CLINICAL STUDY PROTOCOL

A PHASE II, SINGLE-BLIND, RANDOMISED, PLACEBO-CONTROLLED TRIAL TO STUDY THE EFFICACY AND SAFETY OF ANTI-VON WILLEBRAND FACTOR NANOBODY ADMINISTERED AS ADJUNCTIVE TREATMENT TO PATIENTS WITH ACQUIRED THROMBOTIC THROMBOCYTOPENIC PURPURA

CONFIDENTIAL

CRO code: AYX081PR-AL0081

Sponsor code: ALX-0681-2.1/10

EudraCT number: 2010-019375-30

Investigational product:	ALX-0081, anti-von Willebrand factor Nanobody INN: caplacizumab
Clinical Phase:	Phase II study
Indication to be studied:	Acquired thrombotic thrombocytopenic purpura
Sponsor	Ablynx NV, Technologiepark 21, B-9052 Zwijnaarde, Belgium
Sponsor's Contact	[redacted]
Coordinating Investigator	[redacted]
Version	Final version 12.0
Date	24 June 2013

This study will be performed in compliance with the principles of Good Clinical Practice (GCP).

SIGNATURES

Signature Page

I have read the protocol of study ALX-0681-2.1/10, version 12.0. I understand the contents and intend to comply fully with all requirements and the applicable current local and international regulations and guidelines. No changes will be made without formal authorisation by Ablynx NV in the form of a protocol amendment.

Sponsor

(see end of document for electronic signature)

[redacted]

Date

Coordinating Investigator

[redacted]

June 25th, 2013

Date

Investigator Signature Page

I have read the protocol of study ALX-0681-2.1/10, version 12.0. I understand the contents and intend to comply fully with all requirements and the applicable current local and international regulations and guidelines. No changes will be made without formal authorisation by Ablynx NV in the form of a protocol amendment.

Investigator Signature: _____ _____

Investigator Name *(block letters):* _____ Date

Institution: _____

RESPONSIBILITIES AND CONTACT INFORMATION

Sponsor's Study Manager

[redacted]

Ablynx NV

Technologiepark 21

B-9052 Zwijnaarde

Belgium

Phone: +32 (0)9 262 00 00

Fax: +32 (0)9 262 00 02

CRO Project Management

[redacted]

SERIOUS ADVERSE EVENT CONTACT INFORMATION

In the event of a serious adverse event, the Investigator will send a faxed report within 24 hours of notification to:

CRO

[redacted]

MEDICAL EMERGENCIES

In the event of a medical emergency the Medical Monitor (CRO) can be contacted by investigative staff at:

CRO

[redacted]

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LIST OF ABBREVIATIONS

ACS	Acute coronary syndrome
ACT	Activated clotting time
ADA	Anti-drug antibody
ADAMTS13	A disintegrin-like and metalloprotease with thrombospondin repeats 13
AE	Adverse event
ALT	Alanine transaminase
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
AR	Adverse (drug) reaction
ASAP	As soon as possible
AST	Aspartate transaminase
AUC_{0-t}	Area under the plasma concentration vs. time curve up to time t
AUC_{0-24}	Area under the plasma concentration vs. time curve up to 24 hour
AUC_{extra}	Extrapolated AUC obtained from Ct/Lambda z
AUC_{inf}	Area under the plasma concentration vs. time curve up to infinite
$AUC_{0-\tau}$	Area under the plasma concentration vs. time curve between dosing intervals
BED	Biologically effective dose
BMI	Body mass index
BNP	Brain natriuretic peptide or B-type natriuretic peptide
BUN	Blood urea nitrogen
Ca	Calcium
Cl	Chloride
CL	Clearance
C_{max}	Maximum observed plasma concentration
CNTB	Computerised neuropsychological test battery
CRF	Case report form
CRO	Contract research organisation
CRP	C-reactive protein
CRT	Choice reaction time
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
d	Day
DAP	Data analysis plan
DAT	Direct antiglobulin test
DIC	Disseminated intravascular coagulation
DSMB	Data safety monitoring board
EC	Ethics committee
ECG	Electrocardiogram
ELISA	Enzyme-linked immunosorbent assay
FVIII	Coagulation factor VIII
g	Gram
GCP	Good clinical practice
GFR	Glomerular filtration rate
GLP	Good laboratory practice
GP	Glycoprotein

h	Hour
HBsAg	Surface antigen of the hepatitis B virus
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HUS	Haemolytic-uremic syndrome
i.a.	Intra-arterial
IB	Investigator's Brochure
ICH	International conference on harmonisation
IEC	Independent ethics committee
i.m.	Intramuscular
INR	International normalised ratio
IRB	Institutional review board
ITP	Immune thrombocytopenic purpura
ITT	Intention-to-treat
IU	International unit
i.v.	Intravenous(ly)
λ_z	Elimination rate constant
K	Potassium
kg	Kilogram
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LMWH	Low molecular weight heparin
m	Month
MD	Multiple dose
MCH	Mean corpuscular haemoglobin
MCV	Mean corpuscular volume
MCHC	Mean corpuscular haemoglobin concentration
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Magnesium
mg	Milligram
min	Minute
mL	Millilitre
µL	Microlitre
mm	Millimetre
MRT	Mean residence time
MTD	Maximum tolerated dose
Na	Sodium
NA	Not applicable
NOAEL	No observed adverse effect level
NSE	Neuron specific enolase
NT-proBNP	N-terminal pro B-type natriuretic peptide or N-terminal pro brain natriuretic peptide
OLE	Open label extension
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PE	Plasma exchange
PK	Pharmacokinetics
PP	Per protocol

PT	Prothrombin time
PTT	Partial thromboplastin time
QC	Quality control
RBC	Red blood cells
RICO	Ristocetin cofactor activity
RIPA	Ristocetin-induced platelet aggregation
SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Serious adverse (drug) reaction
Sβ100	Protein S-100 beta
s.c.	Subcutaneous(ly)
SD	Single dose
SRT	Simple reaction time
SUSAR	Suspected and unexpected serious adverse reactions
$t_{1/2}$	Terminal phase half-life
t_{max}	Time to reach C_{max}
TnI	Troponin I
TnT	Troponin T
TRALI	Transfusion related acute lung injury
TTP	Thrombotic thrombocytopenic purpura
ULN	Upper limit of normal
ULvWF	Ultra large vWF
VMEM	Visual memory
vWD	von Willebrand disease
vWF	von Willebrand factor
V_z	Volume of distribution
WBC	White blood cells
WFI	Water for injection
WHO	World health organisation
WLL/DR	Word list learning and delayed recall
WLL/SR	Word list learning and selective reminding
WMEM	Working memory

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1. STUDY SYNOPSIS

Study Title

A Phase II, single-blind, randomised, placebo-controlled trial to study the efficacy and safety of anti-von Willebrand factor Nanobody administered as adjunctive treatment to patients with acquired thrombotic thrombocytopenic purpura

Study Number: ALX-0681-2.1/10

Study Phase: II

Study Centre and Patients

This is a multicentre, multinational study in which it is anticipated to include 110 patients with acquired thrombotic thrombocytopenic purpura (TTP) in approximately 53 participating sites in approximately 13 countries in Europe, Middle East, Australia and Northern America.
This population includes symptomatic patients with acute episodes of acquired TTP, requiring treatment with plasma exchange (PE).

Objectives

Primary

- Reduction of time-to-response, defined by the achievement of laboratory blood marker response, confirmed at 48 hours after the initial reporting of this response

Secondary (including longer-term disease sequelae)

- Improvement in number of subjects responding to therapy
- Reduction in PE procedure-related items
- Reduction of time to resolution or improvement of signs and symptoms typical of TTP, including blood markers
- Reduction of number of exacerbations (defined as recurrent thrombocytopenia following a response and requiring a re-initiation of daily PE treatment after ≥ 1 day but ≤ 30 days after the last daily PE) and relapses (defined as *de novo* event of TTP that occurs later than 30 days after the last daily PE)[1,2]
- Improvement of cognitive level at steady state post acute phase
- Improvement of clinical symptoms and organ function
- Reduction in mortality within the PE treatment period and within the subsequent study

drug treatment period (including tapering)

- Reduction of concomitant treatment-related complications
- Evaluation of safety and immunogenicity of adjunctive treatment with ALX-0081
- Determination of pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of ALX-0081 in patients with acquired TTP

Endpoints

Primary Endpoint

- Time-to-response, based on the following criteria:
  - Recovery of platelets ≥ 150,000/µL
  - This response must be confirmed at 48 hours after the initial reporting of platelet recovery equal to or above 150,000/µL by a *de novo* measure of platelets ≥ 150,000/µL and lactate dehydrogenase (LDH) ≤ 2 X upper limit of normal (ULN) (i.e. “confirmed platelet response”)

Secondary Endpoints

All endpoints achieved within 30 day period after end of study drug treatment:

- Number of subjects with complete remission (defined as confirmed platelet response and absence of exacerbation)[1,2]
- Number of (subjects with) exacerbations of TTP (defined as recurrent thrombocytopenia following a confirmed platelet response and requiring a re-initiation of daily PE treatment after ≥ 1 day but ≤ 30 days after the last daily PE), and time to first exacerbation of TTP
- Number of subjects relapsing of TTP (defined as *de novo* event of TTP that occurs later than 30 days after the last daily PE)
- Number of daily PE sessions, number of plasma units administered and number of days of daily PE
- Resolution of non-focal neurological symptoms as defined by neurocognitive function at complete remission, measured by a neurocognitive test battery
- Resolution or improvement (improvement of ≥ 1 grade in the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 scale) of TTP-related signs and symptoms as captured on physical examination and as adverse events, at complete remission and at end of the study drug treatment period (including tapering) (by number of

unique subjects and by total number of adverse events (AEs))

- Total mortality within the PE treatment period and within the subsequent study drug treatment period (including tapering)
- Incidence of PE treatment-related AEs, such as, but not restricted to: haemorrhage from catheter insertion, sepsis, catheter thrombosis, pneumothorax, fluid overload, hypoxia, hypotension, anaphylactoid reactions and transfusion related acute lung injury (TRALI)
- Incidence and severity of ALX-0081 treatment-emergent AEs and relationship to study drug
- Development of anti-drug antibodies (ADA) ≤ 30 days post-last study drug treatment
- PK and PD profile

Tertiary Endpoints

[redacted]

Study Design

This is a Phase II multicentre, single-blinded, parallel design, randomised, placebo-controlled study.

After confirmation of eligibility to study participation, subjects will be randomised in a ratio of 1:1 to either receive ALX-0081 or placebo as adjunctive therapy to PE (Figure 1).

