NCT02878603

CLINICAL STUDY PROTOCOL

ALX0681-C302

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

Short Title:	Follow-up Study for Patients who Completed Study ALX0681-C301 (Post-HERCULES)
Investigational Product:	Caplacizumab (Sponsor code: ALX-0081), an anti-von Willebrand Factor Nanobody
EudraCT n°:	2016-001503-23
Sponsor Protocol Code:	ALX0681-C302
Sponsor:	Ablynx NV Technologiepark 21 9052 Zwijnaarde, Belgium
Clinical Operations Contract Research Organization:	Pharm-Olam Ltd. The Brackens, London Road, Ascot, Berkshire, SL5 8BJ, UK
Phase of Development:	Phase III
Indication:	Acquired thrombotic thrombocytopenic purpura (TTP)
Study Center:	Multicenter study
Protocol Date:	24 May 2016
Protocol Version:	V1.0
Protocol Status:	Final

This study will be performed in compliance with the Clinical Study 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The information contained in this document, especially unpublished data, is the property of Ablynx NV (or under its control), and therefore provided to you in confidence as an Investigator, potential Investigator, or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.

APPROVAL 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:

Name: [redacted]
Function: Senior Medical Director, Ablynx NV

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

Investigator:

I have read Clinical Study Protocol ALX0681-C302 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:

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

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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
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CA	Competent authority
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
EC	Ethics committee
E. coli	*Escherichia Coli*
eCRF	Electronic case report form
ELISA	Enzyme-linked immunosorbent assay
FU	Follow-up
FVIII	Coagulation factor VIII
FVIII:C	Coagulation factor VIII clotting activity
GCP	Good clinical practice
GPIb	Glycoprotein Ib
HIT-6	Headache Impact Test-6
Hb	Hemoglobin
Hct	Hematocrit
ICF	Informed consent form
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
i.m.	Intramuscular

IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITO	Intention-to-observe
ITT	Intention-to-treat
i.v.	Intravenous
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LMWH	Low molecular weight heparin
M	Month
mADA	Modified anti-drug antibodies
MD	Medical Doctor
MedDRA	Medical Dictionary for Regulatory Activities
MW	Molecular weight
nAb	Neutralizing antibody
NOAEL	No observed adverse effect level
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PE	Plasma exchange
PK	Pharmacokinetics
Q6M	Twice yearly (every 6 months)
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RBC	Red blood cell
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
SF-36	Short Form-36 Health Survey
SUSAR	Suspected and unexpected serious adverse reactions
$t_{1/2}$	Terminal half-life
TE	Treatment-emergent
TEAE	Treatment-emergent adverse event
TIMI	Thrombolysis in myocardial infarction

TMA	Thrombotic microangiopathy
TnI	Troponin I
TTP	Thrombotic thrombocytopenic purpura
ULN	Upper limit of normal
ULvWF	Ultra-large von Willebrand factor
US	United States
vWF	von Willebrand factor
vWF:Ag	von Willebrand factor antigen
WBC	White blood cell
WFI	Water for injection
Y	Year

CHANGES COMPARED TO PREVIOUS VERSION(S)

Not applicable

PROTOCOL SYNOPSIS

Protocol title:

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

Protocol short title:

Follow-up Study for Patients who Completed Study ALX0681-C301 (Post-HERCULES)

Investigational product:

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

EudraCT n°:

2016-001503-23

Sponsor protocol code:

ALX0681-C302

Sponsor:

Ablynx NV
Technologiepark 21
9052 Zwijnaarde, Belgium

Phase of Development:

Phase III

Indication:

Acquired thrombotic thrombocytopenic purpura (TTP)

Study center:

Multicenter study

Objectives:

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

- To characterize long term impact of TTP

Study design:

This is a follow-up (FU) study for subjects who completed Study ALX0681-C301 (HERCULES) according to the protocol (i.e., completed the Final [28 day] FU visit).

Subjects who completed Study ALX0681-C301 will be given the option to participate in this FU study and attend twice yearly (Q6M) visits for 3 years starting with a baseline visit coinciding with or scheduled to take place within 1 month after the Final [28 day] FU visit in Study ALX0681-C301*. Assessments at these Q6M visits will include patient reported outcome measures, clinical assessments (including adverse events [AEs], safety laboratory parameters, vital signs and physical examination), and determination of anti-drug antibodies (ADA), vWF antigen (vWF:Ag; pharmacodynamic [PD] parameter), and disease-related markers (a disintegrin-like and malloprotease with thrombospondin repeats 13 [ADAMTS13] activity and Troponin I [TnI]).

The study flow chart is depicted in Figure 1.

Recurrence of TTP episode

Upon recurrence of TTP, defined as recurrent thrombocytopenia requiring initiation of daily plasma exchange (PE), standard of care treatment consisting of daily PE and immunosuppression is to be initiated. In addition, an intravenous (i.v.) loading dose of open-label caplacizumab will be administered prior to initiation of daily PE† followed by daily subcutaneous (s.c.) administration of caplacizumab for the duration of daily PE and for 30 days thereafter. Treatment with caplacizumab may be extended for a maximum of 4 weeks in case of persistent signs and symptoms of underlying disease activity (e.g., ADAMTS13 activity profile remains below 10% based on weekly measurements).
The visit schedule upon initiation of treatment consists of a recurrence visit at presentation, a visit on Day 3 of treatment with caplacizumab, weekly visits during treatment with caplacizumab (starting 1 day after the last daily PE), and a recurrence FU visit 1 week after the end of treatment with caplacizumab. At these visits, information with regard to the TTP recurrence (presenting symptoms, duration, and outcome) and treatment choice will be collected as will safety information (including AEs, safety laboratory parameters, vital signs and physical examination), and determination of pharmacokinetics (PK), ADA, PD

* Note: for subjects for whom the Final (28 day) FU visit in Study ALX0681-C301 occurred prior to local approval and site activation for this study, a time window of + 1 month after site activation is permitted to complete the screening/baseline visit.

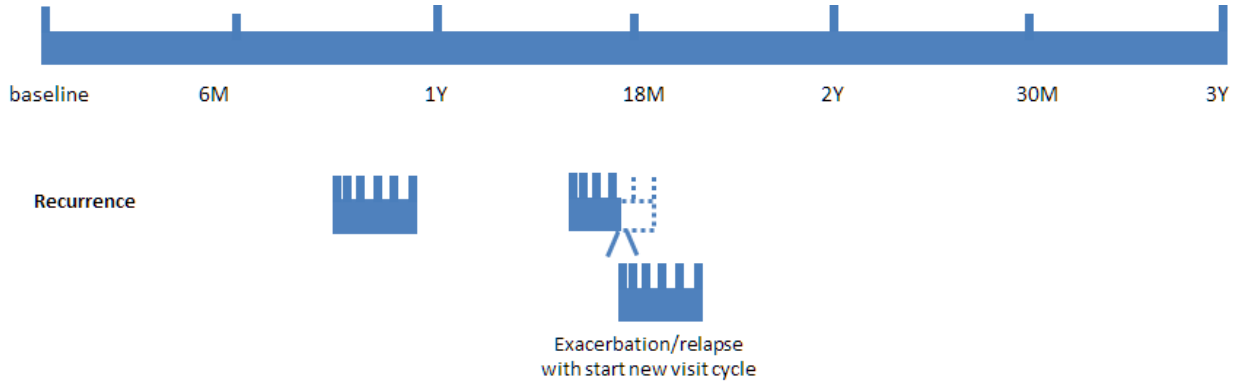
† Up to 1 PE (which may be spread over 2 or more sessions in 24 hours) may be given prior to initiation of treatment with caplacizumab as long as considered part of the PE for the treatment of the presenting TTP episode.

parameters (vWF:Ag and ristocetin cofactor [RICO]), and disease-related markers (ADAMTS13 activity and TnI).

In case of recurrent thrombocytopenia requiring re-initiation of daily PE during an ongoing recurrence period (see Figure 1 and Table 2), a new visit cycle is to be started, with a recurrence visit on the day of the new recurrence followed by all subsequent visits as indicated in Table 2. All remaining visits of the original schedule are no longer applicable and are not to be performed.
Note: an i.v. loading dose of caplacizumab needs to be administered prior to re-initiation of PE for the recurrence.

Q6M visits that are scheduled within a recurrence period will not be held as assessments at such visits would be confounded by the concurrent recurrence.

