 3.2.3.1, subjects who get pregnant during the study should be withdrawn from the study.

3.5.6.2. MEDICATION ERROR

Medication errors include, but are not limited to, the following:

- Administration of the wrong dosage (including overdose) to the subject.
- Administration of the study drug that has not been assigned to the subject.
- Administration of expired study drug.
- Administration by a route (e.g., intramuscularly) other than i.v. or s.c.
- Deviations to the study drug storage conditions only when administered to the subject.

Medications errors with signs and symptoms need to be reported as an AE/SAE.

Medication errors that occurs during the study should be documented and reported to the Sponsor or designee whether or not it results in an AE/SAE.
3.6. **STATISTICS**

3.6.1. **STUDY POPULATIONS**

The following populations will be considered for analysis:

- **Modified Intent-to-treat (mITT) Population:** All randomized subjects who received at least 1 administration of study drug, as randomized.

- **Safety Population:** All subjects who received at least 1 administration of study drug, as treated.

- **Per Protocol (PP) Population:** consists of a subset of the ITT population, and excludes those subjects who have had a major protocol deviation.

The mITT Population will be used for the analysis of efficacy and PK and the Safety Population for analysis of safety, PD, and immunogenicity data.

3.6.2. **STATISTICAL AND ANALYTICAL PLAN**

Details of all data analyses will be specified in the statistical analysis plan (SAP). The SAP will be generated under responsibility of the Sponsor and will be finalized prior to database lock. Any deviation from the reporting and analysis plans will be reported in the section “Changes in the planned analysis” in the Clinical Study Report.

3.6.3. **DEMOGRAPHICS AND BASELINE CHARACTERISTICS**

The statistical evaluation will be descriptive using standard statistical tools (including mean, standard deviation, median, maximum, and minimum) for continuous variables and counts and percentages for categorical variables.

3.6.4. **EVALUATION OF EFFICACY PARAMETERS**

**Primary endpoint:**
Time to platelet count response defined as initial platelet count ≥ 150×10⁹/L with subsequent stop of daily PE within 5 days.

**Secondary:**
All “time to event” endpoints start at the time of the first i.v. loading dose of study drug after randomization.
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 (e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism or DVT; also see section 3.4.3.6) during the study drug treatment period (including extensions).

2. Proportion of subjects with a recurrence of TTP in the overall study period (including 4-week FU period).

3. Proportion of subjects with refractory TTP, defined as absence of platelet count doubling after 4 days of standard treatment, and LDH > ULN.

4. Time to normalization of all 3 of the following organ damage marker levels:
   - Time to LDH ≤ 1 x upper limit of normal (ULN), and cTnI ≤ 1 x ULN, and serum creatinine ≤ 1 x ULN

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 (see section 3.4.3.2), as well as the number of such events in the overall study period (including 4-week FU period).

- Area under the curve (AUC) of platelet count until Day 5, truncated at 150×10^9/L if platelet count is 150×10^9/L or above.

- Mortality rate during 4 time periods: initial daily PE period, full study drug treatment period, FU period (of 4 weeks after stop of study treatment) and overall study period.

- Organ damage markers: Time to LDH ≤ 1 x ULN.

- Organ damage markers: Time to cTnI ≤ 1 x ULN.

- Organ damage markers: Time to serum creatinine ≤ 1 x ULN.

- Proportion of subjects with increases in organ damage markers (cTnI and serum creatinine) above 1 x ULN in 4 time periods: initial daily PE period, full study drug treatment period, FU period (of 4 weeks after stop of study treatment) and overall study period.

- 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.

- Change from baseline in 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.

- 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 ≥ 150×10^9/L on Day 1, 2, 3, 4, 5 and Day 10 and end of study drug treatment (i.e., last weekly visit during the study drug treatment period).
• Time to stop of daily PE.
• Bleeding events.
• Proportion of subjects with at least one treatment-emergent thromboembolic event (based on the Standardized MedDRA Query [SMQ] Embolic and thrombotic events [arterial, venous, and vessel type unspecified and mixed arterial and venous]).
• (S)AEs.
• PE parameters: number of days and total volume (absolute and normalized) in 2 time periods: initial daily PE period and full study drug treatment period.
• Number of days in ICU and in hospital in 4 time periods: initial daily PE period, full study drug treatment period, in the FU period (of 4 weeks after stop of study treatment) and overall study period.
• PD parameters: vWF, FVIII, RICO.
• PK parameters.
• Immunogenicity (ADA).