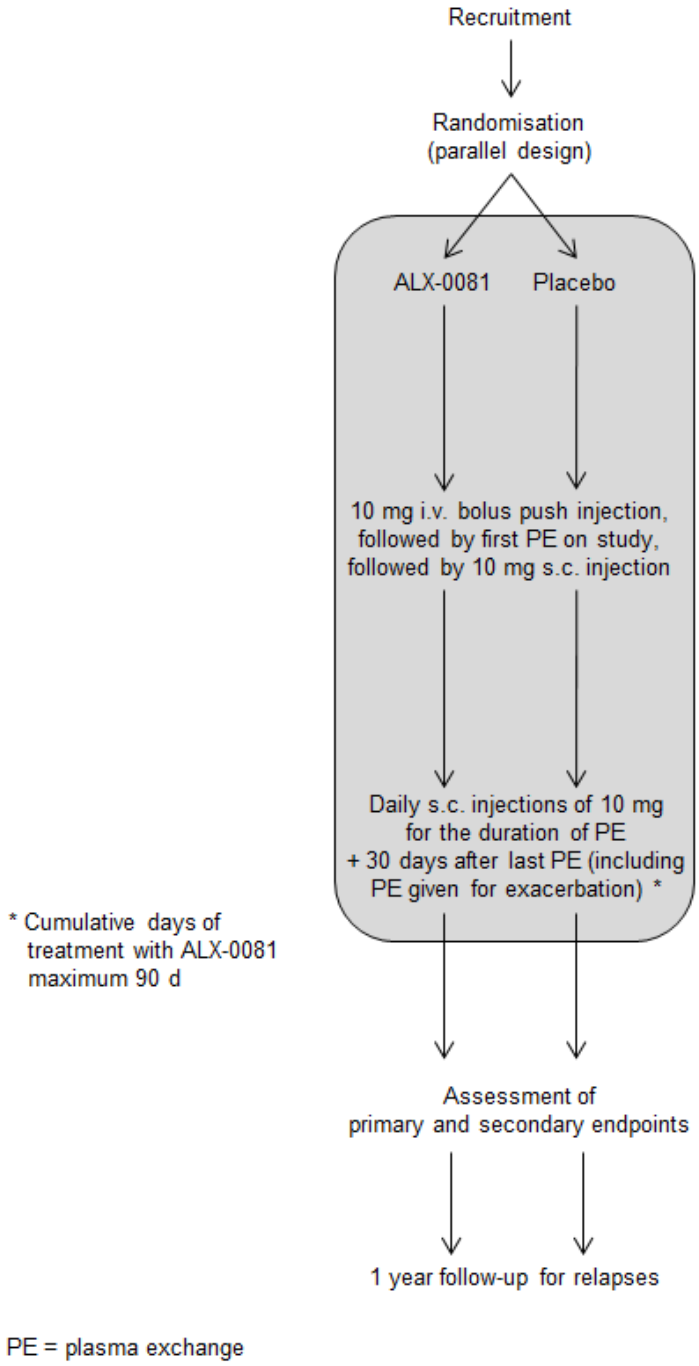


Figure 1: **Treatment flow chart.**
First PE on study: see section 4.2

Subjects will receive a first intravenous (i.v.) bolus of 10 mg ALX-0081 or placebo via push injection within 6h, but not later than 15 minutes prior to the initiation of PE on study (which can either be the very first PE session, if the subject was randomised prior to the initiation of PE, or the second PE session, if the subject was randomised after one, single PE session; see section 4.2). This first PE on study is followed by subcutaneous (s.c.) administration of 10 mg study drug.

Subsequently daily s.c. administrations of 10 mg ALX-0081 (Table 1) or placebo will follow each PE session for the duration of PE (including tapering and PE given for exacerbations) and once daily for 30 days following the very last PE (including tapering) (Table 1). The maximum total daily dose of study drug is 10 mg when administered in conjunction with PE (20 mg only in case twice daily PE sessions are needed) and 10 mg when in the period following the very last PE (including tapering). Study drug administration will continue in case of re-initiation of PE for an exacerbation of TTP, with a maximum total treatment duration limited to 90 days after first administration of study drug.

At ≤ 30 days after the last day of study drug administration, subjects will be assessed for the primary and secondary endpoints of the study, and will be followed for a maximum of 1 year for relapses and other tertiary [redacted] endpoints.

Laboratory parameters for inclusion, study conduct, safety assessments and assessments of response/relapse, re-treatment and study medication dose modification will be assessed at each local site laboratory.

An independent Data Safety Monitoring Board (DSMB) will monitor accruing safety data during the study (SAEs on an ongoing basis and ‘early safety look’ when 16 subjects, 8 ALX-0081 treated and 8 placebo-treated, have completed treatment with study drug) and will make recommendations on continuation of the study as appropriate. An interim analysis for safety with formal stopping rules is foreseen when 28 of the ALX-0081 treated subjects have been treated, and will make a recommendation on study continuation or discontinuation. No review of efficacy data by the DSMB is foreseen.

Planned Sample Size

It is anticipated to include 110 patients with acquired TTP.

Study Period

- 30 months recruitment period is anticipated.

- 12 months of follow-up after last administration of study drug (until last subject completes the 12-month follow-up visit).

Duration of Treatment and Follow-up

Treatment with study drug will be continuous during the full time interval of PE and for 30 days after the very last PE (including tapering and PE given for exacerbations). Study drug administration will continue in case of re-initiation of PE for an exacerbation of TTP, with a maximum treatment duration limited to 90 days after first administration of study drug. Subjects will be followed for 12 months after last administration of study drug.

Study Medication

ALX-0081, anti-von Willebrand factor (vWF) Nanobody

ALX-0081 is a clear, colourless solution formulated as a solution for injection. It is provided in sterile, preservative-free, non-pyrogenic, single-use 2R glass vials with injection stoppers and light blue aluminum crimped caps. One vial contains 2.4 mL solution for injection. One mL solution for injection contains as active ingredient 5 mg of ALX-0081 (INN: caplacizumab).

Excipients

Water for injection (WFI), potassium chloride (KCl), potassium dihydrogen phosphate (KH_2PO_4), disodium monohydrogen phosphate ($Na_2HPO_4x2H_2O$), sodium chloride (NaCl), Glycine, Polysorbate 80

Placebo

Placebo is provided in 2R glass vials. One vial contains 2.4 mL solution for injection with identical excipients as ALX-0081.

Storage and Stability

ALX-0081 and placebo are delivered and stored deep frozen at –20°C (± 5°C) in the original outer package to be protected from light. Stability studies showed that ALX-0081 is stable at -20°C for at least 3 years and can therefore be stored under these conditions at the investigative site. ALX-0081 contains no antimicrobial preservatives. The study drug must not be used after the expiry date indicated on the labels of the outer package.

Dosage, Method of Administration and Duration

Dosage, method of administration and duration of treatment are summarised in Table 1.

Table 1: Dosage, method of administration and treatment duration.

First study drug administration is 10 mg as an i.v. bolus, administered by a push injection, 15 minutes to 6 hours prior to initiation of PE on study.* This first PE on study is followed by subcutaneous (s.c.) administration of 10 mg study drug.

* As discussed in section 4.2, one PE session prior to randomisation is allowed. In such case, the second PE session will be the first PE on study.

S.c. study drug administration **during treatment phase with PE**	
Frequency of PE	*Treatment administration - daily*
1 PE/day	Administer 10 mg study drug within 30 min after end of PE
2 PEs/day	• For subjects receiving anti-vWF Nanobody: administer 10 mg study drug within 30 min after each PE • For subjects receiving placebo, maintain a once daily dosing regimen
Tapering (< 1 PE/day)	Daily administration of 10 mg study drug. On days with PE: within 30 min after end of PE; on days without PE at 24 h (± 1 h) after previous administration

S.c. study drug administration (in hospital and at home) for **30 days after the very last PE** (including tapering and PE given for exacerbations)*: 10 mg study drug once daily.

* As discussed in section 7.2, in case of exacerbation of TTP, standard treatment (PE) should be re-initiated and daily administration of study drug continued. The “study drug post-PE” period (for 30 days after the very last PE) will recommence once PE is again stopped. Maximum treatment duration with study drug will be limited to 90 days after first administration of study drug.

If **clinically relevant bleeding*** occurs
• Stop study drug administration and continue PE if clinically indicated and applicable • Assess vWF:Ag and Factor VIII (FVIII) levels**. If FVIII < 10%, assess for anti-FVIII antibodies and if presence is confirmed, permanently discontinue study drug. • If vWF:Ag and/or FVIII levels are at a clinically significant low level, initiate i.v. Haemate-P 50 U/kg (or equivalent antihaemophilic factor/vWF complex) • i.v. Haemate-P treatment should be discontinued when bleeding has clearly stopped and when vWF > 50% • Restart study medication at 10 mg daily when bleeding has clearly stopped and when vWF > 50% and FVIII levels are within normal range

* Clinically relevant bleeding is defined as moderate to severe (including life-threatening) bleeding requiring urgent medical and/or surgical intervention.

** FVIII chromogene or other measure of FVIII activity

Criteria for Evaluation

Clinical Outcome

- Time-to-response of treatment, defined by a recovery of platelets ≥ 150,000/µL. This response must be confirmed at 48 hours after the initial reporting of platelet recovery

above 150,000/µL by a *de novo* measure of platelets ≥ 150,000/µL and LDH ≤ 2 X ULN

- Number of subjects with complete remission
- Number of (subjects with) exacerbations of TTP and time to first exacerbation of TTP. Number of subjects relapsing of TTP, and time to first relapse of TTP
- Daily PE data, including serious adverse events (SAEs) related to daily PE treatment
- Neurocognitive function, as measured by a neurocognitive test battery. This test will be preceded by the Glasgow Coma Score to measure the state of consciousness of the subject
- Improvement of organ dysfunction and improvement of TTP related signs and symptoms
- Total mortality
- Determination of biomarkers of TTP including but not limited to disintegrin-like and metalloprotease with thrombospondin repeats 13 (ADAMTS13) levels and anti-ADAMTS13 antibody titres (see also PD assessments)

Safety Assessments

- Incidence and severity of ALX-0081 treatment-emergent AEs and relationship to study drug
- Monitoring of safety markers during treatment, including, but not limited to: platelet count and platelet activation, FVIII, activated partial thromboplastin time (aPTT), prothrombin time (PT), fibrinogen, haemoglobin, cardiac markers, liver function, RICO
- Incidence of clinically relevant bleeding
- Bleeding graded according to the modified immune thrombocytopenic purpura (ITP) Bleeding Score
- Vital signs (blood pressure, heart rate and body temperature)
- Cardiovascular monitoring
- Glasgow Coma Score
- Immunogenicity: development of ADA

PK assessment

Predose plasma concentrations against time will be plotted to demonstrate attainment of steady state.

The plasma concentration-time data of ALX-0081 will be analysed using population PK modeling. Typical population values of basic PK parameters will be estimated together with the inter-individual variability. Effects of subject demographics, laboratory parameter values, and other covariates on the pharmacokinetics of ALX-0081 will be explored. The results of

the population PK analyses will be reported separately in an independent Modeling and Simulation report.

PD assessments

- RICO (conducted at central lab)
- vWF, including vWF:Ag and vWF propeptide (conducted at central lab)
- FVIII chromogene (conducted at central lab)

Inclusion Criteria

1. 18 years of age or older
2. Men or women willing to accept an acceptable contraceptive regimen
3. Patients with clinical diagnosis of TTP
4. Necessitating PE (one, single PE session prior to randomisation into the study is allowed)
5. Subject accessible to follow-up
6. Obtained, signed and dated informed consent

Exclusion Criteria

1. Platelet count greater or equal to 100,000/µL
2. Severe active infection indicated by sepsis (requirement for pressors with or without positive blood cultures)
3. Clinical evidence of enteric infection with *E. coli* 0157 or related organism
4. Anti-phospholipid syndrome
5. Diagnosis of disseminated intravascular coagulation (DIC)
6. Pregnancy or breast-feeding
7. Haematopoietic stem cell or bone marrow transplantation-associated thrombotic microangiopathy
8. Known congenital TTP
9. Active bleeding or high risk of bleeding
10. Uncontrolled arterial hypertension
11. Known chronic treatment with anticoagulant treatment that can not be stopped safely, including but not limited to:
    - vitamin K antagonists
    - heparin or low molecular weight heparin (LMWH)
    - non-acetyl salicylic acid non-steroidal anti-inflammatory molecules

12. Severe or life threatening clinical condition other than TTP that would impair participation in the trial
13. Subjects with malignancies resulting in a life expectation of less than 3 months
14. Subjects with known or suspected bone marrow carcinosis
15. Subjects who cannot comply with study protocol requirements and procedures.
16. Known hypersensitivity to the active substance or to excipients of the study drug
17. Severe liver impairment, corresponding to grade 3 toxicity defined by the CTCAE scale. For the key liver parameters, this is defined as follows:
    - bilirubin > 3 x ULN (need to differentiate isolated increase in indirect bilirubin due to haemolysis, this is not an exclusion parameter, but disease related)
    - alanine aminotransferase/aspartate aminotransferase (ALT/AST) > 5 x ULN
    - alkaline phosphatase (AP) > 5 x ULN
    - gamma glutamyl transpeptidase (GGT) > 5 x ULN
18. Severe chronic renal impairment, as defined by GFR < 30 mL/min

Statistical Methods

The primary endpoint (i.e. time-to-response of blood markers comprising recovery of platelets ≥ 150,000/µL) will be formally assessed by means of a survival analysis. Descriptive statistics for efficacy parameters and secondary/tertiary endpoints (including safety, PK and PD analysis) will be presented for all available data, using either the intention-to-treat (ITT) population, the safety population, or the per protocol (PP) population. Additional information on the study populations that will be included is available in Section 10. A Statistical Analysis Plan (SAP) will be prepared before closing the database and will comprise all methods and tests applied for analysis of the data.