Note: Treatment with caplacizumab may not be initiated for subjects who do not fulfil the Caplacizumab treatment criteria. Hence, these subjects will be treated with standard of care only. The visit schedule in case of initiation of only standard of care treatment includes a recurrence visit at presentation and a recurrence FU visit at 30 days after end of daily PE (see Appendix 1 for schedule of assessments).



M: month; Y: year

Figure 1: Study flow of Study ALX0681-C302.

Treatment in case of recurrence:

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

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

Initiation of treatment with caplacizumab[‡]:

Daily PE period

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

30-day post-daily PE period

Daily s.c. administration of 10 mg study drug will continue for a period of 30 days after stop of daily PE. No adjustment to this period will be made for tapering of PE. Subjects (and/or caregivers) will be trained on preparing and administering caplacizumab and are to administer the study drug after discharge from the hospital.

Treatment extension period

Treatment with caplacizumab beyond these 30 days will be guided by a number of risk factors for relapse of the presenting TTP episode and may be accompanied by an optimization of the immunosuppressive treatment. The risk factors will include the ADAMTS13 activity profile, as well as other signs and symptoms of continued underlying disease activity, such as presence of inhibitors if measured as routine practice by the site. Continued caplacizumab treatment should be given for additional 7-day periods with a maximum of 28 days for subjects whose ADAMTS13 activity profile remains below 10% based on weekly measurements and/or exhibit other clinical signs or symptoms of underlying disease. Caplacizumab treatment should be stopped when ADAMTS13 activity shows a sustained upward trend of >10% and/or when there is an improvement in other signs and symptoms of underlying disease activity and at the latest on Day 28 of the study drug treatment extension period.

Study population:

Subjects who completed Study ALX0681-C301 (HERCULES) will be given the option to participate in this follow-up study.

[‡] Pregnant subjects or those with a history of a severe and/or serious hypersensitivity reaction to caplacizumab may participate in the study but will not receive treatment with caplacizumab. Also, treatment with caplacizumab may not be initiated for subjects who did not have a baseline visit.

[§] Up to 1 PE (which may be spread over 2 or more sessions in 24 hours) may be given prior to initiation of treatment with caplacizumab as long as considered part of the PE for the treatment of the presenting TTP episode.

Number of subjects:

All subjects enrolled in Study ALX0681-C301 are eligible to participate in Study ALX0681-C302.

Inclusion criteria:

Each potential subject must satisfy all of the following criteria to be enrolled in the study:
1. Completed the Final (28 day) FU visit in Study ALX0681-C301.
2. Is ≥18 years of age at the time of signing the informed consent form (ICF).
3. Provided informed consent prior to initiation of any study specific activity/procedure.

Exclusion criteria:

The criteria for exclusion are the following:
1. Not being able/willing to comply with the study protocol procedures.
2. Currently enrolled in a clinical study with another investigational drug or device.

Caplacizumab treatment criteria:

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

Treatment with caplacizumab is not permitted for subjects who:
1. Are pregnant or intend to get pregnant in the near future (check on use of contraceptives, see section 3.3.7).
2. Have a history of severe and/or serious hypersensitivity reaction to investigational medicinal product (IMP) in Study ALX0681-C301 or Study ALX0681-C302.

Study medication:

The study medication is provided in a kit containing the following components:
- One glass vial containing lyophilized powder (caplacizumab) for reconstitution (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, e.g., during transfer from vial to syringe, the nominal administered dose is 10 mg when injecting the entire content (nominally 0.9 mL) of the syringe.
  - Excipients: 0.21 mg citric acid, 5.58 mg tri-sodium citrate di-hydrate, 70 mg sucrose, 0.11 mg polysorbate-80 per vial (pH 6.5 +/- 0.5).
  - Dosage form: powder for solution for injection; reconstitution with WFI yields solution for injection.
  - Route of administration: i.v. (first dose), s.c. (all subsequent doses).

Study duration:

The anticipated study duration per subject is approximately 3 years.

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

- Assessment period:
  Three years, during which twice yearly visits starting from Screening/Baseline will be conducted.

Recurrence of disease (TTP exacerbation/relapse):

A recurrence visit at presentation, a visit on Day 3 of treatment with caplacizumab, weekly visits during treatment with caplacizumab (starting 1 day after the last daily PE), and a recurrence FU visit 1 week after the end of treatment with caplacizumab.

Note: In case the criteria for treatment with caplacizumab are not met (see Caplacizumab treatment criteria), a recurrence visit at presentation and a recurrence FU visit at 30 days after end of daily PE is to be performed.

Assessments:

- Screening/Baseline and Q6M visits (for timing of assessments, please refer to Table 1)
  - Medical history (including general and TTP-related medical history) and demographics
  - Cognitive assessment: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (only in those countries where RBANS is available in the local language[s])
  - Adverse events
  - Concomitant medication
  - Physical examination, vital signs
  - Quality of life assessment: short form 36 (SF36) questionnaire
  - Headache Impact Test (HIT-6™)
  - Laboratory assessments:
    - Hematology (hemoglobin [Hb], hematocrit [Hct], red blood cells [RBC], white blood cells [WBC], platelets)
    - Chemistry (aspartate aminotransferase [AST], alanine aminotransferase [ALT], lactate dehydrogenase [LDH], creatinine, protein, C-reactive protein [CRP], cholesterol)
    - Organ damage marker: troponin (TnI)
    - ADAMTS13 activity
    - PD parameter: vWF:Ag
    - Immunogenicity: ADA panel
  - Urine:
    - Albumin (to calculate albumin creatinine ratio)

- At TTP recurrence (for timing of assessments, please refer to Table 2):
  - Review of caplacizumab treatment criteria
  - TTP recurrence information
  - Concomitant medication
  - Study drug administration
  - PE information
  - Quality of life assessment: SF36 questionnaire
  - Adverse events
  - Physical examination, vital signs
  - Laboratory assessments:
    - Hematology (Hb, Hct, RBC, WBC, platelets)
    - Chemistry (AST, ALT, LDH, creatinine, protein, cholesterol and CRP)

  - Organ damage marker: troponin (TnI)
  - ADAMTS13 activity
  - Immunogenicity: ADA panel
  - Pharmacokinetics (not assessed if treatment with caplacizumab has not been initiated)
  - PD parameters: vWF:Ag and RICO (the latter will not be assessed if treatment with caplacizumab has not been initiated).
- Urine:
  - Albumin
- Pregnancy test (blood or urine) for female subjects of childbearing potential (Note: pregnancy is an exclusion criterion for treatment with caplacizumab)

Statistics:

Main Endpoints

- Proportion of subjects with TTP-related events (defined as TTP-related death, recurrence of TTP or reported major thromboembolic event), number of TTP-related events and time to event
- Mortality rate during the study
- Proportion of subjects with recurrence of disease, number of recurrences, and time to recurrence
- Proportion of subjects with reported major thromboembolic events (e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism or deep venous thrombosis), number of events, and time to event
- Cognitive function
- Quality of life
- Immunogenicity of (repeated) treatment with caplacizumab

Statistical Methods

The sample size is not based on statistical considerations but rather on the number of subjects who complete Study ALX0681-C301 (HERCULES) and accept the option to participate in this FU Study (ALX0681-C302).

All subjects who enrolled in this FU study will be included in the safety and efficacy analyses. Statistical analyses are considered descriptive.

Interim analyses may be conducted in view of supporting regulatory submissions.

SCHEDULES OF ASSESSMENTS

Table 1: Schedule of assessments for twice yearly visits

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

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

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

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

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

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

Table 2: Schedule of assessments in case of TTP recurrence **

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

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

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

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

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

** Treatment with caplacizumab may not be initiated for subjects who do not fulfil the caplacizumab treatment criteria. These subjects will be treated with standard of care only. For the Schedule of Assessments, please refer to Appendix 1.

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

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

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

[h] PD parameters include RICO and vWF:Ag.