Note: The components of composite key secondary endpoints will also be analyzed separately as ‘other secondary endpoint’.

3.6.4.1. **ANALYSIS OF PRIMARY EFFICACY ENDPOINT**

Time to platelet count response in the caplacizumab arm and placebo arm will be compared by conducting a two-sided stratified Log-rank test (significance level of 5%) based on a Kaplan-Meier (KM) analysis, with severity of neurological involvement as stratification factor. 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). The censoring plan will be detailed in the SAP. The analysis will be performed on the mITT population (ICH E9 guidance), which comprises all randomized subjects who have received at least one study drug dose. Subjects will be analyzed according to the treatment to which they were assigned. Crossover of subjects who experience a recurrence of TTP during the study to open-label caplacizumab will not affect the primary efficacy endpoint analysis as an exacerbation can only occur after the primary endpoint has been reached.

3.6.4.2. **SECONDARY EFFICACY ENDPOINTS**

*Key secondary endpoints*

Confirmatory hypothesis testing will be conducted 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 DVT) during the study drug treatment period (including extensions): Cochran-Mantel-Haenszel test with adjustment for severity of neurological involvement (stratification factor used in randomization). Subjects who have crossed over from placebo to caplacizumab will be evaluated in the initial treatment arm (placebo) only.

2. Proportion of subjects with a recurrence of TTP in the overall study period (including 4-week FU period): Cochran-Mantel-Haenszel test with adjustment for severity of neurological involvement (stratification factor used in randomization). Subjects who have crossed over from placebo to caplacizumab will be evaluated in the initial treatment arm (placebo) only.

3. Proportion of subjects with refractory TTP, defined as absence of platelet count doubling after 4 days of standard treatment, and LDH >ULN: Cochran-Mantel-Haenszel test with adjustment for severity of neurological involvement (stratification factor used in randomization). Subjects who have crossed over from placebo to caplacizumab will be evaluated in the initial treatment arm (placebo) only.

4. Time to normalization of all three organ damage marker levels: stratified Log-rank test based on a KM analysis with adjustment for severity of neurological involvement 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. Subjects who have crossed over from placebo to caplacizumab before having reached the endpoint will be censored at time of crossover.

In addition to the confirmatory statistical tests, standard summary statistics will be provided for all key secondary endpoints. Both (a) 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 DVT) during the study drug treatment period (including extensions) and (b) proportion of subjects with a recurrence of TTP in the overall study period will also be evaluated descriptively for the following three groups:

1. Subjects randomized to caplacizumab
2. Subjects randomized to placebo (in case of crossover only assessed while on placebo)
3. Subjects who have crossed over from placebo to caplacizumab (only assessed from start of caplacizumab treatment)

Other secondary endpoints
All other endpoints will be summarized using standard statistics such as number of observations, means, standard deviations, and proportions, as appropriate.

3.6.5. EVALUATION OF PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS

The procedures for obtaining caplacizumab plasma concentrations are found in section 3.4.3.

Evaluation of Pharmacokinetics and Pharmacodynamics
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/or graphical form.

All PD data will be summarized using descriptive statistics and will be listed and summarized in tabular and/or graphical form.

PK/PD Model
vWF:Ag concentration data from the current study will be analyzed as well as caplacizumab concentration data using a population PK/PD model. This analysis will be performed on the mITT population (data will be pre-processed to ensure consistency in the dataset for doses, dosing times and PE procedure). The generated data from the current study will be pooled with clinical data previously used for developing the PK/PD modeling dealing with the three phase I studies and the two phase II study on high risk PCI patients and TTP patients. The final PK/PD model previously developed for describing the PK of caplacizumab, administered as adjunctive treatment to PE in TTP patients will be validated and eventually adjusted based on the new available data in TTP patients. Typical population values of basic PK and PD parameters will be estimated together with the inter-individual variabilities. Effects of subject demographics, laboratory parameter values, and other covariates on the PK of caplacizumab and on PD parameters will be explored. ADAMTS13 data will be investigated as a marker of the disease status. An additional model will be also developed for describing platelet count data. The results of the population PK/PD analysis will be reported in an independent Modeling and Simulation report.
3.6.6. EVALUATION OF SAFETY PARAMETERS

The DSMB will evaluate the safety data periodically (see section 3.1).