Description of Study Days and Schedules of Assessments

See Table 9 for a general overview of study assessments. Assessments at screening, during the treatment phase and during the follow-up phase are listed in Table 10, Table 11 and Table 13 in Section 8.1, respectively.

2. BACKGROUND INFORMATION

2.1 Introduction

2.1.1 Role of vWF in Platelet Aggregation

The multimeric plasma protein vWF is essential for recruiting circulating platelets to the damaged vessel wall upon vascular injury. This recruitment is mediated through binding of the vWF A1-domain with the platelet receptor glycoprotein GPIb-IX-V.
Upon expression by endothelial cells, vWF is secreted into the circulation as ultra-large multimers or ultra-large vWF (ULvWF). These multimers are processed into smaller regular sized multimers through enzymatic cleavage by ADAMTS13. In these regular sized multimers of vWF, the GPIb-IX-V platelet receptor binding site in the A1 domain is cryptic and will not spontaneously react with platelets. A conformational activation of the GPIb-IX-V platelet receptor binding site in the A1 domain is triggered by immobilisation or under conditions of shear stress. This then results in platelet adhesion and subsequently in thrombus formation.

2.1.2 Role of vWF and vWF Processing in Pathophysiology of TTP

TTP is a rare and life-threatening disorder of the blood coagulation system, in which accumulation of ULvWF multimers has been implicated, leading to an increased risk of thrombus formation in small blood vessels due to excessive platelet aggregation. The condition is characterised by systemic platelet aggregation in the microcirculation, producing fluctuating ischaemia in many organs. If sustained, this may cause tissue infarction, associated with profound thrombocytopenia and erythrocyte fragmentation.
ULvWF multimers have the natural ability to spontaneously interact with the platelet receptor GPIb-IX-V. In healthy subjects, these ULvWF multimers are immediately processed into regular sized vWF multimers via cleavage by ADAMTS13. However, in patients with TTP, processing of the ULvWF multimers is impaired, resulting in the persistence of the constitutively active A1 domain of the ULvWF which readily interacts with the GPIb-IX-V platelet receptor. This eventually results in formation of the characteristic blood clots found in the TTP patient population.

2.1.3 Role of vWF in Other Pathologies

Coronary heart disease

In patients without impairment of vWF processing, the initial pro-thrombotic activity of the ULvWF multimers is immediately pacified by their processing into regular sized multimers via cleavage by ADAMTS13. The resulting regular sized multimers have an inactive A1 domain which becomes only “reactivated” for binding the platelet GPIb-IX-V receptor upon immobilisation and through a conformational change under shear stress. This “reactivation” of the A1 domain becomes a critical component in the unwanted thrombus formation in patients with coronary heart disease undergoing a percutaneous coronary intervention (PCI) procedure. In coronary arteries, blood flow conditions are recognised as high shear, which triggers the said conformational change of the A1 domain in regular sized vWF-multimers, resulting in platelet adhesion to the injury of the coronary artery vessel wall (caused by the PCI procedure) and subsequent thrombus formation. Therefore, Ablynx also performed clinical studies to develop ALX-0081 for the prevention of thrombosis in coronary heart disease, and more specifically acute coronary syndrome (ACS).

von Willebrand disease

In von Willebrand disease (vWD), there are 3 kinds of disorders. Type 1 of the disease is pertinent when the vWF is quantitatively reduced, but not absent, with a resulting symptomatology that consists of non-severe mucosal bleeding or bruising. Type 2 vWD concerns patients who carry gene mutations/deletions resulting in qualitatively abnormal vWF. A subcategory of Type 2 patients (Type 2N), have genetic alterations provoking a markedly decreased binding affinity for FVIII. Type 2, with the exception of Type 2N, has variable bleeding, usually mild to moderate and is in general restricted to limited bruising and mucosal bleeding. In Type 3 vWD virtually no vWF is present. In patients with Type 2N and Type 3 vWD the carrier function of vWF for FVIII is compromised. These patients may present with severe bleeding phenotype resembling haemophilia A, mainly provoked by the loss of FVIII. In symptomatic patients (i.e. Type 2N and 3) or in cases where clinical interventions could lead to an increased bleeding risk (i.e. tooth extraction, surgeries) vWF concentrate is used as therapeutic, stabilising the patient’s bleeding risk and restoring the normal function of vWF/FVIII-mediated haemostasis.

2.2 ALX-0081, anti-vWF Nanobody

ALX-0081 is a bivalent Nanobody, consisting of two identical monovalent building blocks, that target vWF. ALX-0081 is able to interact with vWF in both its active (i.e. functional for

interaction with GPIb-IX-V as regular size multimers and as ultra-large multimers) and in its inactive stage (regular size multimers prior to conformational change of A1 domain). Nanobodies are therapeutic proteins based on the smallest functional fragments of heavy chain antibodies, occurring in the *Camelidae* family. They have a high degree of sequence and structural homology to human immunoglobulin VH domains.

ALX-0081 avidly binds to its vWF multimeric target, thereby blocking the interaction of any sizes and activation stages of multimeric vWF with the GPIb-IX-V platelet receptor. The interaction of ALX-0081 with vWF is highly specific and it does not interact with human blood cells or platelets. Furthermore, its interference with the platelet GPIb-IX-V receptor is selectively through the binding of the vWF A1 domain and it does not affect the capacity of vWF to interact with fibrillar collagens or with collagen type VI. The Nanobody does not affect the activity of the vWF-protease ADAMTS13, nor does it interfere with the binding of FVIII to vWF.

In *in vitro* assays with plasma from TTP patients, ALX-0081 selectively inhibits the interaction of the constitutively active A1 domain in the ULvWF multimers with the platelet GPIb-IX-V receptor. Therefore it prevents the characteristic platelet string formation, typical of TTP, which constitutes of small thrombi leading to platelet agglutination in the microvasculature, resulting in local ischaemia and platelet consumption.

Given the established role of the interaction between vWF and platelet GPIb-IX-V in the pathogenesis of TTP, it is anticipated that ALX-0081 may provide a new option for the treatment of this condition. Therefore, targeting the activity of ULvWF and preventing the interaction with GPIb-IX-V is an attractive concept for treatment and prevention of thrombotic complications in TTP.

2.3 Nonclinical Study Data

This section gives an overview of the most relevant pharmacological, pharmacokinetic and toxicological properties of ALX-0081. See the Investigator's Brochure for full details on the nonclinical development of ALX-0081.

2.3.1 Pharmacology

The affinity of ALX-0081 for the vWF A1-domain was estimated with a Biacore assay at < 10 pM. The efficacy of ALX-0081 was studied *in vitro* and showed that ALX-0081 is able to inhibit platelet adhesion to collagen specifically under high shear conditions and block ristocetin-induced platelet aggregation (RIPA) with a complete inhibition at a concentration of ~ 0.4 µg/mL.

ALX-0081 cross-reacts with vWF of baboon, cynomolgus monkey and guinea pig and therefore these species are suitable for PD and toxicological studies. In tissue cross reactivity studies using immunohistochemistry on human, cynomolgus monkey and guinea pig tissues, no unexpected staining was observed.

The efficacy and safety of ALX-0081 was investigated *in vivo* in a modified Folts' model for stable angina in baboons. In all of the animals tested, the antithrombotic activity of ALX-0081 was stronger than that observed for Plavix® (clopidogrel), Aspirin® (acetylsalicylic acid) and Heparin® (heparin). Similar efficacy of ALX-0081 was observed compared to the potent antithrombotic drug ReoPro® (Abciximab). The plasma concentration of ALX-0081 in baboons required for full inhibition of thrombus formation was between 0.3 and 0.5 µg/mL. A bleeding model involving measurement of the amount of blood from a well defined wound in baboons showed less bleeding with ALX-0081 than with Plavix® or ReoPro® even at doses exceeding the effective dose 10-fold. These results clearly demonstrate that the therapeutic window of ALX-0081 is much wider compared to the current marketed drugs Plavix® and ReoPro® (Figure 2)

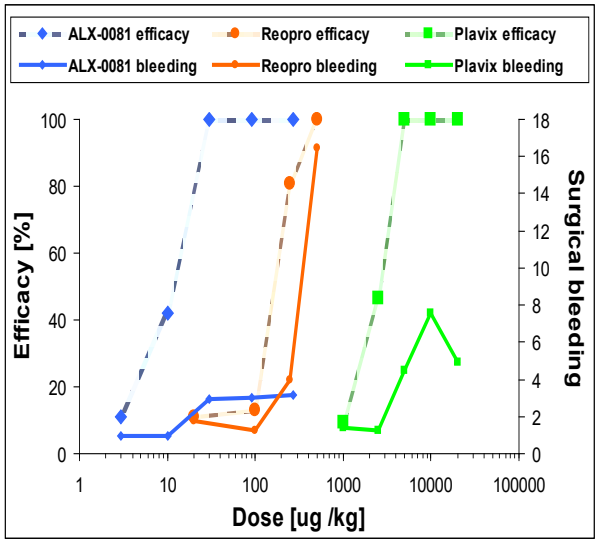


Figure 2: **Therapeutic window of ALX-0081, ReoPro® and Plavix® in a baboon model. Efficacy expressed as % inhibition of cyclic flow reductions in a modified Folts' model and safety expressed as n-fold increase bleeding from a well defined incision compared to a control level is shown in function of dose administered.**

The antithrombotic activity of ALX-0081 in baboons is of short duration (several hours) and it can be reversed by administration of vWF, indicating that vWF can be used as an antidote for ALX-0081.

Due to the lack of a relevant animal model, no *in vivo* efficacy of ALX-0081 to neutralise ULvWF was demonstrated. Initial *in vitro* data using plasma from TTP patients in flow chamber experiments point towards therapeutic potential of ALX-0081 in the TTP setting. In these experiments, endothelial cells were stimulated to produce ULvWF strings on their

surface. These strings support adhesion of platelets even under static and low shear conditions (Figure 3A). In the presence of normal plasma the ULvWF strings are rapidly cleaved by the protease activity of ADAMTS13, whereas in plasma from patients with TTP platelet deposition to the vWF strings is retained due to the lack of functional ADAMTS13 (Figure 3B). Importantly, ALX-0081 added to the TTP plasma completely blocks platelet deposition (Figure 3C), thereby demonstrating that ALX-0081 not only inhibits the regular sized vWF multimers but also ULvWF released by endothelial cells. However, if platelets were allowed to form platelet strings prior to ALX-0081 addition, ALX-0081 was not able to detach these platelets.[3]

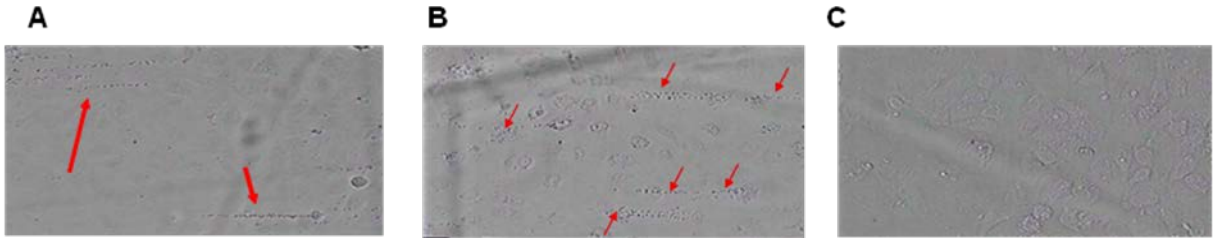


Figure 3: Effect of ALX-0081 on platelet adhesion to ULvWF.
Images captured from real-time video microscopy: captures of platelets perfused over stimulated endothelial cells under conditions of low shear stress (300s-1). Platelets resuspended in buffer (A) or in plasma from TTP patients (B) adhere to ULvWF thereby forming platelet strings (red arrows) on the surface of endothelial cells. In the presence of plasma from TTP patients, ALX-0081 completely abolishes the platelet interaction with ULvWF (C).