1. INTRODUCTION

1.1. THROMBOTIC THROMBOCYTOPENIC PURPURA

Acquired thrombotic thrombocytopenic purpura (TTP) is a rare, potentially life-threatening, (sub)acute onset thrombotic microangiopathy (TMA) 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 ultra-large von Willebrand factor (ULvWF) forming platelet aggregates in the microvasculature. Episodes are associated with significant mortality and morbidity acutely and may result poorer long term outcomes [1, 2]. In the longer term, patients with acquired TTP are at risk of recurrence of disease [3]. Reported recurrence rates vary considerably. Among patients followed for at least six months, the median incidence of recurrence was 18% (3-84%). The highest incidence (84%) occurred in the study with the longest mean follow-up (FU) time (13 years) [3]. The risk for recurrence seems to be the highest in the first year [4]. Frequent relapses may promote continuous damage from ongoing or intermittent episodes of endothelial injury, platelet dysfunction, and microvascular thrombosis [5]. Residual damage from the initial TMA-induced microvascular thrombotic event may mediate the subsequent development of vascular disease. Moreover, recent reports have suggested that survivors of an acute TTP episode are at risk for longer-term complications (e.g., a high incidence of hypertension, renal insufficiency, persistent cognitive deficits, depression, poorer quality of life and premature death) [1, 3, 6-9].

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.

Neurological involvement is considered to be one of the differentiating factors for TTP compared to other TMAs. 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%) [4] to 68% in the French cohort study [10]. Longer term neurological consequences reflected as cognitive deficits have been reported [6, 7]. In one study, 24 patients from the Oklahoma Registry with documented ADAMTS13 deficiency at the time of initial TTP episode, who had no evidence of TTP, and were functioning independently in their normal work and daily activities at the time of the evaluation, underwent a variety of tests assessing 11 domains of cognitive function. Results of these tests were compared to normative data from the United States (US) reference population. The group performance for these 24 subjects was substantially worse (16^{th} percentile) than that of population norms for neurologically normal subjects. Eighteen (75%) of the TTP patients performed below expectations (scores greater than 1 standard deviation below the mean) compared to the population norms in one or more of the following domains: complex attention and sequencing, manual dexterity, rapid language generation and list learning [7]. In addition, a health-related quality of life survey of patients from the Oklahoma TTP Registry (using a standardized questionnaire, the Short Form-36 [SF-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 reference population [11].

Another report from the Oklahoma Registry based on the annual follow-up for a median of 7.8 years of 57 patients in the registry who had recovered from acquired TTP associated with severe ADAMTS13 deficiency, concluded that TTP survivors have a greater risk for poor health and premature death than the US reference population [1]. The prevalence of hypertension was not significantly different at the time of TTP diagnosis. However, at the time of the report, its prevalence was greater than expected (40% versus expected value of 23%, p = 0.011). Major depression was also more prevalent for these patients than expected (prevalence of 19% versus expected 6%, p = 0.005). For these 57 patients, there was a higher than expected mortality rate (19%) and the 11 patients who died all did so before their expected age of death.

1.1.1. TREATMENT OF ACQUIRED TTP

Plasma exchange (PE) is the current standard of care for treatment of acquired TTP. PE replenishes ADAMTS13, partially normalizing vWF processing, and removes pathogenic autoantibodies. Daily exchanges are to continue for a minimum of 2 days after the platelet count has normalized [12]. Immunosuppression, most commonly in the form of corticosteroids is often started together with PE to reduce the production of autoantibodies. Despite standard of care treatment, an exacerbation occurs in approximately 30% of patients within 30 days of stopping PE [13]. Severe ADAMTS13 deficiency (<10%) has been identified as a potential biomarker of active underlying disease and an elevated risk of relapse in these patients [14, 15].

In spite of recent advances in understanding the disease, there are no approved pharmacologic therapies for acquired TTP. Caplacizumab represents a novel approach to treating the microthrombotic component of acquired 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. When used in conjunction with PE for initial and recurrent episodes of acquired TTP, its ability to prevent further microthrombus formation may translate into better long term outcomes for these patients.

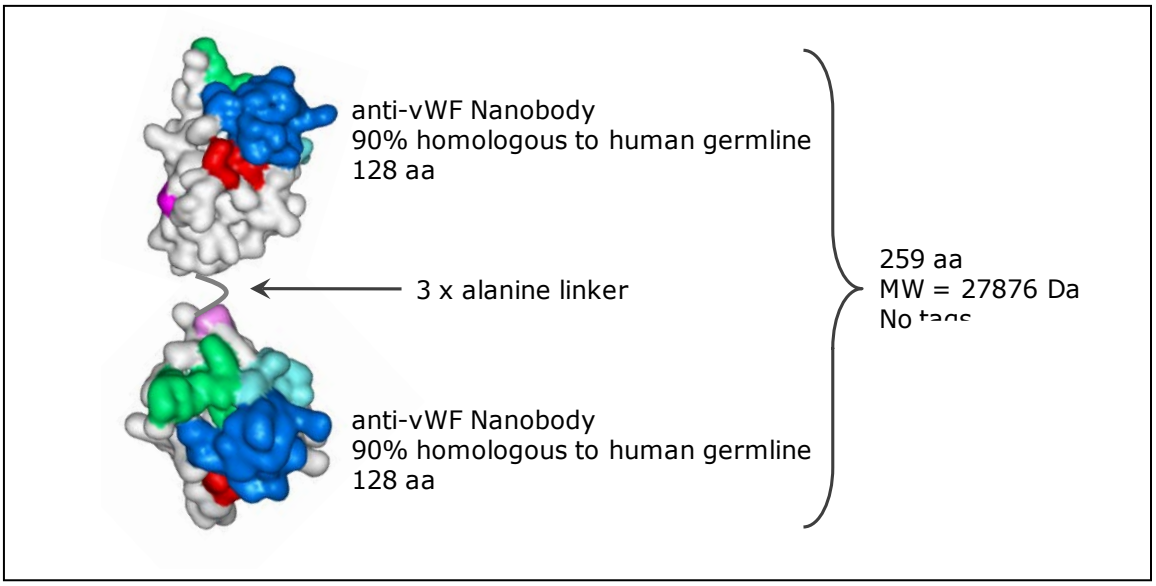
1.2. CAPLACIZUMAB

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 2).



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

Figure 2: 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 3).

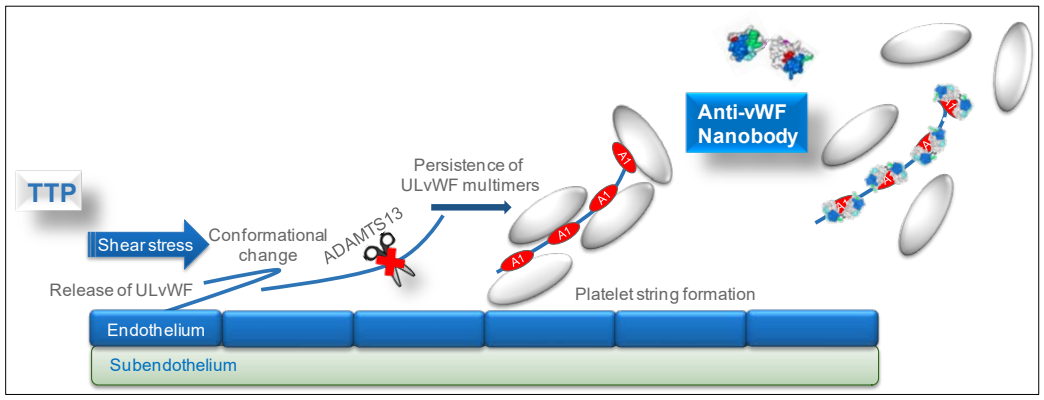


Figure 3: Mechanism of action of caplacizumab in TTP.

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 clinical studies 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).

More information on the pharmaceutical properties of caplacizumab is 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 intravenous (i.v.), subcutaneous (s.c.) and intramuscular (i.m.). The terminal half-life ($t_{1/2}$) of caplacizumab - more precisely caplacizumab bound to vWF - ranges between 5-36 hours across the 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. 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%.

- 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 relation to study drug (high dose group, 26-week toxicity study in cynomolgus monkey).
  - One case of profound but reversible decrease of platelet count 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 a randomized, double-blind, placebo-controlled, single center, dose-escalation Phase Ib study to evaluate the safety of ascending doses of caplacizumab in patients with stable angina undergoing percutaneous coronary intervention (PCI). An open label extension stage 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.

Summaries of the results of these studies are provided in the Investigator's Brochure.

Phase II studies

One Phase II study has been completed in the development of caplacizumab for the treatment of acquired TTP. Study ALX-0681-2.1/10 was a randomized, single-blind,

placebo-controlled multicenter trial to study the efficacy and safety of anti-von Willebrand factor Nanobody caplacizumab (ALX-0081) administered as adjunctive treatment to PE to patients with acquired TTP. A Phase II study was completed in the development path for the treatment of acute coronary syndrome. This indication is not being pursued.