The following analyses will be performed to assess the safety of subjects in this study.

- The incidence and type of AEs.
- The incidence and type of SAEs.
- The incidence and type of related AEs (including bleeding-related AEs, PE-related AEs, and corticosteroid-related AEs).
- The laboratory parameters and change from baseline in these laboratory parameters.
- The incidence of antibodies to caplacizumab.

All safety and immunogenicity analyses will be performed using the Safety Population of all subjects who received at least 1 dose of study drug. Analyses will be performed using the treatment that the subject actually received.

AEs will be fully described and coded according to the Medical Dictionary for regulatory Activities (MedDRA). A treatment-emergent analysis of AEs will be done. Frequency of subjects presenting AEs, AEs leading to withdrawal, adverse drug reactions, and SAEs will be tabulated for each treatment group by system organ class and preferred term. AEs of special interest will be analyzed separately.

For laboratory parameters, descriptive statistics (mean, median, standard deviation, 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.

Vital signs variables will be fully depicted using descriptive statistics (for actual values and changes from baseline) and shift tables according to their normal ranges. ECG findings will be reported.

Abnormal findings in physical examinations will be listed.

Immunogenicity will be assessed through listing of individual results by subject and summary tables. Immunogenicity data will be correlated with PK and PD readout. In addition, immunogenicity will be correlated with possible safety findings.
3.7. DATA QUALITY ASSURANCE AND DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

An audit could be conducted to evaluate systems, processes, and expertise for the subcontracted activities and to assess compliance with the contractual agreements, the protocol, applicable Standard Operating Procedures, and regulatory requirements. During or after the conduct of the study, process-related audits may be performed as well. When performed, an audit certificate will be provided in appendix of the final study report.

The clinical research facility will be monitored by the study monitor, to ensure correct performance of the study procedures and to assure that the study is conducted according to the relevant regulatory requirements.

Regulatory authorities, the IEC/IRB, and/or the Sponsor representative may request access to all source documents, eCRFs and other study documentation for an on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

Quality control principles will be applied throughout the performance of this study.
3.8. DATA PROTECTION

During this clinical study, all clinical data will be identified only through an ID number in order to protect the rights of the subjects to privacy and to the protection of their personal data in accordance with the European Data Protection Directive 95/46/EC. Global principles and standards for Processing Personal Data and for meeting Data Transfer Obligations will be applied. If local requirements are more specific or expansive, Ablynx NV and subcontractors will abide to the strongest requirements.
4. ETHICS

4.1. ETHICS COMMITTEES AND COMPETENT AUTHORITIES

The Clinical Study Protocol(s) and the ICF(s) will be submitted for review and approval by the IEC/IRB prior to the eligibility screening/baseline. The composition of the IEC/IRB is in accordance with the recommendations of the World Health Organization, the ICH E6 Guideline for GCP, the European Union Clinical Trial Directive (CTD) (Directive 2001/20/EC) and the USA Code of Federal Regulations (CFR) (21 CFR 56).

The Investigator/Sponsor (or CRO on behalf of the sponsor) will keep the IEC/IRB informed about the progress of the study. All changes in research activities and all unanticipated problems involving risks to human subjects will be immediately reported to the responsible persons. The study may be suspended pending further review by the IEC/IRB, unless suspension would jeopardize the subject’s health. The Investigator will take care that all subjects are kept informed.

No substantial amendments will be made to the study without prior IEC/IRB approval and CA approval (if applicable according to local regulations), except when required to eliminate apparent immediate hazards to human subjects.

Notification of the end of the study will be sent to the CA and to the IEC/IRB, within the number of days as specified by local regulations after completion of follow-up for the last subject. In case the study is ended prematurely, the IEC/IRB and the CA will be notified within the number of days as specified by local regulations, including the reasons for the premature termination. A summary of the results of the study will be sent to the CA and the IEC/IRB within 1 year after the end of the study.