2.3.2 Pharmacokinetics

ALX-0081 shows a non-linear kinetic profile. In all species, a first phase characterised by a rapid decline in plasma levels can be described at the higher doses immediately after administration (i.v.) or after peak plasma levels are reached (s.c./intramuscular [i.m.]). This is thought to be caused by rapid distribution of the unbound drug in combination with rapid elimination via renal clearance (glomerular filtration). In cross-reactive species this decline is followed by a second phase.[4,5] The terminal half-life ($t_{1/2}$) of ALX-0081 -more precisely ALX-0081 bound to vWF- ranges between 5-36 hours across the relevant species. A biodistribution study with radiolabelled ALX-0081 supported this hypothesis and clearly showed that ALX-0081 bound to vWF follows a hepatic clearance pathway, whereas unbound drug is excreted via the kidneys.[6]

Since excess ALX-0081 over a vWF occupancy ratio of 1 is cleared rapidly, trough drug concentrations did not increase significantly even upon multiple administrations at high doses in toxicology studies, again pointing towards a low potential for accumulation. Clinical anticipated administration routes are i.v. and s.c. The absolute bioavailability of ALX-0081 after s.c. administration, in cynomolgus monkey, ranged from 82 to 97%.[7]

2.3.3 Toxicology

Currently, the toxicology program for ALX-0081 consists of single dose (SD) toxicity studies both in cynomolgus monkey (i.v. and s.c.) and guinea pig (i.v.), 2-week repeated dose toxicity studies in cynomolgus monkey (i.v., s.c.) including safety pharmacology assessment and 13-week repeated dose toxicity studies in guinea pig and cynomolgus monkey with an 8-week recovery including safety pharmacology and fertility functional assessment. Local tolerance was assessed separately in rabbit.

The pivotal toxicology studies were performed for 13- week duration in cynomolgus monkey and guinea pig as the non-rodent and rodent species, respectively. In both studies, animals were given s.c. 4 times daily doses of ALX-0081 at 6 hour intervals (0, 0.1, 1 or 10 mg/kg per dose) for 13 weeks.

Data obtained during the in life phase show that vWF/FVIII levels were decreased with a non-cumulative pharmacology effect in cynomolgus monkey and guinea pig (FVIII only), with a mean maximum decrease from individual baseline of FVIII of 84 % in all dose groups in cynomolgus monkey. The complete data set including recovery phase is under assessment. In guinea pig, FVIII decreases with a mean of 47.0% (preliminary data reported for 13-week toxicity study, raw data without QC).

Full neutralisation of vWF activity, defined as below the limit of detection, was demonstrated by RICO assays (PD marker) in both guinea pig and cynomolgus monkey (preliminary data analysis).

Clinical observations in the 13-week toxicity study in cynomolgus monkey revealed slight to fairly severe haematomas and swellings at the injection sites in a dose-related manner. Macroscopic examination at necropsy revealed haemorrhagic s.c. tissue at the injection sites in several ALX-0081-treated animals of all dose groups. In addition, slightly increased bleeding at injection sites was recorded in one male (4 mg/kg/day) and two females (4 and 40 mg/kg/day). The same female at 4 mg/kg/day showed exaggerated menstrual bleeding on Day 30 and the same female at 40 mg/kg/day had a nose bleed. All bleeding events were described to be related to the pharmacological effect of ALX-0081.

In the 13-week toxicity study in guinea pig, no ALX-0081 treatment related adverse effects were observed in clinical signs, water and food consumption, body weight, clinical pathology parameters and urinalysis. Macroscopic examinations at necropsy revealed haemorrhagic s.c. tissue at the injection sites in all dose groups. The observations are similar to those seen in cynomolgus monkey. Incidence and severity increased with dose and the observed effects were also considered to be related to the pharmacological effect of ALX-0081.

There were no ALX-0081 treatment-related effects on electrocardiogram (ECG) and organ weight. No changes in ophthalmological and auditory parameters were noted in both guinea pig and cynomolgus monkey.
In summary, these findings confirms that even at high doses (and exposures) effects on FVIII levels are within expected ranges, the clinical observations in the nonclinical species correlate with the minor findings in clinical trials so far and that continuous treatment with high doses of ALX-0081 might lead to symptoms which resemble the mild vWD type 1 and 2.

A GLP embryo-fetal developmental toxicity study in guinea pigs has been conducted. No embryo-fetal toxicity and no teratogenic potential have been observed. The no observed adverse effect level (NOAEL) was higher than 20 mg/kg/day since no adverse effects were observed.

Local tolerance has been studied in rabbits, by administration via the i.v., s.c., i.m., intra-arterial (i.a.) and paravenous routes in doses up to 1.2 mg/kg b.w. administered in 0.5 mL/kg. No test item-related alterations were observed.

Immunogenicity was evaluated during toxicology studies in guinea pig and cynomolgus monkey. In general, ADA could be detected in a limited subset of animals after i.v or s.c. single or multiple dose (MD) administration in both species, which did however not compromise the exposure. Moreover, PD markers were not affected by measured ADA in any of the studies, indicating indirectly that these antibodies were not neutralising the activity of ALX-0081.

In conclusion, ALX-0081 has been well tolerated in guinea pig and cynomolgus monkey used as relevant toxicology animal species as a consequence of (i) high target specificity (ii) a mode of action specific for pathological conditions and (iii) a unique self-regulating PK profile which leads to rapid clearance of excess drug.

2.4 Clinical Experience

Currently, Ablynx is developing anti-vWF Nanobody for the treatment of TTP. For full details on the clinical development of ALX-0081, see the Investigator's Brochure.
Completed and ongoing clinical trials with anti-vWF Nanobody are listed in Table 2.

Table 2: Overview and current status of clinical trials with anti-vWF Nanobody.

Study number (EudraCT N°)	Study title	Phase	Status
Clinical trials supporting ACS indication			
ALX-0081-01/06 (2006-006502-28)[8]	A Phase I, double blind, randomized, placebo-controlled, parallel group study in healthy male volunteers to investigate the safety, tolerability and pharmacokinetics of the Nanobody ALX-0081 administered intravenously as single ascending doses	Ia	Completed
ALX-0081-1.2/08 (2007-007263-24)[9]	A Phase I double blind, placebo controlled study of ALX-0081 multiple dose administrations in stable angina patients undergoing PCI	Ib	Completed
ALX-0081-2.1/09 (2009-012206-39)	A Phase II randomized, open label clinical trial in high risk percutaneous coronary intervention (PCI) patients receiving standard antithrombotic treatment plus either ALX-0081 or GPIIb/IIIa inhibitor (ReoPro®) over a period of 24 hours	IIa	Completed (final data analysis and reporting ongoing)
Clinical trial supporting TTP indication			
ALX-0681-1.1/08 (2008-006624-60)[10]	A Phase I study in healthy volunteers to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of anti-vWF Nanobody administered subcutaneously	I	Completed

An overview of all subjects who have received one or more doses of anti-vWF Nanobody is provided in Table 3.

Table 3: Extent of exposure for anti-vWF Nanobody.

	Dose	Duration (Days)	No. Subjects
SUBCUTANEOUS			
Healthy Volunteers			
ALX-0681-1.1/08	2 mg	1	3
Adults – male and female	4 mg	1	3
	8 mg	1	3
	10 mg	1	3
	16 mg	1	3
	10 mg	7	6
	10 mg	14	6
Total			**27**
INTRAVENOUS			
Healthy Volunteers			
ALX-0081-01/06	0.5 mg x 1 infusion (1h)	1	3
Adults - male	1 mg x 1 infusion (1h)	1	3
	2 mg x 1 infusion (1h)	1	3
	4 mg x 1 infusion (1h)	1	3
	8 mg x 1 infusion (1h)	1	3
	12 mg x 1 infusion (1h)	1	6
Total			**21**
Stable Angina Patients undergoing PCI			
ALX-0081-1.2/08	2 mg x 1 infusion (1h)	1	3
Adults - male and female	4 mg x 1 infusion (1h)	1	3
	6 mg x 1 infusion (1h)	1	3
	9 mg x 1 infusion (1h)	1	3
	6+4+4+4 mg q6h infusions (1h)	1	6
	6+4+4+4 mg q6h bolus	1	20
Total			**38**
High risk PCI patients			
ALX-0081-2.1/09	6+4+4+4 mg q6h bolus	1	181
Adults - male and female			
TOTAL			**267**

In the following sections, a summary of the setup and results for the studies listed in Table 2 is provided.

2.4.1 Clinical Trials Supporting ACS Indication

Up to now, three clinical trials with anti-vWF Nanobody, supporting its development for the treatment of ACS, have been approved. The Phase Ia trial in healthy male volunteers has been completed successfully, as well as the SD and MD stages of the Phase Ib trial in stable angina patients undergoing elective PCI. An open-label extension (OLE) of the latter trial to evaluate administration of ALX-0081 by i.v. bolus injection compared to i.v. infusion has completed the treatment phase. Finally, a Phase II trial in high risk PCI patients, comparing ALX-0081 and ReoPro® was initiated in July 2009.

The Phase Ia trial was designed to assess the safety, tolerability and PK of ALX-0081 in healthy male volunteers. The first dose of study medication was i.v. 500 µg ALX-0081 or placebo (dose level 1) followed by 2-fold, 4-fold, 8-fold, 16-fold and 24-fold of the first dose in dose levels 2-6, respectively.

The subsequent Phase Ib study was designed to determine the maximum tolerated dose (MTD) and/or biologically effective dose (BED) and the Phase II recommended dose of ALX-0081 in ACS patients. In addition, this study aimed to determine the safety and tolerability of escalating doses of ALX-0081 in patients undergoing PCI and to document the biological and clinical response to therapy. In Stage A of the study, single ascending doses (2, 4, 6 and 9 mg) of ALX-0081 (n = 3 per dose level) or placebo (n = 1 per dose level) were administered as a 1h i.v. infusion. In the second stage of the trial (Stage B), multiple dosing was evaluated and subjects received an initial dose of 6 mg, followed by 3 subsequent doses of 4 mg every 6 hours (n = 6 ALX-0081 and n = 2 placebo). Route of administration was also i.v. infusion. Following Stage B, an open label extension was initiated with 22 subjects (Stage C) (n = 20 ALX-0081 and n = 2 placebo) in order to determine the optimal i.v. route of administration for ALX-0081 in man (bolus injections or 1 hour infusions).