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

The efficacy and safety of caplacizumab in the treatment of acquired TTP have been evaluated in Study ALX-0681-2.1/10 comparing it to placebo when added to daily PE and in the 30-day post-daily PE period [16]. The study was terminated early due to recruitment challenges, with a total of 75 subjects enrolled and included in the intention-to-treat (ITT) analysis. The primary endpoint was the time to confirmed normalization of the platelet count. The median time to confirmed response was 2.97 days in the caplacizumab treatment group and 4.79 days in the placebo group. Based on the stratified log-rank test, the time to response was significantly shorter in the caplacizumab treatment group, compared with the placebo treatment group (p=0.005), taking into account presence or absence of one PE session prior to randomization. This is also demonstrated by a hazard (i.e., event rate) ratio (95% confidence interval) for the caplacizumab versus placebo treatment groups of 2.197 (1.278, 3.778).

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

- A substantially higher number and proportion of subjects in the caplacizumab treatment group achieved complete remission following the initial course of daily PE compared with subjects in the placebo treatment group (29 [80.6%] subjects versus 18 [46.2%] subjects, respectively).
- Fewer subjects in the caplacizumab treatment group had exacerbations of TTP compared with the placebo treatment group (3 [8.4%] and 11 [28.2%] subjects, respectively).
- A similar number and proportion of subjects in the caplacizumab treatment group and the placebo treatment group had an exacerbation and/or a relapse of TTP (13 [36.1%] and 13 [33.3%] subjects, respectively). 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 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 to <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 17/22 subjects. In 14 of 17 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 15 of 17 placebo subjects without exacerbation or relapse (ADAMTS13 data available for 17/24 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 9 of them. Seven of 9 placebo subjects with an exacerbation had ADAMTS13 activity <10% around the time of the exacerbation, one subject had a borderline ADAMTS13 activity value of 11%, and one subject had an ADAMTS13 activity value of 100% (with a baseline ADAMTS13 activity value of 90%). In summary, the data support ADAMTS13 activity as a potential marker to identify patients at risk for exacerbation or relapse.

The safety results were as expected for the population of patients with acquired TTP. No unanticipated safety concerns for treatment with caplacizumab were identified in this study.

The overall duration of exposure to study drug was similar in the two treatment arms.

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. 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 died from the serious TEAE of refractory TTP. Serious adverse events (SAEs) were reported in a similar number of subjects in the two treatment arms (57.1% in the caplacizumab group and 51.4% in the placebo group). The number of subjects with any TEAE leading to discontinuation of study drug was 4 and 2 in the caplacizumab and placebo groups, respectively.

The occurrence of treatment-emergent major thromboembolic adverse events was investigated in the clinical study database, using the Standardized MedDRA Query for 'embolic and thrombotic events'. The proportion of subjects with at least one of these events together with the total number of events were summarized and reported per treatment group. Transient episodes were not considered major thromboembolic events and

were, therefore, not included in this analysis. TTP-related mortality during the study was evaluated based on AE reporting, with relatedness to TTP as judged by the Investigator. The safety population consisted of 35 caplacizumab-treated and 37 placebo-treated subjects. Four major thromboembolic events were reported in 4 subjects in the caplacizumab group (1 pulmonary embolism and 3 TTP exacerbations). In the placebo group, 20 major thromboembolic events were reported in 14 subjects (2 acute myocardial infarctions, 1 ischemic and 1 hemorrhagic stroke, 1 pulmonary embolism, 1 deep vein thrombosis, 1 venous thrombosis and 13 TTP exacerbations). Two TTP-related deaths occurred during the study, both in the placebo treatment group (causes of death: refractory TTP and cerebral hemorrhage). In total, 11.4% of caplacizumab-treated subjects versus 43.2% of placebo-treated subjects experienced one or more thromboembolic events or died. The results of this analysis suggest that treatment with caplacizumab has the potential to reduce the significant morbidity and mortality associated with acquired TTP.

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 study.

Treatment-emergent anti-drug antibodies (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 similar bleeding profiles: 36 (19.9%) patients in the caplacizumab treatment group and 28 (15.3%) patients in the abciximab treatment group reported bleeding events. Three (1.7%) caplacizumab-treated patients and 2 (1.1%) abciximab-treated patients experienced 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. The proportion of SAEs was low in both treatment groups. Serious TEAEs were reported in 24 (13.3%)

patients in the caplacizuamb treatment group and 18 (9.8%) patients in the abciximab treatment group and were most frequently 'injury, poisoning and procedural complications' and 'cardiac disorders'. By Day 30 there was 1 death in the abciximab group and none in the caplacizumab group. After 1 year of FU, there were 5 deaths 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 possibly related to treatment.

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.

Phase III study

One Phase III study is currently ongoing in the development of caplacizumab for the treatment of acquired TTP:
Study ALX0681-C301 (HERCULES) is a randomized, double blind, placebo-controlled 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 study eligibility and after the start of PE treatment, approximately 92 subjects with a clinical diagnosis of acquired TTP are to be randomized in a ratio of 1:1 to either receive caplacizumab or placebo in addition to standard of care therapy. Subjects are treated for 30 days after stop of daily PE treatment (with a possibility of weekly extensions for a maximum of 4 weeks in case of persistent signs and symptoms of continued underlying disease activity) with a 4 week FU period. Subjects who experience a first exacerbation or a first relapse during treatment extension are to crossover to open-label caplacizumab.

The primary endpoint is time to platelet count response defined as initial platelet count $\geq 150\times10^9$/L with subsequent stop of daily PE within 5 days.
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) 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 lactate dehydrogenase (LDH) > upper limit of normal (ULN).
4. Time to normalization of all 3 of the following organ damage marker levels:
   - Time to LDH ≤ 1 x ULN, and cardiac Troponin I (cTnI) ≤ 1 x ULN, and serum creatinine ≤ 1 x ULN

Subjects who completed Study ALX0681-C301 (HERCULES) will be given the option to participate in follow-up Study ALX0681-C302.

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 study.

Overall, Study ALX-0681-2.1/10 (TITAN study) 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 were associated with tangible clinical benefits in terms of reduced mortality/morbidity [17]. 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. Study ALX0681-C301 and this 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 the TITAN study revealed no unexpected findings in relation to AEs. The main safety finding associated with caplacizumab treatment was an increase in bleeding-related AEs, 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 clinical benefits of caplacizumab in the TTP indication. Nonetheless, vWF preparations can be used as antidote to 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 study, drug induced TE antibodies were detected in 9% of caplacizumab treated subjects. No immunogenicity related safety findings were reported. Whether retreatment with caplacizumab includes a risk for inducing ADA is currently unknown.

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 an acute episode of 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 TTP exacerbations while on treatment.
This treatment benefit is expected to apply for every TTP episode treated with caplacizumab. Treatment with caplacizumab at every TTP occurrence might prevent patients from developing longer term morbidity induced by recurrent organ ischemia induced at each TTP occurrence.

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

2. OBJECTIVES

The objectives of this study are:

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

3. STUDY DESIGN

3.1. OVERALL STUDY DESIGN

3.1.1. STUDY OVERVIEW

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

The study flow chart is depicted in Figure 4.

Subjects who completed Study ALX0681-C301 will be given the option to participate in this FU study and attend twice yearly (Q6M) visits for 3 years starting with a baseline visit coinciding with or scheduled to take place within 1 month after the Final (28 day) FU visit in Study ALX0681-C301[††]. Assessments at these Q6M visits will include patient reported outcome measures, clinical assessments (including AEs, safety laboratory parameters, vital signs and physical examination), and determination of ADA, vWF:Ag (PD parameter), and disease-related markers (ADAMTS13 activity and Troponin I [TnI]).

Recurrence of TTP episode

Upon recurrence of TTP, defined as recurrent thrombocytopenia requiring initiation of daily PE, standard of care treatment consisting of daily PE and immunosuppression is to be initiated. In addition, an i.v. loading dose of open-label caplacizumab will be administered prior to initiation of daily PE[‡‡] followed by daily subcutaneous s.c. administration of caplacizumab for the duration of daily PE and for 30 days thereafter. Treatment with caplacizumab may be extended for a maximum of 4 weeks in case of persistent signs and symptoms of underlying disease activity (e.g., ADAMTS13 activity profile remains below 10% based on weekly measurements).
The visit schedule upon initiation of treatment consists of a recurrence visit at presentation, a visit on Day 3 of treatment with caplacizumab, weekly visits during treatment with caplacizumab (starting 1 day after the last daily PE), and a recurrence FU visit 1 week after the end of treatment with caplacizumab. At these visits, information with regard to the TTP recurrence (presenting symptoms, duration, and outcome) and treatment choice will be

[††] Note: for subjects for whom the Final (28 day) FU visit in Study ALX0681-C301 occurred prior to local approval and site activation for this study, a time window of + 1 month after site activation is permitted to complete the screening/baseline visit.