4.2. ETHICAL CONDUCT OF THE STUDY

This study will be conducted in compliance with the ICH Guidance for Industry E6 GCP (including archiving of essential study documents), the Declaration of Helsinki, the applicable regulations of the country(ies) in which the study is conducted, and with the Commission Directives 2001/20/EC and 2005/28/EC.

ICH-adopted guidelines and other relevant international guidelines, recommendations, and requirements will be taken into account as comprehensively as possible, as long as they do not violate Local laws.
The Investigator will be responsible for the care of the subjects throughout the study. If the Investigator is not present at the study site, he/she will leave instructions for the staff and a telephone number where he/she can be reached.

4.3. SUBJECT INFORMATION AND CONSENT

Each subject must give written consent according to local requirements after the nature of the study has been fully explained. The consent form must be signed before performance of any study-related activity. The consent form that is used must be approved by both the Sponsor or designee and by the reviewing IEC/IRB. The informed consent should be in accordance with principles that originated in the Declaration of Helsinki, current ICH and GCP guidelines, applicable regulatory requirements, and Sponsor policy.

Before undertaking any study-related procedure in the study, the Investigator or an authorized member of the investigational staff must explain to potential subjects or his/her legal representative the aims, methods, objectives, potential clinical benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects or his/her legal representative will be informed that their participation is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled and that all data collected up to the point of withdrawal will be used and reported in an anonymized way. Finally, they will be told that the Investigator will maintain a subject identification register for the purposes of long-term follow-up if needed and that their records may be accessed by health authorities, authorized Sponsor staff, and Sponsor representative without violating the confidentiality of the subject, to the extent permitted by the applicable law(s) or regulations. By signing the ICF the subject or his/her legal representative is authorizing such access, and agrees to allow his/her study physician to recontact the subject for the purpose of obtaining consent for additional safety evaluations, if needed.

If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written ICF and any other written information to be provided to subjects is read and explained to the subject or the subject’s legally acceptable representative, and after the subject or the subject’s legally acceptable representative has orally consented to the subject’s participation in the trial, and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject.
or the subject’s legally acceptable representative, and that informed consent was freely
given by the subject or the subject’s legally acceptable representative.

Subject ICF: The language used in the oral and written information about the study,
including the ICF, should be as nontechnical as practical and should be understandable to
the subject or the subject’s legal representative. The subject will be given sufficient time to
read the ICF and given the opportunity to ask questions. After this explanation and before
entry into the study, consent should be appropriately recorded by means of the subject’s
personally dated signature and by the Investigator who conducted the ICF discussion. After
having obtained the consent, a copy of the ICF must be given to the subject. The other
original of the ICF will be retained by the Investigator in the “Investigator Site File”.

Subject’s legal representative ICF: In emergency situations, when the subject is not able to
personally provide informed consent, the consent of the subject’s legally acceptable
representative, if present, should be requested. The subject’s legally acceptable
representative consent must be addressed to the representative and provided in a separate
document. When prior consent of the subject is not possible, and the subject’s legally
acceptable representative is not available, enrollment of the subject should require
measures described in the protocol and/or elsewhere, with documented approval/favorable
opinion by the IRB/IEC, to protect the rights, safety, and wellbeing of the subject and to
ensure compliance with applicable regulatory requirements. The subject or the subject’s
legally acceptable representative should be informed about the trial as soon as possible and
re-consent to continue must be given.

In this clinical study, the following Patient Information Consent Form will be used, prepared
and applicable in the different participating countries, according with their local normative:
• Patient ICF (for re-consenting after subject becomes conscious) and Legal Acceptable
  Representative consent – for initial consenting for unconscious subjects.
• Independent Physician Authorization Form: Form signed by independent physician not
  participant in the clinical study.

Summary of the procedure:
The Investigator or a designee is to explain the study and ICF to the subject or the subject’s
legally-acceptable representative and answer any questions. The ICF is to be signed by the
subject or the subject’s legally-acceptable representative, before any study-related
procedures are performed. A copy of the ICF is to be provided to the subject or the subject’s
legally-acceptable representative. In some countries the consent may be signed by an
authorized designee per local regulations or requirements, including but not limited to
independent physicians qualified to provide consent for subjects who are unable to provide
consent for themselves.