The conclusions of both trials can be summarised as follows:

- Single and multiple i.v. administrations of ALX-0081 are safe and well tolerated
- The BED (providing a complete inhibition of vWF-mediated platelet aggregation for > 24 hours) and Phase II recommended dose is a SD of 6 mg, followed by 3 subsequent doses of 4 mg every 6 hours, given as i.v. bolus injections
- RICO can be used as a reliable biomarker for the PD effect of ALX-0081, i.e. inhibition of vWF-mediated platelet aggregation

- In subjects receiving the BED, mean RIPA values below 10% were maintained for a maximum of 24 hours and clinically relevant RICO inhibition was maintained for a maximum of 30 hours
- Non-linear PK properties were determined
- Half-life values were similar after single and repeated dosing. ALX-0081 plasma concentration values at 6, 12, 18 and 24 hours during repeated dosing showed that the trough values did not increase but appeared to have reached a steady state
- There were no apparent clinical differences between the treatment groups with regards to the number of subjects with (S)AEs, nor with regards to the AE profile
- The only adverse drug reactions clearly attributable to ALX-0081 administration were alterations of the coagulation parameters. Mild, transient and non-dose dependent decreases in FVIII and vWF were observed, but were not considered clinically relevant. A summary of the safety findings of both trials is provided in the following table

Table 4: Safety summary of Phase I trials with i.v. administration of anti-vWF Nanobody.

Trial	Group	# Subj	vWF Ag decrease	FVIII decrease	Bleeding signs	IPR	AEs	SAEs
Phase Ia	Placebo	19	0	0	0	1 (5%)	1 (5%)	0
	ALX-0081	21	8 (38%)	6 (29%)	0	3 (14%)	5 (24%)	0
Phase Ib	Placebo	6 + 2OLE	0	2 (25%)	2 (25%)	3 (38%)	8 (100%)	2 (25%)
	ALX-0081	18 + 20OLE	38 (100%)	38 (100%)	3 (8%)	21 (55%)	33 (87%)	7 (18%)

- No immunogenic responses were detected up to 30 days after administration of ALX-0081

Based on the results of the Phase I studies, a Phase II, randomized, open-label clinical trial was initiated in high risk acute coronary syndrome (ACS) patients undergoing PCI. The objective of the study was to compare the safety, and more specifically bleeding risk, of ALX-0081 versus the GPIIb/IIIa inhibitor ReoPro® (abciximab) in 364 high risk PCI patients (181 and 183 in the ALX-0081 and abciximab treatment groups respectively), and to assess tolerability, as well as biological and clinical effectiveness.

The Phase II study has just been completed, and reporting is currently ongoing. Based on the available results, there were no significant safety concerns raised for treatment with ALX-0081 in this study, and the results seen were as would be expected for this patient

population of high risk PCI patients. For additional details and interim results of this study, please refer to the Investigator's Brochure.

2.4.2 Clinical Trial Supporting TTP Indication: Phase I Study in Healthy Volunteers

The goal of this Phase I trial (ALX-0681-1.1/08) in healthy volunteers was to determine the MTD or BED and the Phase II dosing and scheduling of ALX-0081, in order to support the further clinical development of ALX-0081 in TTP patients.
In total, 36 healthy volunteers were included in this randomised, placebo-controlled study to evaluate the safety of single ascending doses and multiple doses of ALX-0081 administered s.c. (Table 5).

Table 5: Dosing schedule for Phase I trial with ALX-0081 by s.c. administration.

Cohort	Dose (mg)	Number of daily doses	Subjects receiving ALX-0081	Subjects receiving placebo
SD				
Cohort 1	2	1	3	1
Cohort 2	4	1	3	1
Cohort 3	8	1	3	1
Cohort 4	16	1	3	1
Cohort 5	10	1	3	1
MD				
Cohort 6	10	7	6	2
Cohort 7	10	14	6	2

PK results

After s.c. administration, ALX-0081 plasma concentrations increased in all dose groups with a mean t_{max} ranging from 4 to 10 h postdose. Mean peak plasma concentrations (C_{max}) were 219.7, 385.7, 443.7, 528.0 and 611.0 ng/mL for the 2, 4, 8, 10 and 16 mg dose groups, respectively. Overall, half-lives were comparable within the 4 to 16 mg dose range. PK results from the MD part of the study show that steady state was reached already after first dosing. The steady-state PK parameters, after once daily repeated s.c. administration of ALX-0081 10 mg for 7 or 14 days, were comparable, indicating that no accumulation occurred. The results of the regression analysis showed no dose proportionality for C_{max} and AUC_{0-24} and dose proportionality for AUC_{last} and AUC_{inf}.

PD results

Inhibition of the biomarker RICO was observed in all doses groups ranging from 70% inhibition in the 2 mg dosing group to approximately 90% inhibition in the other SD groups. Reversal towards basal levels took place after approximately 72 h post dosing. A rapid and sustained inhibition of approximately 90% was observed after dosing in both MD groups. Values returned to basal levels at day 15 and day 22 after 7 days and 14 days MD respectively. In all dose groups of the SD part of the study complete RICO inhibition (defined as values < 20%) was observed from 4-18 h (2 mg), 12-18 h (4 mg), 4-24 h (8 mg), 4-36 h (10 mg) and 4-48 h (16mg) after dosing. In both groups of the MD part of the study RICO was completely inhibited from 2-168 h after dosing, i.e. from day 1-8 (7 day) and from 2-360 h after dosing, i.e. day 1-16 (14 day). A summary of the main PD findings is provided in Table 6.

Table 6: Summary of main PD results (number (%) of subjects with event).

Dose level	Subjects (*n*)	RICO < 20%			vWF < 50%	FVIII < 50%
		Subjects (%)	Start (h)*	Stop (h)*		
SD						
2 mg	3	2 (67)	2-4	12-18	3 (100)	0 (0)
4 mg	3	2 (67)	4-6	18-36	1 (33)	1 (33)
8 mg	3	3 (100)	2-4	18-48	3 (100)	3 (100)
16 mg	3	3 (100)	1-4	48	0 (0)	2 (67)
10 mg	3	3 (100)	2-6	24-36	3 (100)	3 (100)
Placebo	5	0 (0)	NA	NA	0 (0)	0 (0)
MD						
10 mg (7d)	6	6 (100)	2-4	168-192	5 (83)	3 (50)
Placebo (7d)	2	0 (0)	NA	NA	0 (0)	0 (0)
10 mg (14d)	6	6 (100)	2-4	336-360	5 (83)	5 (83)
Placebo (14d)	2	0 (0)	NA	NA	0 (0)	0 (0)

* Time relative to first administration
NA: not applicable

Safety

Overall the study drug ALX-0081 was well tolerated and there was no difference in the number of subjects with AEs and their respective severity between the ALX-0081 treatment groups and placebo. In all doses of the SD part of the study the related AEs were low and in all verum categories no more than 1 subject reported 1 related AE. In the MD 7 days part of the study, a total of 5/6 subjects (83%) reported 13 related AEs in the verum group compared to 2/2 subjects (100%) reporting 2 related AEs in the placebo group. In the MD 14 days part of the study a total of 6/6 subjects (100%) reported 46 related AEs in the verum group compared to 1/2 subjects (50%) reporting 1 related AE in the placebo group. A dose

dependency was not observed, but more related AEs were shown after longer treatment in the MD group of the study, including an increase of the number of bruises and bleedings, all being of mild intensity. All injection and puncture site reactions were of mild intensity and therefore clinically not relevant. The SD part of the study showed no dose relationship regarding incidence and severity of AEs. Since there was only one active dose level used in the MD part of the study no conclusions can be drawn concerning dose dependency of AEs. Main safety results are summarised in Table 7.

Table 7: Summary of main safety results (number (%) of subjects with event, both related and unrelated events).

Dose level	Subjects (*n*)	AE	SAE	Bleeding	Haematoma at injection site	Haematoma at blood sampling site	Other haematoma
SD							
2 mg	3	2 (67)	0 (0)	1 (33)	0 (0)	1 (33)	0 (0)
4 mg	3	2 (67)	0 (0)	1 (33)	0 (0)	0 (0)	0 (0)
8 mg	3	3 (100)	0 (0)	0 (0)	0 (0)	1 (33)	0 (0)
16 mg	3	3 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (33)
10 mg	3	1 (33)	0 (0)	0 (0)	0 (0)	1 (33)	0 (0)
Placebo	5	3 (60)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
MD							
10 mg (7d)	6	6 (100)	1 (17)*	5 (83)	1 (17)	0 (0)	3 (50)
Placebo (7d)	2	2 (100)	0 (0)	1 (50)	0 (0)	1 (50)	0 (0)
10 mg (14d)	6	6 (100)	0 (0)	5 (83)	5 (83)	4 (67)	5 (83)
Placebo (14d)	2	2 (100)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)

* unrelated SAE, meniscus lesion of the knee

Immunogenicity

Anti-ALX-0081 antibody response was measured on day 1 (predose), day 7, day 60 and day 22 for the 14 day part of the study. A total of 4 subjects had positive pre-dose assay read-outs and 1 subject had an initial positive response at follow-up. However, no samples were confirmed as showing treatment emergent positive responses, indicating the absence of an immunogenic response to ALX-0081.

Overall conclusion

In summary it can be concluded that s.c. administration of ALX-0081 as a SD or administered as daily injection for up to 14 days was well tolerated and no difference could be detected regarding the number of subjects with AEs and their severity between ALX-0081- and placebo-treated subjects. All injection and puncture site reactions were of mild intensity and were classified as clinically not relevant. The PD parameters for

coagulation FVIII and vWF showed a fast and reversible decrease compared to pre-dose values. None of the observed decreases in FVIII were recorded as abnormal/clinically significant PD assessments or as AEs. Values normalised between 24 and 72 h after last dosing, depending on the dose. The biomarker RICO was completely inhibited in all subjects from a SD of 10 mg onwards for 24h, indicating biological efficacy. The biomarker was continuously suppressed below complete inhibition levels throughout the entire multiple dosing part, indicating continuous biological efficacy for > 14 days. Immunogenicity assay results indicated the absence of an immunogenic response to repeated daily administrations of s.c. ALX-0081 for up to 14 days as analysed for a minimum 45 days following completion of treatment.

2.5 Safety/Risk Profile

The risk assessment for the application of ALX-0081 can currently be determined on the basis of the preclinical data available, the data from the 3 Phase I studies in healthy volunteers and in patients with stable angina undergoing a PCI procedure, the postulated mode of action, the clinical presentation of patients with vWD and the knowledge of other generally used antithrombotic agents. In this respect, it is noteworthy that so far, preclinical models have been highly predictive for the human situation in terms of PK/PD and safety.

2.5.1 Potential Risks

Toxicity

Subchronic toxicity studies of ALX-0081 (13 weeks) have been performed in cynomolgus monkeys and guinea pigs. In both studies the NOAEL proved to be above 4x10 mg ALX-0081/kg body weight, the maximum allowable volume of administrations per day for a guinea pig or cynomolgus monkey study. The biomarker RICO was inhibited during the toxicity studies, thereby indicating the absence of neutralising antibodies against ALX-0081. Comparing the results obtained with the 13 weeks cynomolgus monkey toxicity study with a fixed daily dose of 10 mg in humans, revealed a $Ratio_{AUC24}$ of 82, demonstrating the presence of wide therapeutic window. Using PK modeling a predicted human exposure of 10.3 µg.h/mL (AUC_{24h}) following a possible bid 10 mg administration (20 mg/subject/day) can be compared to exposure reached in toxicity studies with a resulting ratio of 54 for cynomolgus monkey. Due to the conservative correction factor applied in the exposure margin calculations of guinea pigs and the limitations in volume that could be administrated to guinea pigs, a 10-fold systemic exposure margin could not be demonstrated in the guinea

pigs. Importantly, the NOAEL was not reached during the subchronic toxicity study in guinea pigs.
Hence the data obtained from the 13 weeks cynomolgus monkey study allow us to conclude that the safety margins in terms of relative systemic exposure to ALX-0081 can be considered as very wide.