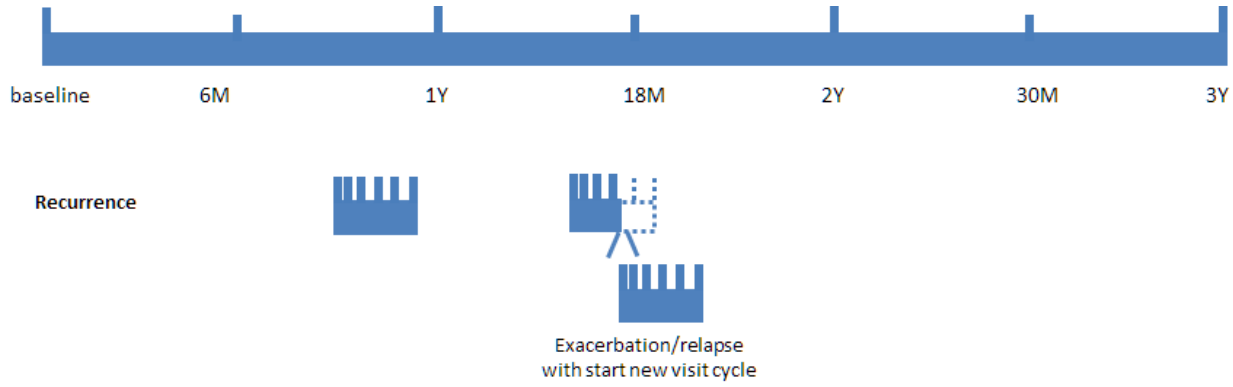
[‡‡] Up to 1 PE (which may be spread over 2 or more sessions in 24 hours) may be given prior to initiation of treatment with caplacizumab as long as considered part of the PE for the treatment of the presenting TTP episode.

collected as will safety information (including AEs, safety laboratory parameters, vital signs and physical examination), and determination of PK, ADA, PD parameters (vWF:Ag and RICO), and disease-related markers (ADAMTS13 activity and TnI).

In case of recurrent thrombocytopenia requiring re-initiation of daily PE during an ongoing recurrence period (see Figure 4 and Table 2), a new visit cycle is to be started, with a recurrence visit on the day of the new recurrence followed by all subsequent visits as indicated in Table 2. All remaining visits of the original schedule are no longer applicable and are not to be performed.
Note: an i.v. loading dose of caplacizumab needs to be administered prior to re-initiation of PE for the recurrence.

Q6M visits that are scheduled within a recurrence period will not be held as assessments at such visits would be confounded by the concurrent recurrence.

Note: Treatment with caplacizumab may not be initiated for subjects who do not fulfil the caplacizumab treatment criteria (see section 3.2.3). Hence, these subjects will be treated with standard of care only. The visit schedule in case of initiation of only standard of care treatment includes a recurrence visit at presentation and a recurrence FU visit at 30 days after end of daily PE (see Appendix 1 for schedule of assessments).



M: month; Y: year

Figure 4: Study flow of Study ALX0681-C302.

Treatment in case of recurrence:

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

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

Initiation of treatment with caplacizumab[§§]:

Daily PE period

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

30-day post-daily PE period

Daily s.c. administration of 10 mg study drug will continue for a period of 30 days after stop of daily PE. No adjustment to this period will be made for tapering of PE. Subjects (and/or caregivers) will be trained on preparing and administering caplacizumab and are to administer the study drug after discharge from the hospital.

Treatment extension period

Treatment with caplacizumab beyond these 30 days will be guided by a number of risk factors for relapse of the presenting TTP episode and may be accompanied by an optimization of the immunosuppressive treatment. The risk factors will include the ADAMTS13 activity profile, as well as other signs and symptoms of continued underlying disease activity, such as presence of inhibitors if measured as routine practice by the site. Continued caplacizumab treatment should be given for additional 7-day periods with a maximum of 28 days for subjects whose ADAMTS13 activity profile remains below 10% based on weekly measurements and/or exhibit other clinical signs or symptoms of underlying disease. caplacizumab treatment should be stopped when ADAMTS13 activity shows a sustained upward trend of >10% and/or when there is an improvement in other signs and symptoms of underlying disease activity and at the latest on Day 28 of the study drug treatment extension period.

Estimated Study Duration

The anticipated study duration per subject is approximately 3 years. The end of the study is defined as the last visit of the last subject participating in the study.

[§§] Pregnant subjects or those with a history of a severe and/or serious hypersensitivity reaction to caplacizumab may participate in the study but will not receive treatment with caplacizumab. Also, treatment with caplacizumab may not be initiated for subjects who did not have a baseline visit.

[***] Up to 1 PE (which may be spread over 2 or more sessions in 24 hours) may be given prior to initiation of treatment with caplacizumab as long as considered part of the PE for the treatment of the presenting TTP episode.

Determination of Sample Size

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

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 the safety data. The DSMB meetings will be convened every year. 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). Ad hoc meetings will be determined by the DSMB based on incidence of SAEs. 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. BLINDING

Not applicable. Upon a recurrence of TTP all subjects will receive open-label treatment with caplacizumab in addition to standard of care.

3.2. SELECTION OF STUDY POPULATION

Subjects who completed Study ALX0681-C301 (HERCULES) will be given the option to participate in this follow-up Study ALX0681-C302.

3.2.1. INCLUSION CRITERIA

Each potential subject must satisfy all of the following criteria to be enrolled in the study:
1. Completed the Final (28 day) FU visit in Study ALX0681-C301.
2. Is ≥ 18 years of age at the time of signing the informed consent form (ICF).
3. Provided informed consent prior to initiation of any study specific activity/procedure.

3.2.2. EXCLUSION CRITERIA

The criteria for exclusion are the following:
1. Not being able/willing to comply with the study protocol procedures.
2. Currently enrolled in a clinical study with another investigational drug or device.

3.2.3. CAPLACIZUMAB TREATMENT CRITERIA

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

Treatment with caplacizumab is not permitted for subjects who:
1. Are pregnant or intend to get pregnant in the near future (check on use of contraceptives, see section 3.3.7).
2. Have a history of a severe and/or serious hypersensitivity reaction to investigational medicinal product (IMP) in Study ALX0681-C301 or Study ALX0681-C302.

3.2.4. REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

3.2.4.1. WITHDRAWAL OF SUBJECTS FROM THE STUDY

Participation in the study is strictly voluntary. A subject has the right to withdraw from the study at any time, for any reason. In case of withdrawal, an Early Termination Visit will be done. Note: no further assessments/visits will be done in case subjects terminate study participation for reasons of lost to follow-up or informed consent withdrawal.

In the event a subject is discontinued from the study, the Medical Monitor is to be informed.

3.2.4.2. CRITERIA FOR STUDY DRUG TREATMENT DISCONTINUATION

Temporary discontinuation of study drug should be considered in cases where the subject develops severe or serious bleeding. All subjects in the study experiencing bleeding events should be treated using the standard medical and/or surgical intervention (also see section 3.3.6). Treatment with study drug should only be restarted when the bleeding has stopped.
Note: vWF preparations can be used as antidote to caplacizumab if needed. vWF and FVIII preparations as combination products are commercially available.

Permanent discontinuation of study drug should be considered in cases where the subject develops:

- a severe hypersensitivity reaction, as discussed with Sponsor/Medical Monitor
- 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:

- Pregnancy
- If the Investigator deems it is in the subject's best interest

Subjects who have to discontinue study drug but who have not been permanently discontinued from the study, should proceed with the Q6M visits and/or the recurrence visit schedule as originally planned to perform the assessments as specified in the Schedules of Assessments.