The person concerned must be duly informed about the research project as soon as this
becomes possible and must re-consent once possible. He or she may subsequently give or
withhold consent. If the person concerned refuses to give post hoc consent, the biological material and data may no longer be used for the research project. The consent for the representative must be addressed to the representative and provided in a separate document (not the same as the one intended for the subject), EC must be informed of the procedure for consenting this type of subjects and approve of it.

In addition, insurance coverage provided during the study is explained.

### 4.4. PRIVACY

The collection and processing of personal data from subjects enrolled in this study will be limited to those data that are necessary to investigate the safety, quality, and utility of the investigational study drug(s) used in this study.

These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Sponsor personnel whose responsibilities require access to personal data agree to keep the identity of study subjects confidential. Subjects will be identified by his/her assigned unique subject number or subjects ID number and his/her year of birth. Personal data will only be collected and processed using these unique identification items.

The informed consent obtained from the subject includes explicit consent for the processing of personal data and for the Investigator to allow direct access to his/her original medical records for study-related monitoring, audit, IEC/IRB review, and regulatory inspection. This consent also addresses the transfer of the data to other entities and to other countries.
5. DATA HANDLING AND RECORD KEEPING

5.1. DISTRIBUTION OF ACTIVITIES

Contact details of the Sponsor and third parties are available in the “Investigator Site File”.

5.2. DOCUMENTATION

Study documentation required for study start (as specified in the ICH E6 Guideline for GCP (CPMP/ICH/135/95) shall be exchanged between Ablynx NV and the CRO prior to the administration of study drug.

5.2.1. CASE REPORT FORM COMPLETION

Case report forms will be completed for each subject (incl. screen failures).

The Investigator will ensure that data are recorded on the eCRF as specified in the Clinical Study Protocol and in accordance with the instructions in the eCRF completion guidelines. The Investigator will ensure the accuracy, completeness, legibility, and timeliness of the data recorded in the eCRF, and of the provision of answers to data queries according to the Clinical Study Agreement. All eCRF entries, corrections, and alterations must be made by the Investigator or other authorized study-site personnel. The Investigator will sign the completed eCRF. A copy of the completed eCRF will be archived at the study site.

5.2.2. SOURCE DOCUMENTATION

At a minimum, source documentation must be available for the following: informed consent process, medical history, subject identification, eligibility, and study identification; date of informed consent; dates of visits; results of all efficacy evaluations; results of safety parameters as required by the protocol; record of all AEs; and follow-up of AEs; prior and concomitant medication; study drug receipt records; study drug administration information; any medical notes (original documents, data and records, e.g., laboratory data); date of study completion, and reason for early discontinuation of study procedures or withdrawal from the study, if applicable.

In addition, the author of an entry in the source documents should be identifiable.
At a minimum, the type and level of detail of source data available for a study subject should be consistent with that commonly recorded at the site as a basis for standard medical care (Patient’s Medical File).

Following the ICH-GCP guidelines, direct access to source documentation (medical records) must be allowed.

5.2.3. RECORD RETENTION

In compliance with the ICH/GCP guidelines, the Investigator/Institution will maintain all eCRFs and all source documents that support the data collected from each subject, as well as all study documents as specified in ICH/GCP section 8, Essential Documents for the Conduct of a Clinical Study, and all study documents as specified by the applicable regulatory requirement(s). The Investigator/Institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least 15 years after completion of the study, at least 2 years after the last approval of a marketing application in an ICH region and/or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained. The Sponsor will receive the original study-related documents (for eCRF, an electronic copy will be provided by the Sponsor).

If the responsible Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

The Investigator should take measures to prevent accidental or premature destruction of the study documents.

If it becomes necessary for the Sponsor or the appropriate regulatory authority to review any documentation relating to this study, the Investigator must permit access to such essential documents and subject data.
The Sponsor and the vendor(s) to whom the Sponsor has transferred duties and functions are responsible for organizing and maintaining a clear documentation of the course of the study.