Risk for bleeding

The most prominent risk of the currently used non-specific antithrombotic agents is an elevated bleeding diathesis or apparent bleeding. Beside any unexpected effects, bleeding also represents the most relevant safety concern for ALX-0081. In this context ALX-0081 was investigated in a preclinical surgical bleeding model.[11] In this study, surgical blood loss in animals receiving ALX-0081 was comparable to blood loss in Heparin® treated animals, and 2- and 4-fold less than in Plavix® and ReoPro® treated animals, respectively. This indicates that ALX-0081 may be safer than Plavix® and ReoPro® in terms of bleeding risk. The ALX-0081 doses used in this surgical bleeding model were more than 10-fold the documented effective antithrombotic dose.

In the 13-week and 26-week RD toxicity studies in cynomolgus monkey, anti-FVIII antibodies (AFA) were detected in 4 male animals with no associated clinical signs, and in one animal with associated haemolytic anaemia, signs of inflammation and extremely low FVIII:C activity. More details are included in Section 4.3 of the Investigator's Brochure.

A good understanding of the biology of vWF and the clinical presentation of patients with deficiency of vWF helps to understand the observations seen in the conducted preclinical and clinical studies and to assess the risk for bleeding appropriately. It is well known that most patients suffering from a deficiency of vWF (vWD) have mild-to-moderate quantitative deficiencies of vWF and FVIII, which are co-ordinately reduced to 5 to 30 percent of normal plasma levels (5 to 30 IU/dL).[12] This reduction is not associated with spontaneous bleeding but with bleeding after surgery (which is typical of coagulopathies) and mucosal tract haemorrhages such as epistaxis and menorraghia (which are typical of thrombocytopathies). It should be taken into account that these patients have a chronic, i.e. life-long, impairment of vWF and their vWF levels always stay far below 30 IU/dL. These patients don't receive regular prophylaxis, because their bleeding tendency is less severe. Only in patients with chronic and complete absence of vWF or levels below 5-10 IU/dL is a prophylaxis with vWF and FVIII indicated.

Since ALX-0081 interacts with the A1 domain of vWF, RICO is inhibited also during the toxicity studies. In addition, statistical significant drops in FVIII and vWF:Ag levels were observed in cynomolgus monkeys. In guinea pigs, the observed effects on FVIII were less pronounced. Although drops for FVIII were observed in both species, sufficient FVIII remained available to ensure proper coagulation (see also 2.3.3). No signs of bleeding, other than bruising at the injection sites were observed in the guinea pig study. In the cynomolgus monkeys study, slightly increased bleeding at injection sites were recorded in one male (4 mg/kg/day) and two females (4 and 40 mg/kg/day). Mucosal bleedings (1 exaggerated menstrual bleeding and 1 nose bleed) were observed in the same females. Importantly, although systemic exposure reached levels up to 80-fold higher than what can be expected in men during the Phase II trial, no signs of internal bleeding were observed. The observed clinical effects in cynomolgus monkeys are in line with the clinical presentation of patients with a mild to moderate vWD.

From the safety data collected from the Phase I studies in healthy volunteers and patients with stable angina, a single i.v. administration of 0.5 mg up to 12 mg and respective multiple administrations up to 18 mg total dose of ALX-0081 as a short infusion over 1 hour were well tolerated in all participating subjects. The observed mild decreases in FVIII and vWF levels were expected as they indicate the biological effectiveness of the drug. None of the observed decreases in FVIII chromogene or vWF levels were recorded as clinically significantly.

In healthy subjects, s.c. administration of ALX-0081 as a SD or administered as daily injection for up to 14 days was well tolerated and no difference could be detected regarding the number of subjects with AEs and their severity. All injection and puncture site reactions were of mild intensity and were classified as clinically not relevant. S.c. administration of ALX-0081 as a SD or administered as daily injection for up to 14 days resulted in a fast and reversible decrease of FVIII and vWF. The average decrease of vWF levels ranged from approximately 50% decrease in low dose groups to 70% decrease, compared to pre-dose level, in the high dose groups. For FVIII, a rapid average decrease can be found in all doses groups ranging from 30%, compared to pre-dose level, in the 2 mg dosing group to 50-65% in the other SD groups. Reversal takes place after approximately 72 h after dosing. A sustained decrease of approximately 50% can be found after dosing in both MD groups. Levels are back to basal levels after approximately 48 h post dosing in the MD groups. None of the observed decreases in FVIII were recorded as abnormal/clinically significant PD assessments or as AEs.

In summary, in all healthy subjects and patients with stable angina, the treatment with ALX-0081 resulted in a rapid and reversible reduction of vWF and FVIII levels, but this reduction never reached the levels indicating spontaneous bleeding for patients with mild or

more severe forms of vWD. It is therefore expected that the further administration of ALX-0081 does not result in a clinically significant reduction of vWF and FVIII mandating prophylaxis or treatment for an imminent bleeding risk. Of note, vWF as antidote is readily available in the respective treatment institutions and would immediately antagonise the activity of ALX-0081 and Preclinical studies have demonstrated that vWF concentrates can indeed antagonise the activity of ALX-0081.

Immunogenicity

ALX-0081 is structurally not identical to an endogenous protein and has no agonistic function. Consequently, the risk for developing antibodies with potential adverse consequences such as the neutralisation of an endogenous protein or a hyper-agonistic function is considered to be low. At present, the development of ADA after i.v. and after s.c. administration of ALX-0081 has been evaluated in the conducted Phase I trials. I.v. treatment during the Phase I trials consisted of either SD treatment or MD administrations with 4 doses during 24 h. S.c. treatment included repeated daily administration of ALX-0081 for up to 14 days. In none of the Phase I trials, treatment-emergent ADA were observed. During the planned Phase II TTP trial, ALX-0081 will be given on top of current standard of care treatment, thereby limiting the potential consequences of the development of ADA. For many of these TTP patients, immunosuppressive treatment will be part of their standard of care treatment. Other TTP patients carry an underlying disease (e.g. human immunodeficiency virus (HIV) or cancer) associated with a depressed immune status. In both groups of TTP patients the probability for development of ADA is anticipated to be reduced.

2.5.2 Potential Benefits

Although the introduction of PE and transfusion has significantly reduced the mortality rates from TTP over the last three decades, the condition still carries a significant risk of mortality and morbidity. The mortality rate of acute bouts in acute idiopathic TTP, in patients managed with the current therapies remains in the order of 10% to 30%.[1,13,14] In the case of secondary TTP, PE and transfusion are recognised to be less effective and the mortality rate is considerably higher. In the cases when the disease is secondary to pregnancy, in which PE is regarded as reasonably effective the mortality rate of an acute bout of TTP is approximately 25%, rising to over 40% in cases with concurrent pre-eclampsia.[15] However, in cases secondary to, for example, underlying malignancies or bone marrow transplant the mortality rate remains at 40% to 60% despite the use of such treatment regimens.[14,16,17]

Potential effect of ALX-0081 on pathophysiology of TTP

ULvWF-mediated platelet aggregation is recognised as a key element in the pathogenesis of idiopathic TTP both in acute disease, in refractory and relapsing patients, and in the familial form of the disease. In secondary TTP, although the underlying etiologies are varied, ULvWF also appears to play a fundamental role in the underlying pathophysiological processes that have been proposed to underlie the condition. The inhibition of ULvWF-mediated platelet aggregation represents a rational approach to treatment that may prove to be of value in the management of all subtypes of TTP. Given the continuing significant level of mortality from TTP and the observed complications of PE and transfusion, there is a clear need for the development of such additional therapeutic approaches to supplement, or potentially reduce the need for, these methods of treatment. On the basis of the available information, ALX-0081 may offer such an additional option to further improve the management of TTP.

Potential benefit of ALX-0081 in TTP: efficacy

The current therapy of TTP with PE and transfusion provides replacement ADAMTS13 and removes antibodies against the enzyme, thus progressively leading to a normalisation of ULvWF processing. However, this treatment requires multiple exchanges and transfusions over many days, during which time there is no direct pharmacological targeting of the active process of ULvWF-mediated platelet aggregation. ALX-0081 has been demonstrated to inhibit platelet-vWF interactions and particularly ULvWF-mediated platelet interaction *in vitro* and has also been shown to have no impact on ADAMTS13 function and, therefore, would not be anticipated to interfere with the enzyme replaced by plasma transfusion. In a modified Folt's model in baboons, which represents a relevant model for ACS, ALX-0081 has been demonstrated to exert a strong antithrombotic effect with a lower degree of bleeding compared with other antithrombotic agents. In an initial Phase I study, ALX-0081 has been demonstrated to inhibit ristocetin induced platelet aggregation (a vWF-mediated process) in the blood of healthy volunteers.

On the basis of these findings, it can be reasonably anticipated that ALX-0081 could be utilised, in combination with PE and transfusion, to directly inhibit the continuing formation of small thrombi and platelet consumption in the microvasculature. This may permit more rapid control of the underlying thrombotic process and accompanying platelet consumption, with the potential benefits of a reduced degree of ischaemic and haemorrhagic complications. It may also result in a more rapid clinical recovery with a shorter period and reduced number of PEs and transfusions. In addition, the demonstrated inhibition of ULvWF-mediated platelet interaction by ALX-0081 and the observed antithrombotic effects raise the potential for its longer-term use after patients have recovered from an acute bout of TTP to prevent relapses of the disease. A reduced frequency of acute bouts of TTP would represent a significant

benefit, with a potential for a reduction in the mortality and morbidity associated with TTP and a further reduction in the need for PE and transfusions over a patient's lifetime.

Potential benefit of ALX-0081 in TTP: quantification of major contribution to patient care

For acquired TTP, the hypothesis of the proposed Phase II trial is to demonstrate a decrease of 44% in the time-to-response, objectivated by a recovery of platelets ≥ 150,000/µL. Platelet count increase is a sign of diminished pathological platelet aggregation, as well as a better protection against bleeding. The decrease of LDH is a sign of decreased haemolysis and/or tissue ischaemia. This response must be confirmed up to 48 hours after the time-to-response.

Potential benefit of ALX-0081 in TTP: safety

While a more rapid recovery from TTP and a potential for a reduction in exacerbations and relapses would be of clear clinical benefit in terms of treatment efficacy, the potential for a reduction in the duration and frequency of PE and transfusion would also provide additional benefits in terms of patient safety.

Although PE and transfusion are currently regarded as the standard treatment in the management of TTP, the procedures carry the risk of significant complications. The PE procedure requires high fluid volumes and flow rates necessitating the use of central venous dual lumen haemodialysis catheters. Complications from the procedure include haemorrhage from catheter insertion, sepsis, catheter thrombosis, pneumothorax, fluid overload, hypoxia and hypotension.[18-22] Anaphylactoid reactions complicate 0.25% to 0.5% of procedures.[13,19] In addition, the infusion of plasma containing blood products can cause a non-infective TRALI. This condition is recognised as one of the most frequent causes of transfusion-related fatalities with an incidence estimated to be 0.02% to 0.05% per plasma containing unit[18] with a daily average of 17 plasma units, the daily risk can be calculated to a range of 0.34% to 0.85%. Most patients with TTP require multiple PEs and transfusions. Patients with acute idiopathic TTP require daily treatments, and an average of approximately 16 treatments is required to achieve remission.[13] In refractory cases the frequency of treatment may be increased to twice-daily.[13] In the case of patients with familial TTP, regular prophylactic plasma infusions at two to three week intervals are recommended.[23] Anaphylaxis and TRALI thus represent clear risks to patients with TTP whose treatment requires such a frequency and regularity of PEs and transfusions. While it is thought that this risk may be lower if solvent/detergent (S/D) treated plasma is used instead of fresh frozen plasma, the use of large volumes of S/D plasma may be associated with an increased risk of venous thromboembolism.[13,18] Overall, it is estimated that approximately 30% to 40%

of patients will experience adverse effects from PE and transfusion, and the mortality rate from the procedure is of the order of 2% to 3%.[2,19]

As summarised above, the information currently available from the preclinical and clinical studies with ALX-0081 also indicates that it is a well tolerated agent and, in particular, the potential for the risk of bleeding appears to be low. The currently available data suggest, therefore, that the potential reduction in PE and transfusion and their associated complications may be achieved without significant adverse effects from the use of ALX-0081 itself. If this is borne out in clinical research, it could represent a clear safety benefit for the use of the product in the treatment of patients with TTP.