3.2.4.3. STUDY TERMINATION

If the Sponsor abandons the study prior to commencement of any protocol activities, and/or after IEC/IRB and 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

3.3.1. OVERVIEW OF TREATMENTS ADMINISTERED

Upon each recurrence of TTP, open-label caplacizumab in addition to standard of care therapy should be initiated. Caplacizumab should be administered daily at least for the duration of daily PE and for 30 days thereafter. Treatment with caplacizumab may be extended for a maximum of 4 weeks in case of persistent signs and symptoms of continued underlying disease activity.
Note: Initiation of treatment with caplacizumab is not allowed in case of pregnancy and for subjects with a history of severe and/or serious hypersensitivity to IMP in Study ALX0681-C301 or Study ALX0681-C302. In addition, treatment with caplacizumab may not be initiated for subjects who did not have a baseline visit. Also see section 3.2.3.

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

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

Initiation of treatment with caplacizumab (in addition to standard of care):

Daily PE period

- Loading i.v. dose: subjects will receive a single loading dose of 10 mg study drug by i.v. bolus injection from 6 hours to 15 minutes prior to start of daily PE treatment.
  Up to 1 PE (which may be spread over 2 or more sessions in 24 hours) may be given prior to initiation of treatment with caplacizumab as long as considered part of the PE for the treatment of the presenting TTP episode.
- Daily s.c. dose: within 2 hours after completing each daily PE, a s.c. injection of 10 mg study drug will be administered daily throughout the full duration of PE treatment.

30-day post-daily PE period

Daily s.c. administration of 10 mg study drug will continue for a period of 30 days after stop of daily PE. No adjustment to this period will be made for tapering of PE. After discharge from hospital, subjects are allowed to self-administer (after learning how to prepare and s.c. inject the study drug). Towards the end of the daily PE period and when hospital discharge is foreseen, subjects (or caregiver) should be trained in the s.c. administration of the study drug under the supervision of the Investigator or designee to allow for administration when

at home. After discharge from hospital, subjects or caregiver will need to be able to administer s.c. study drug. For more details, please refer to section 3.3.6.

Treatment extension period
Treatment with caplacizumab beyond these 30 days will be guided by a number of risk factors for relapse of the presenting TTP episode and may be accompanied by an optimization of the immunosuppressive treatment. Caplacizumab should be extended for additional 7-day periods up to a maximum of 28 days for subjects who in the opinion of the Investigator have persistent active underlying disease. In parallel, optimization of the immunosuppressive treatment may be considered and includes reversal of corticosteroid tapering through increase or re-initiation of corticosteroid treatment, or start/continuation of other immunosuppressive treatment such as rituximab (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.
Caplacizumab treatment 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 period.

Recurrences during the Recurrence Period
In case of recurrent thrombocytopenia requiring re-initiation of daily PE during an ongoing recurrence period (see Figure 4 and Table 2), a new visit cycle is to be started, with a recurrence visit on the day of the new recurrence followed by all subsequent visits as indicated in Table 2. All remaining visits of the original schedule are no longer applicable and are not to be performed.
Note: an i.v. loading dose of caplacizumab needs to be administered prior to re-initiation of PE for the recurrence.

3.3.2. RANDOMIZATION

Not applicable. This is a FU study for subjects who completed Study ALX0681-C301. Upon a recurrence of TTP, subjects will receive open-label treatment with caplacizumab in addition to standard of care.

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.

3.3.3. IDENTITY OF STUDY DRUG

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

- One glass vial containing lyophilized powder (caplacizumab) for reconstitution.
- 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, e.g., 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.
  - Excipients: 0.21 mg citric acid, 5.58 mg tri-sodium citrate di-hydrate, 70 mg sucrose, 0.11 mg polysorbate-80 per vial (pH 6.5 +/- 0.5).
  - Dosage form: powder for solution for injection; reconstitution with WFI yields solution for injection.
  - Route of administration: i.v. (first dose), s.c. (all subsequent doses).

3.3.4. DRUG ACCOUNTABILITY

The Pharmacist or his/her designee is responsible for acknowledging 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, who performed the injection) 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 recurrence visits. At each recurrence visit, site personnel will review the patient diary. At each visit, site personnel will record the new information in the electronic case report form (eCRF) (also see section 3.3.6), and return the diary to the subject. Subjects will be instructed to return the completed diary at the latest at the recurrence FU 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.

3.3.5. STUDY DRUG HANDLING

Instructions for study drug receipt, handling, storage and administration are available in the manual concerning study drug.

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 caplacizumab, 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 its administration.

Dispensing
The Investigator or qualified designee(s) will dispense study drug to subjects who have met the entry and caplacizumab treatment 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 malfunction 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.

3.3.6. 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. Of note, up to 1 PE (which may be spread over 2 or more sessions in 24 hours) may be given prior to initiation of treatment with caplacizumab as long as considered part of the PE for the treatment of the presenting TTP episode.
- Daily s.c. dose: From caplacizumab treatment 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.

It is expected that subjects are hospitalized for the duration of the daily PE period.
At the clinical site, subjects will be observed in order to assess adverse reactions (e.g., hypersensitivity 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, who performed the 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

As unbound caplacizumab is assumed to be rapidly cleared by the kidney 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 (also see section 3.2.4). In addition, plasma levels of 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 FVIII:C levels which are slow to respond to study drug interruption and replacement therapy (also see section 3.2.4). Subjects who have to discontinue study drug but who have not been permanently discontinued from the study, should proceed with the Q6M visits and/or the recurrence visit schedule as originally planned to perform the assessments as specified in the Schedules of Assessments.

3.3.7. CONCOMITANT THERAPY

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).

Allowed medication
Throughout the study, the Investigator may prescribe any concomitant medication needed as supportive care.

Standard of care treatment (per standard site practice) can include:
- PE with plasma (e.g., fresh frozen plasma, solvent detergent/viral-inactivated plasma, cryosupernatant)
- Corticosteroid treatment
- Use of other immunosuppressive agents (e.g., rituximab)

Disallowed medication

Desmopressin promotes the release of vWF and is not indicated in patients with TTP as it may worsen the condition.

Following medications should be used with caution during a recurrence period:
- Medications associated with the occurrence of TTP such as but not limited to clopidogrel and ticlopidine should be avoided and if prescribed, should be used with caution.
- Anticoagulant treatment (such as vitamin K antagonists, heparin or low molecular weight heparin [LMWH], or non-acetyl salicylic acid non-steroidal anti-inflammatory molecules) should be used with caution due to an increased bleeding risk.

Contraceptives
In case of a recurrence, 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 initiation of treatment of caplacizumab until at least 2 months after last caplacizumab administration.
No additional contraceptive method is needed in case of surgical sterilization (at least 3 months prior to initiation of treatment of caplacizumab), hysterectomy, or a partner who has been vasectomized (at least 3 months prior to initiation of treatment of caplacizumab).

Male subjects are not obliged to use a contraceptive method specifically for this study (including the caplacizumab treatment period). 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.

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 dispensed but not-dosed, 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, who performed the injection) of each study drug administration. For more information on the study patient diary, please refer to section 3.3.4.

3.4. ASSESSMENTS

3.4.1. TIMING OF ASSESSMENTS

3.4.1.1. ELIGIBILITY PROCEDURES

Subjects who completed Study ALX0681-C301 will be given the option to participate in this FU Study ALX0681-C302 by signing a separate ICF, which will be obtained before any study-specific procedures are performed. The date of ICF signing will be recorded in the eCRF. After informed consent has been obtained, each subject will be assigned a unique subject ID number, which will be correlated/connected to their subject ID number in Study ALX0681-C301.

At the Final (28 day) FU visit in Study ALX0681-C301 or within one month thereafter, 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. For subjects for whom the Final (28 day) FU visit in Study ALX0681-C301 occurred prior to local approval and site activation for this study, a time window of +1 month after site activation is permitted to complete the screening/baseline visit.

3.4.1.2. ASSESSMENT PERIOD (Q6M VISITS)

Subjects will be asked to attend Q6M visits for 3 years starting from a screening/baseline visit.