The Trial Master File maintained during the study by the assigned vendor(s) will be sent back to the Sponsor at the end of the study, after final review and upon Sponsor approval.

Patients medical files, consent forms, and identification codes if relevant, will be kept by the Investigator in his/her personal files during the timeframe specified in local regulations or until the Sponsor decides that these documents no longer need to be retained (CPMP/ICH/135/95 § 4.95).

5.2.4. MONITORING

The monitor will perform on-site monitoring visits as specified in a monitoring plan to ensure that all aspects of the protocol, contractual agreements and regulatory requirements are followed and that subjects’ human rights, safety, and well-being are protected. The monitor will record dates of monitoring in a study center visit log that will be kept at the site. At these visits, the monitor will perform source data verification and check the data entered into the eCRF for completeness and accuracy. The nature and location of all source documents will be identified to ensure that all sources of original data required to complete the eCRF are known to the Sponsor and investigational staff and are accessible for verification by the Sponsor site contact. If electronic records are maintained at the investigational site, the method of verification must be discussed with the investigational staff.

Direct access to source documentation ([electronic] medical records) must be allowed at any time. Findings from this review of captured data will be discussed with the investigational staff. The Sponsor expects that, during on-site monitoring visits, the relevant investigational staff will be available, the source documentation will be accessible, and a suitable environment will be provided for review of study-related documents. The monitor will meet with the Investigator on a regular basis during the study to provide feedback on the study conduct. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits will be resolved.
6. FINANCING AND INSURANCE

Insurance

Ablynx NV holds and will maintain an adequate insurance policy covering damages arising from Ablynx-sponsored clinical research studies.

Ablynx NV will indemnify the Investigator in accordance with the provisions as set in an a separate written agreement between Ablynx and the relevant Investigator/clinical site.

Financing

The financial aspects of the study will be documented in an agreement between the Sponsor and the Investigator/Institution.

The subjects will be compensated for reasonable expenses made related to the study such as travel costs to visit the study center for assessments related to the study.

Financial Disclosure

Any identified Investigator or subinvestigator directly involved in the treatment or evaluation of research subjects will disclose for the time period during which the Investigator is participating in the study and for 1 year following completion of the study that he/she entered a financial arrangement between the Sponsor and the Investigator/Institution. The Investigator should promptly update this information if any relevant changes occur during this period.
7. USE OF INFORMATION AND PUBLICATION

By signing this protocol, the Investigator reaffirms to the Sponsor that he or she will maintain in confidence all information furnished to him, or resulting from this study. He or she will only divulge such information as may be necessary to the IEC/IRB and the members of the staff and the subjects who are involved in this study.

All data and records provided by the Sponsor or generated during the study (other than subject’s medical records) and all data and inventions covered in the course of conducting the study, whether patentable or not, are the sole and exclusive property of the Sponsor.

The Investigator and all other study team members at any service provider involved will keep strictly confidential all information provided by the Sponsor related to this study and all data and records generated in the course of the study. They will not use the information, data, or records for any other purpose than conducting the study without prior written approval of the Sponsor.

Publication of any results from this study will be according to the principles of the Declaration of Helsinki, in particular point 30, and will require prior review and written agreement of the Sponsor.
8. REFERENCES

9. APPENDICES

9.1. GLASGOW COMA SCALE SCORE

The GCS is scored between 3 and 15, 3 being the worst, and 15 the best. It is composed of three parameters: Best Eye Response, Best Verbal Response, Best Motor Response, as given below:

**Best Eye Response. (4)**
1. No eye opening.
2. Eye opening to pressure.
3. Eye opening to sound.
4. Eyes open spontaneously.

**Best Verbal Response. (5)**
1. No verbal response.
2. Sounds.
3. Words.
5. Orientated.

**Best Motor Response. (6)**
1. No motor response.
2. Extension.
3. Abnormal flexion.
5. Localising.
6. Obey commands.

A Coma Score of 13 or higher correlates with a mild brain injury, 9 to 12 is a moderate injury and 8 or less a severe brain injury.

Source: Teasdale G., Jennett B., LANCET (ii) 81-83, 1974. [33]
This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

Date: Friday, 22 July 2016, 17:39   Romance Daylight Time
Meaning: Approved
========================================