Potential benefit of ALX-0081 in TTP: quality of life

Following recovery from a bout of TTP, many patients describe cognitive abnormalities for many years and report troublesome problems with memory, concentration, decreased energy and fatigue. Such symptoms have a negative impact on the quality of patients' daily lives. Furthermore, this deficit in quality of life may occur in all patients who have TTP, regardless of the aetiology and severity.[24] It is thought that these symptoms may be reflective of the residual effects of tissue ischaemia. On this basis, it could be reasonably proposed that the potential for a more rapid recovery from TTP and the limitation of thrombus formation in the microvasculature that ALX-0081 should provide, may result in an improved longer-term outcome for the patients in terms of their quality of life.

Summary

The research conducted into TTP over the past three decades has improved the understanding of the pathophysiology of the disease allowing for the potential development of novel agents targeting the underlying disease processes. There are no currently approved therapies for TTP, and although there are newer therapies currently undergoing evaluation, the studies of these potential treatments are at a relatively early stage.

ALX-0081 represents a novel approach to the treatment of TTP and the information available from *in vitro*, *in vivo* and early clinical studies all suggest a clear rationale for its use in this disease and a reasonable expectation that it will provide significant benefit in terms of efficacy, safety and quality of life for patients with TTP.

Through its inhibition of ULvWF-mediated platelet aggregation and resulting antithrombotic effect ALX-0081 may permit more rapid control of acute bouts of TTP when used in combination with PE and transfusion. This would potentially reduce the risk of organ ischaemia and a more rapid normalisation of the platelet count could also reduce the risk of haemorrhagic complications. Its use may also result in improved outcomes in poorly responsive patients, including those with secondary TTP where mortality from the disease

remains high. In addition, ALX-0081 may be of value in the prevention of relapses after recovery from an acute episode.

2.6 Rationale for Dose Selection

The initial i.v. administration of investigational drug prior to the first PE on study is justified based upon a Phase I study in healthy volunteers as well as a Phase Ib trial in ACS patients. In both studies, an immediate PD effect was observed, namely RIPA ≤ 10% in healthy volunteers and RICO ≤ 20% in ACS patients (see section 2.4). It is believed that all active ULvWF present in the blood that has not yet aggregated platelets can be inhibited from further platelet aggregation by saturating it with the immediate i.v. injection of 10 mg anti-vWF Nanobody. This would allow for predicted protection by the investigational product against further platelet aggregation until the time of start of PE therapy.
The further administrations of the investigational drug will be performed by the s.c. injection route. The proposed s.c. dosing regimen of the ALX-0081 was investigated in a Phase I study with healthy volunteers. The daily dosing of ALX-0081 10 mg as s.c. injection resulted in a complete and sustainable inhibition of the biomarker RICO indicating the complete suppression of vWF-mediated platelet aggregation. PK modeling of these subjects with normal vWF pre-treatment levels demonstrated that the required occupancy of the target vWF resulting in maximum PD effect (i.e. RICO ≤ 20%) is seen for a wide range of ALX-0081 plasma concentrations, i.e. between 100-500 ng/mL for 7 treatment days and between 100-350 ng/mL for 14 treatment days. This implies that the maximum pharmacological effect can already be achieved at relative low plasma levels of ALX-0081. Taking into consideration that vWF plasma concentrations in patients with signs and symptoms of TTP can be considerably higher than in healthy volunteers, these data suggest that the proposed doses allow for full target occupancy and subsequent complete inhibition of the biomarker in patients with vWF levels within the range of 1 to 3 fold above the previously studied levels in healthy subjects and patients suffering from ACS. This range of target occupancy (i.e. saturation of plasma vWF) lies within the reported levels of plasma vWF for patients undergoing PE as treatment for TTP. [25,26]

The dosing scheme allows for a study drug treatment interruption based on clinically significant adverse drug reaction (i.e. bleeding events).

3. OBJECTIVES

Primary

- Reduction of time-to-response, defined by the achievement of laboratory blood marker response, confirmed at 48 hours after the initial reporting of this response

Secondary (including longer-term disease sequelae)

- Improvement in number of subjects responding to therapy
- Reduction in PE procedure-related items
- Reduction of time to resolution or improvement of symptoms typical of TTP, including blood markers
- Reduction of number of exacerbations (defined as recurrent thrombocytopenia following a response and requiring a re-initiation of daily PE treatment after ≥ 1 day but ≤ 30 days after the last daily PE) and relapses (defined as *de novo* event of TTP that occurs later than 30 days after the last daily PE)
- Improvement of cognitive level at steady state post acute phase
- Improvement of clinical symptoms and organ function
- Reduction in mortality within the PE treatment period and within the subsequent study drug treatment period (including tapering)
- Reduction of concomitant treatment-related complications
- Evaluation of safety and immunogenicity of adjunctive treatment with ALX-0081
- Determination of PK and PD characteristics of ALX-0081 in patients with acquired TTP

4. TRIAL DESIGN

4.1 Study Endpoints

4.1.1 Primary Endpoint

- Time-to-response, based on the following criteria:
  - Recovery of platelets ≥ 150,000/µL
  - This response must be confirmed at 48 hours after the initial reporting of platelet recovery equal to or above 150,000/µL by a *de novo* measure of platelets ≥ 150,000/µL and LDH ≤ 2 X ULN (i.e. “confirmed platelet response”)

4.1.2 Secondary Endpoints

All endpoints achieved within 30 day period after end of study drug treatment:

- Number of subjects with complete remission (defined as confirmed platelet response and absence of exacerbation)
- Number of (subjects with) exacerbations of TTP (defined as recurrent thrombocytopenia following a confirmed platelet response and requiring a re-initiation of daily PE treatment after ≥ 1 day but ≤ 30 days after the last daily PE) and time to first exacerbation of TTP
- Number of subjects relapsing of TTP (defined as *de novo* event of TTP that occurs later than 30 days after the last daily PE)
- Number of daily PE sessions, number of plasma units administered and number of days of daily PE
- Resolution of non-focal neurological symptoms as defined by neurocognitive function at complete remission, measured by a neurocognitive test battery
- Resolution or improvement (improvement of ≥ 1 grade in the CTCAE v4.0 scale) of TTP-related signs and symptoms as captured on physical examination and as adverse events, at complete remission and at end of the study drug treatment period (including tapering) (by number of unique subjects and by total number of AEs)
- Total mortality within the PE treatment period and within the subsequent study drug treatment period (including tapering)
- Incidence of PE treatment-related AEs, such as, but not restricted to: haemorrhage from catheter insertion, sepsis, catheter thrombosis, pneumothorax, fluid overload, hypoxia, hypotension, anaphylactoid reactions and TRALI

- Incidence and severity of ALX-0081 treatment-emergent AEs and relationship to study drug
- Development of ADA ≤ 30 days post-last study drug treatment
- PK and PD profile

4.1.3 Tertiary Endpoints

4.2 Overall Study Design

This is a Phase II multicentre, single-blinded, parallel design, randomised, placebo-controlled study. The study population is symptomatic patients with acute episodes of acquired TTP, requiring treatment with PE. After confirmation of eligibility to study participation, subjects will be randomised in a ratio of 1:1 to either receive ALX-0081 or placebo as adjunctive therapy to PE (Figure 4). Subjects will be randomised prior to the start of PE treatment. In exceptional cases however (due to need or ability to start PE in a time frame which does not allow all required screening and/or baseline study procedures to be performed), a subject may be randomised after the first, single PE session, but prior to the start of the second PE session. This overall second PE session should be started within 24 hours of the end of the very first PE session, and will be considered the first PE on study.

The subjects will be followed in different phases during this study (also see Figure 5):

- Screening and baseline measurements after admission to hospital
- Treatment phase
    - Single i.v. bolus study drug administered via push injection
    - Daily PE adjunctive s.c. treatment phase
    - Post-daily PE s.c. treatment phase (including PE tapering if applicable, and study drug post-PE for 30 days after the very last PE)
- Follow-up phase

Laboratory parameters for inclusion, study conduct, safety assessments and assessments of response/relapse, re-treatment and study medication dose modification will be assessed at each local site laboratory.

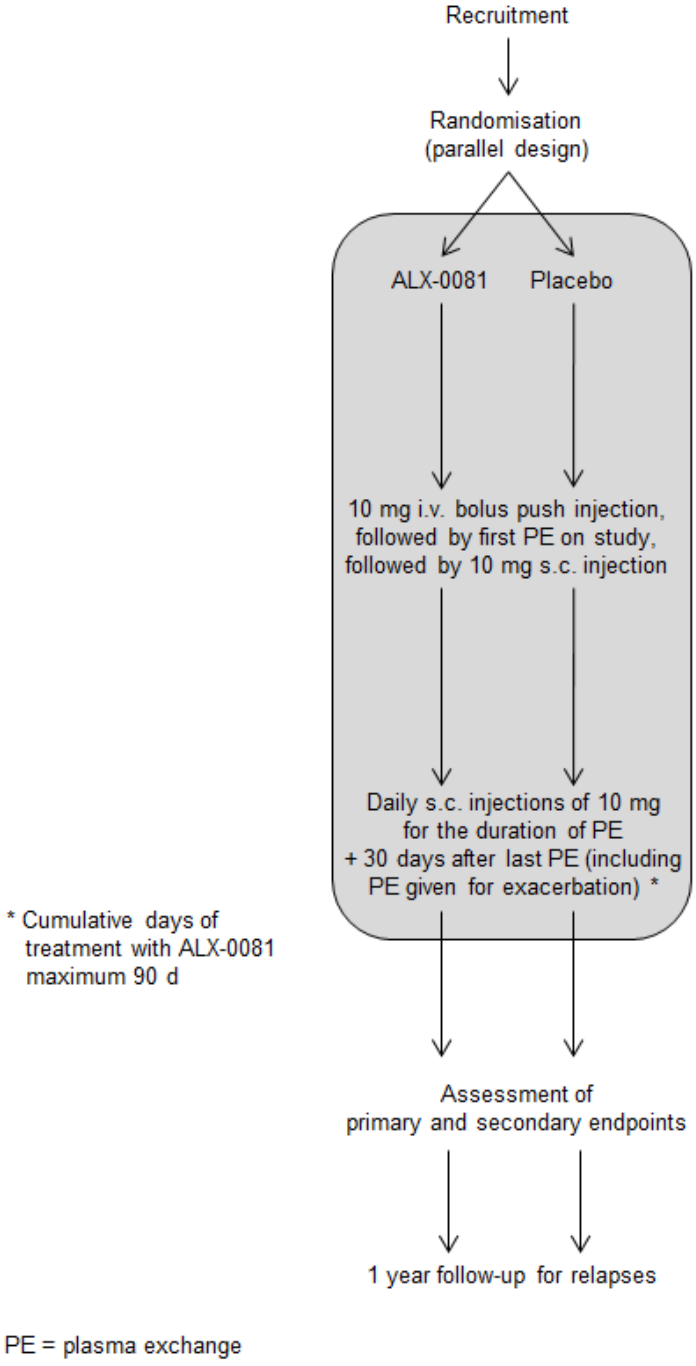


Figure 4: **Treatment flow chart.**
First PE on study: see section 4.2

4.3 Overview of Treatment and Dosing Regimen for Study Drug

The primary treatment for acquired TTP is daily PE. Immunosuppressive treatment is also often administered. The centres will follow their respective guidelines for the treatment of TTP patients, regarding all items other than the study drug. Discontinuation of daily PE depends on normalisation of platelet count, neurological status and other clinical and laboratory parameters. The frequency of PE is occasionally reduced ('tapered') rather than stopping completely at time of response, however this is not based on randomised clinical trial data and is not recommended per this protocol (although it is allowed if considered necessary by the Investigator).
The study drug will be administered as adjunctive treatment at specific times relative to the PE procedures.
The first administration is a single i.v. bolus injection, administered by a push injection. All subsequent administrations are s.c. injections. The study drug consists of 10 mg of ALX-0081 or placebo, once daily (except if PE is given twice daily, then study drug is 10 mg twice daily) as described in Section 7.2.