Assessments at the Q6M visits will include (also see Schedules of Assessments):

- Concomitant medication
- Adverse events
- Physical examination, vital signs
- Clinical laboratory analyses include chemistry (aspartate aminotransferase [AST], alanine aminotransferase [ALT], LDH, creatinine, protein, C-reactive protein [CRP], cholesterol) and hematology (hemoglobin [Hb], hematocrit [Hct], red blood cells [RBC], white blood cells [WBC], platelets). Urinalysis includes assessment of albumin.
- Cognitive assessment: Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (only at screening/baseline and the 36-month visit and only in those countries where RBANS is available in the local language[s])
- Quality of life assessment: SF36 questionnaire
- Headache Impact Test (HIT-6™)
- Organ damage marker: troponin (TnI)
- ADAMTS13 activity

- PD parameter: vWF:Ag
- Immunogenicity: ADA panel

3.4.1.3. RECURRENCE PERIOD

Upon recurrence of TTP, defined as recurrent thrombocytopenia requiring initiation of daily PE, standard of care treatment consisting of daily PE and immunosuppression is to be initiated. In addition, open-label caplacizumab will be administered daily for the duration of daily PE and for 30 days thereafter. Treatment with caplacizumab may be extended for a maximum of 4 weeks in case of persistent signs and symptoms of underlying disease activity (e.g., ADAMTS13 activity profile remains below 10% based on weekly measurements).
The visit schedule upon initiation of treatment consists of a recurrence visit at presentation, a visit on Day 3 of treatment with caplacizumab, weekly visits during treatment with caplacizumab (starting 1 day after the last daily PE), and a recurrence FU visit 1 week after the end of treatment with caplacizumab. Q6M visits that are scheduled within a recurrence period will not be held as assessments at such visits would be confounded by the concurrent recurrence.

In case of recurrent thrombocytopenia requiring re-initiation of daily PE during an ongoing recurrence period (see Figure 4 and Table 2), a new visit cycle is to be started, with a recurrence visit on the day of the new recurrence followed by all subsequent visits as indicated in Table 2. All remaining visits of the original schedule are no longer applicable and are not to be performed.
If the new recurrence visit coincides with a visit of the original recurrence visit schedule, then assessments already performed for the original recurrence visit do not need to be repeated for the new recurrence visit.

Assessments will include (also see Schedules of Assessments):
- Review of caplacizumab treatment criteria (at the recurrence visit only)
- Pregnancy test (blood or urine) for female subjects of childbearing potential (Note: pregnancy is an exclusion criterion for treatment with caplacizumab)
- TTP recurrence information (at the recurrence visit, the Week 1 visit and the recurrence FU visit only)
- Concomitant medication
- PE information (at the Week 1 visit only)
- Study drug administration
- Quality of life assessment: SF36 questionnaire (at the recurrence FU visit only)
- Adverse events

- Clinical laboratory analyses include hematology (Hb, Hct, RBC, WBC, platelets) and chemistry (AST, ALT, LDH, creatinine, protein, cholesterol and CRP). Urinalysis includes assessment of albumin.
- Physical examination, vital signs
- Organ damage marker: troponin (TnI)
- ADAMTS13 activity
- Immunogenicity: ADA panel
- PK (not assessed if treatment with caplacizumab has not been initiated)
- PD parameters: vWF:Ag and RICO (the latter will not be assessed if treatment with caplacizumab has not been initiated).

3.4.2. DEMOGRAPHICS AND MEDICAL HISTORY

Demographics and medical history will be assessed at the visits indicated in the Schedules of Assessments.

Demographic data will include: year of birth, gender, race (if allowed), and ethnicity (if allowed).

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

3.4.3. TTP-RECURRENCE INFORMATION

TTP recurrence information will be assessed at the visits indicated in the Schedules of Assessments.

TTP recurrence information includes information on presenting symptoms (e.g., systemic, bleeding, renal, neurological, and cardiovascular signs and symptoms), duration and outcome of the TTP recurrence.

The duration of TTP recurrence is defined as time to platelet count response defined as initial platelet count ≥ 150×10^9/L with subsequent stop of daily PE within 5 days.

Treatment outcome will include assessment of refractoriness to treatment (defined as absence of platelet count doubling after 4 days with elevated LDH), time to platelet count

response (platelet count ≥ 150×10^9/L), duration of daily PE, and number of days in hospital/intensive care unit.

3.4.4. ASSESSMENTS OF EFFICACY

3.4.4.1. COGNITIVE ASSESSMENT

The cognitive status of the subjects will be assessed using the Repeatable Battery for Assessment of Neuropsychological Status (RBANS) [18, 19] according to the visits defined in the Schedules of Assessments (only in those countries where RBANS is available in the local language[s]).

The RBANS is a 30-min comprehensive screening test with five individual domains (immediate memory, delayed memory, attention, language, and visuospatial ability) to examine the cognitive mental status of a subject. The results of the RBANS are reported as a total scale (overall score) and scores for each individual domain, based on the normal population values adjusted for age, provided by the RBANS manual. The overall score is a summary of performance across all five individual domain scores. Scores are standardized to a mean score of 100 with a standard deviation of 15.

3.4.4.2. HEADACHE IMPACT TEST (HIT-6)

Headache frequency and severity information will be assessed using the HIT-6™ [20, 21] according to the visits defined in the Schedules of Assessments.

The HIT-6 questionnaire is an easy to administer assessment that can be used as a clinical evaluation of the impact of headache on a patient's quality of life in both clinical practice and clinical research. The HIT-6 can be completed in approximately 5 to 10 minutes.
The HIT-6 questionnaire is a composite measure from other headache inventory questionnaires including Headache Disability Inventory, Migraine Disability Assessment questionnaire, Headache Impact Questionnaire, and the Migraine-Specific Quality of life Questionnaire.
The questionnaire includes 6 questions covering the 6 areas of functioning most impacted in headache sufferers including pain, role functioning (the ability to carry out usual activities), social functioning, vitality (energy/ fatigue), cognitive functioning, and psychological/emotional distress. Scores range from 36 to 78, with higher scores reflecting worse condition.

3.4.4.3. SF36 QUESTIONNAIRE

The SF-36 [22, 23] will be completed at visits as indicated in the Schedules of Assessments.

The SF-36 consists of 36 items that can be summarized into 8 domains: physical functioning, role limitations due to physical health problems (role-physical), bodily pain, general health, vitality, social functioning, role limitations due to emotional problems (role-emotional), and mental health. Two summary measures, the physical component summary and the mental component summary, can be derived based on these domain scores.

The concepts measured by the SF-36 are not specific to any disease, allowing comparison of relative burden of different diseases, in addition to the relative benefit of different treatments.

3.4.5. PHARMACOKINETIC ASSESSMENTS

3.4.5.1. SAMPLE COLLECTION AND HANDLING

In case of a recurrence, blood samples of approximately 2.0 mL will be taken for analysis of caplacizumab concentrations[†††], at 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.

3.4.5.2. 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.

3.4.6. PHARMACODYNAMIC ASSESSMENTS

3.4.6.1. SAMPLE COLLECTION AND HANDLING

Throughout the study, blood samples of approximately 3.5 mL will be taken for analysis of vWF:Ag levels, according to the time points defined in the Schedules of Assessments.
In case of a recurrence, an additional blood sample of approximately 3.5 mL will be taken for analysis of RICO [†††], at the time points defined in the Schedules of Assessments.

[†††] PK and RICO will not be assessed if treatment with caplacizumab has not been initiated.

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.

3.4.6.2. BIOANALYSIS

Determination of RICO and vWF:Ag levels in plasma will be done by a validated method.

3.4.7. ASSESSMENT OF DISEASE RELATED MARKERS

3.4.7.1. SAMPLE COLLECTION AND HANDLING

Throughout the study, separate blood samples will be taken for analysis of ADAMTS13 activity and TnI as biomarker for organ damage at the time points defined in the Schedules of Assessments:

- for analysis of ADAMTS13 activity, a sample of approximately 3.5 mL.
- for analysis of TnI, a sample of approximately 3.5 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.

3.4.7.2. BIOANALYSIS

Determination of ADAMTS13 activity and TnI will be done by a validated method. Bioanalytical procedures (ADAMTS13 activity only) will be described in a separate Bioanalytical Analysis Plan.

3.4.8. IMMUNOGENICITY

3.4.8.1. 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 during treatment with caplacizumab, 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. For further details on sample collection, shipment, storage and processing, please refer to a separate Lab Manual.

3.4.8.2. BIOANALYSIS

Determination of ADA will be done using a validated screening, confirmatory and titration ADA bridging assay, with further characterization using the modified ADA (mADA) assay and potentially with a neutralizing Antibody (nAb) assay (functional assay and/or epitope characterization [CDR binding] assay). The immunogenicity data will be processed according to a dedicated Bioanalytical Analysis plan.

3.4.9. ASSESSMENTS OF SAFETY

Safety assessments consist of AEs, laboratory assessments, vital signs, and physical examinations. The time points are defined in the Schedules of Assessments.

As indicated in section 3.4.8.1, in case of a severe and/or serious hypersensitivity reaction during treatment with caplacizumab, an additional blood sample should be collected as soon as possible after the start of the event to characterize the reaction. Bioanalytical procedures will be described in a separate Bioanalytical plan.

3.4.9.1. 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.

3.4.9.2. LABORATORY ASSESSMENTS

Blood and urine 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 and assessment of platelet count and LDH levels performed as per standard of care during the recurrence period (if available).

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:
- Chemistry: AST, ALT, LDH, creatinine, protein, CRP, cholesterol
- Hematology: Hb, Hct, RBC, WBC, platelets
- Urinalysis: albumin

Upon recurrence, a pregnancy test (urine or blood) will be performed in female subjects of childbearing potential at the recurrence visit. Note: pregnancy is an exclusion criterion for treatment with caplacizumab.

Laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the Investigator.

All clinically significant laboratory findings will be recorded as AEs in the eCRF (also see section 3.4.9.1).

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.

3.4.9.3. VITAL SIGNS

Vital signs parameters blood pressure and pulse (assessed after 5 min in supine position), and height and weight will be measured at the time points indicated in the Schedules of Assessments.

All parameters will be recorded in the eCRF. Clinically relevant abnormalities should be recorded as AE in the eCRF.

3.4.9.4. PHYSICAL EXAMINATION

A complete physical examination will be performed at the time points indicated in the Schedules of Assessments.

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

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.

3.4.10. TOTAL BLOOD VOLUME

The total amount of blood taken during the study will vary depending on the number of recurrences.

The total volume of blood taken during the study will be approximately 182 mL in case of no recurrences and 560 mL in case of 1 recurrence.

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 above 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 in case allowed 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.
Note that blood samples for ADA, PD parameters and disease-related markers need to be collected prior to start of the PE treatment and/or study drug administration (whatever comes first; at the recurrence visit and the Treatment Day 3 visit) or prior to study drug administration (at all subsequent recurrence visits).

3.5. ADVERSE EVENT EVALUATION AND REPORTING

3.5.1. ADVERSE EVENTS

AE definitions will be consistent with 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.

A TEAE is any AE temporally associated with the use of study drug, whether considered related to the study drug or not.

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 if considered clinically significant by the Investigator.

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.

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

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

- Yes
- No
- Not applicable

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 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.

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, on medication (yes/no), period of intake, nature of the AE, and relation to study drug (if applicable).

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 expedite reports of 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 expedite all reports of 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 risk 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.

All AEs occurring during the study 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 subject receiving treatment with caplacizumab, or in his partner, during treatment with caplacizumab and within 2 months after the last dose of caplacizumab.

All pregnancy 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 3.2.4, subjects who get pregnant during treatment with caplacizumab should be withdrawn from study treatment (not 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 to a subject that does not have a TTP recurrence episode.
- 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.

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

Medication errors that occur 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:

- **Intention-to-observe (ITO) population**: All subjects who enrolled in Study ALX0681-C302.
- **Recurrence population:** All subjects in the ITO population who have experienced at least one recurrence in Study ALX0681-C302.

Unless otherwise specified, the ITO population will be used for the analysis of the Q6M FU data on efficacy, disease-related markers, PD, immunogenicity and safety. The recurrence population will be used for analysis of data collected during recurrence periods. Depending on whether subjects have been treated with caplacizumab or not, or have been retreated with caplacizumab, different subsets of the recurrence population may be defined for specific analyses. This will be detailed in the statistical analysis plan (SAP).

3.6.2. STATISTICAL AND ANALYTICAL PLAN

Interim analyses may be conducted in view of supporting regulatory submissions.

All data for enrolled subjects will be loaded in the database, and will be cleaned prior to final database lock (or interim database lock, if applicable) according to the specifications detailed in a data validation plan.

The SAP will be generated under responsibility of the Sponsor and will be finalized prior to final database lock (or interim database lock in case of an interim 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. Details of the data analyses will be specified in the SAP.

3.6.3. DEMOGRAPHICS, MEDICAL HISTORY AND TTP RECURRENCE INFORMATION

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

The following efficacy analyses will be performed:

- TTP-related events (defined as TTP-related death, recurrence of TTP or reported major thromboembolic event [e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism or deep venous thrombosis]):
  - Summary of the (cumulative) proportion of subjects with TTP-related events over time (including after 12M FU visit, after 24M FU visit, and after 36M FU visit), as well as the number of such events.
  - Summary of the time to first TTP-related event (starting from screening/baseline visit), based on a Kaplan-Meier (KM) analysis.
- Mortality: mortality rate during the study.
- Recurrence of disease:
  - Summary of the (cumulative) proportion of subjects with recurrence of disease over time (including after 12M FU visit, after 24M FU visit, and after 36M FU visit), as well as the number of such events.
  - Summary of time to first recurrence (starting from end of previous TTP episode), based on a KM analysis.
  - Summary of TTP recurrence information, including duration of daily PE.
  - Descriptive analysis of incidence of recurrence in relation to ADAMTS13 levels after previous TTP episode.
- Reported major thromboembolic events (e.g., myocardial infarction, cerebrovascular accident, pulmonary embolism or deep venous thrombosis):
  - Summary of the (cumulative) proportion of subjects with reported major thromboembolic events over time (including after 12M FU visit, after 24M FU visit, and after 36M FU visit), as well as the number of such events.
  - Summary of the time to first reported major thromboembolic event (starting from screening/baseline visit), based on a KM analysis.
- Cognitive assessment:
  - Summary of RBANS cognitive assessment score, including change from baseline, over time.
  - Descriptive comparison of RBANS cognitive assessment score with reference population.
- Quality of life assessment:
  - Summary of HIT-6 scores, including change from baseline, over time.
  - Summary of SF-36 scales, including change from baseline, over time, and at the end of recurrence period.

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

(1) caplacizumab-treated, defined as subjects in the ITO population who have been randomized to caplacizumab in Study ALX0681-C301, evaluated up to their first recurrence[‡‡‡]; (2) standard of care-treated, defined as subjects in the ITO population who have been randomized to placebo in Study ALX0681-C301, evaluated up to their first recurrence.

All efficacy endpoints related to assessments during the recurrence period will be analyzed using the recurrence population. The effect of retreatment of caplacizumab on these endpoints will be evaluated.

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

3.6.5. EVALUATION OF PHARMACOKINETIC AND PHARMACODYNAMIC, DISEASE RELATED MARKERS AND IMMUNOGENICITY PARAMETERS

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 sampling time using descriptive statistics and will be listed and summarized in tabular and/or graphical form.

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

Immunogenicity will be assessed through listing of individual (ADA, mADA and nAb) results by subject, summary tables and immunogenicity time profiles. Immunogenicity data will be correlated with PK and PD readout using descriptive statistics per subject category based on pre-Ab and TE ADA status (using ADA results obtained in Study ALX0681-C301), summarized in tabular and/or graphical form. In addition, immunogenicity will be correlated with possible safety findings. The effect of retreatment with caplacizumab on immunogenicity will be assessed.

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

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.

All safety analyses will be performed using the ITO population for the overall study period and using the recurrence population for recurrence periods specifically. Details will be provided in the SAP.

AEs will be fully described and coded according to the Medical Dictionary for regulatory Activities (MedDRA). Frequency of subjects presenting AEs, AEs leading to discontinuation of study drug, adverse drug reactions, and SAEs will be tabulated 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. 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.

Abnormal findings in physical examinations will be listed.

3.7. DATA QUALITY ASSURANCE AND DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Audits may 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 ensure 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 and year of birth 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.

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 the aims, methods, objectives, potential clinical benefits, and potential hazards of the study, and any discomfort participation in the study may entail. Subjects 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 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, 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, and after the subject has orally consented to the subject's participation in the study, 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, and that informed consent was freely given by the subject.

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. 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".

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 vendor prior to the first visit.

5.2.1. CASE REPORT FORM COMPLETION

Case report forms will be completed for each subject.

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 (if applicable); 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 or study treatment (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 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 or resulting from this study. He/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

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9. APPENDIX

Appendix 1: Schedule of Assessments in Case of TTP Recurrence (in Case Treatment With Caplacizumab is not Initiated)

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

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

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

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

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

Signature Page

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 organizations electronic signature policies and procedures.

[redacted]

Date: [redacted]
Meaning: Approved
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