Note that, in case of re-initiation of daily plasma exchange due to exacerbation, no i.v. bolus injection will be administered prior to the first new PE session; daily s.c. study drug administration will continue per protocol.

4.4 Study Duration

The anticipated recruitment period is 30 months. The maximum total duration of individual study participation is a maximum of 15 months: a treatment phase of up to 90 days and a follow-up period of maximum of 1 year after remission or after 90 days of treatment, whichever comes first. Subjects will be hospitalised for at least 1 day after the last daily PE.

4.5 DSMB and Premature Termination of the Study

4.5.1 Data Safety Monitoring Board

An independent DSMB will monitor accruing safety data during the study (SAEs on an ongoing basis and 'early safety look' when 16 subjects, 8 ALX-0081 treated and 8 placebo treated, have completed treatment with study drug) and will make recommendations on continuation of the study as appropriate. An interim analysis for safety with formal stopping

rules is foreseen when 28 of the ALX-0081 treated subjects have been treated, and will make a recommendation on study continuation or discontinuation. No formal review of efficacy data by the DSMB is foreseen.

4.5.2 Premature Termination of the Study

The Sponsor in consultation with the DSMB and the CRO has the right to terminate the study prematurely for safety reasons. In addition, the Sponsor may terminate the study prematurely for administrative reasons at any time. In all cases all necessary measures have to be taken to guarantee appropriate safety follow-up of all subjects already included in the study.
The Independent Ethics Committees (IEC) or Institutional Review Board (IRB) and the Regulatory Authorities will be informed in writing about any premature termination of the study.

5. SELECTION AND WITHDRAWAL OF SUBJECTS

The target population for this trial includes symptomatic patients with acute episodes of acquired TTP, requiring treatment with PE.

5.1 Inclusion Criteria

1. 18 years of age or older
2. Men or women willing to accept an acceptable contraceptive regimen
3. Patients with clinical diagnosis of TTP
4. Necessitating PE (one, single PE session prior to randomisation into the study is allowed)
5. Subject accessible to follow-up
6. Obtained, signed and dated informed consent

5.2 Exclusion Criteria

1. Platelet count greater or equal to 100,000/µL
2. Severe active infection indicated by sepsis (requirement for pressors with or without positive blood cultures)
3. Clinical evidence of enteric infection with *E. coli* 0157 or related organism
4. Anti-phospholipid syndrome
5. Diagnosis of DIC
6. Pregnancy or breast-feeding
7. Haematopoietic stem cell or bone marrow transplantation-associated thrombotic microangiopathy
8. Known congenital TTP
9. Active bleeding or high risk of bleeding
10. Uncontrolled arterial hypertension
11. Known chronic treatment with anticoagulant treatment that can not be stopped safely, including but not limited to:
    - vitamin K antagonists
    - heparin or LMWH
    - non-acetyl salicylic acid non-steroidal anti-inflammatory molecules
12. Severe or life threatening clinical condition other than TTP that would impair participation in the trial

13. Subjects with malignancies resulting in a life expectation of less than 3 months
14. Subjects with known or suspected bone marrow carcinosis
15. Subjects who cannot comply with study protocol requirements and procedures.
16. Known hypersensitivity to the active substance or to excipients of the study drug
17. Severe liver impairment, corresponding to grade 3 toxicity defined by the CTCAE scale. For the key liver parameters, this is defined as follows:
    - bilirubin > 3 x ULN (need to differentiate isolated increase in indirect bilirubin due to haemolysis, this is not an exclusion parameter but disease related)
    - ALT/AST > 5 x ULN
    - AP > 5 x ULN
    - gamma glutamyl transpeptidase (GGT) > 5 x ULN
18. Severe chronic renal impairment, as defined by GFR < 30 mL/min

5.3 Participation in concurrent clinical trials

The use of another investigational drug or device within 30 days prior to screening is not allowed. Participation in non-interventional/observational studies and registries during the study period is allowed. Participation in another clinical trial is not allowed until the end of the follow up period or within 30 days after the last study treatment in case of early subject withdrawal from the study. Subjects that already participated in the current study (ALX 0681-2.1/10) and that have either completed the study per protocol or have discontinued prematurely, are not allowed to be re-included.

5.4 Withdrawal of Subjects from Study

5.4.1 Definitions

A 'completed' subject is one who has completed all phases of the study, including all follow-up visits specified.
A ‘withdrawal’ is a subject who stops prematurely for reasons related to the study, e.g. an AE. A subject who simply wishes to withdraw from the study should also be considered a withdrawal.

5.4.2 Subject Discontinuation or Withdrawal

Subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified and without penalty or loss of benefits to which the subject is otherwise entitled.
Subjects may be withdrawn from the study by the Investigator at any time due to an AE or any other reason if it is the opinion of the Investigator that continued participation in the study is no longer in the best interest of the subject. These reasons include, but are not limited to the following:

- Adverse drug reaction or AE or any other reason for which, in the opinion of the Investigator, subject's continued participation in the study is not in the best interest of the subject
- Withdrawal of consent (subject must be withdrawn)
- Subject fails to return to the site and does not respond to the attempts of the investigational site to contact him (lost to follow-up)
- Protocol violation(s), such as non-compliance with study medication or visit schedule or treatment with prohibited concomitant medications
- Pregnancy (treatment with study drug, if during treatment phase, must be discontinued and subject must be withdrawn from the study)

Relapse of TTP on study (defined as *de novo* event of TTP that occurs later than 30 days after the last daily PE) is not considered a reason for study withdrawal. However re-initiation of study drug treatment as an adjunctive treatment to PE in case of TTP relapse is not permitted.

Subjects discontinuing study drug administration should be encouraged to remain in the study and complete the originally scheduled follow-up visits.

For all subjects withdrawing from the trial for whatever reason, all data will be collected, documented and reported. The case report form (CRF) must be completed up to the time of withdrawal and the Premature Termination Form must be completed. Except for subjects who refuse to return to the investigational site, all subjects withdrawn after at least one administration of study drug should undergo a post-study assessment.

In case of withdrawal from the study due to an AE, subjects should be followed by the Investigator until the AE has resolved.

5.4.3 Procedure for Handling Withdrawals and Replacements

All cases of premature termination, or exclusion of individual subjects, will be discussed with the Sponsor and it will be decided in consultation with the Sponsor whether this subject will need to be replaced. Subjects withdrawn due to adverse drug reactions or adverse events will not be replaced.

If a withdrawal has to be replaced the replacement subject will undergo the same procedures and assessments as 'new' subjects.

If a subject withdraws before allocation of a subject number:

- The replacement will be regarded as a 'new' subject and therapy allocated accordingly.

If a subject withdraws after allocation of a subject number:

- The replacement will be allocated to the same randomisation as the subject to be replaced, but will be allocated a new subject number.

  The new (replacement) number is attributed by the statistician responsible for randomisation and the corresponding medication shipped to the site.

6. STUDY DRUGS

Study drugs include the anti-vWF Nanobody (ALX-0081) and the matching placebo administered during the course of the study.

6.1 Formulation, Packaging and Labelling

6.1.1 Study Drug Formulation

ALX-0081, anti-vWF Nanobody

ALX-0081 is a clear, colourless solution formulated as a solution for injection. It is provided in sterile, preservative-free, non-pyrogenic, single-use 2R glass vials with injection stoppers and light blue aluminum crimped caps. One vial contains 2.4 mL solution for injection. One mL solution for injection contains as active ingredient 5 mg of ALX-0081 (INN: caplacizumab).

Excipients

Phosphate buffer solution (pH 7.1):

WFI, KCl, KH_2PO_4, $Na_2HPO_4x2H_2O$ and NaCl. Glycine (0.2 M) and polysorbate 80 (0.02%) are used to stabilise the protein in the solution.

Placebo

Placebo is provided in 2R glass vials. One vial contains 2.4 mL solution for injection with identical excipients as ALX-0081.

6.1.2 Study Drug Packaging

Ablynx NV will, via a contract manufacturer, supply the following medication:

- Vials containing 2.4 mL solution of 5 mg/mL of ALX-0081
- Matching placebo vials

The study medication will be packed and dispatched in containers. The batch number and the minimal shelf-life will be given on the outer package. A batch release certificate and a GMP-conformity statement will be provided. Study drugs are provided as vials for injection and supplied to the study centre.

6.1.3 Study Drug Labelling

The study drug will be labelled in accordance with applicable regulatory requirements. At the minimum, the following information will be provided:

- Study number (ALX-0681-2.1/10)
- Name and address of Sponsor
- Batch number and vial number
- Volume
- Pharmaceutical form and route of administration (respectively i.v. or s.c.)
- Storage conditions
- Retest or expiry date
- “For clinical trial use only” and “Keep out of reach and sight of children”

6.2 Storage and Stability

ALX-0081 and placebo are delivered and stored deep frozen at –20°C (± 5°C) in the original outer package to be protected from light. Stability studies showed that ALX-0081 is stable at -20°C for at least 3 years and can therefore be stored under these conditions at the investigative site. ALX-0081 contains no antimicrobial preservatives. The study drug must not be used after the expiry date indicated on the labels of the outer package.

Upon receipt of the study medication, the responsible pharmacist or his/her designee will inspect and count all study medication for completeness. Subsequently, he/she must immediately return the enclosed acknowledgement of receipt form, duly completed and signed (the date of receipt must be noted).

The pharmacist or his/her designee is responsible for storage of the study medication at the study site in an appropriate lockable room at –20°C (± 5°C). The medication may not be exposed to direct sunlight or to direct warmth given off by heaters and should be protected from moisture.

6.3 Study Drug Preparation and Administration

All study medications will be prepared at the investigational site by a pharmacist or his/her designee.

Study drug preparation and administration during hospitalisation

During hospitalisation, all study medications will be administered by the Investigator or by medically trained personnel under his/her supervision.

ALX-0081 solution for injection is for single use only. Remaining ALX-0081 solution for injection should be discarded. Procedures for proper handling and disposal should be observed.

Study drug preparation for dispension to subjects, and administration thereafter

Vials will be thawed in a 25°C water bath or at room temperature until all ice has visibly disappeared and inspected prior to dispension to subjects. Transport of study medication from the hospital to the subject's home should be secured between 2-8°C. The subject should be instructed to keep the study medication cooled within a refrigerator (2-8°C) until use. Injections must be prepared and administered by medically trained personnel.

Vials can be used during 10 days after thawing. All thawed vials and unused injections should be returned to the pharmacy on a weekly basis. Note that returned vials can no longer be used for administration.

For detailed instructions on the preparation of the solution for injection, its administration and disposal please refer to the IB.

6.4 Return of Study Drug

Generally, all unused study drug (medication and packaging) must be returned to the Sponsor on termination of the study and after a drug accountability and reconciliation check. Upon permission/request of the Sponsor, and if allowed by local procedures and regulations, unused study drug may be destroyed on site. The destruction has to be clearly documented, and can only occur after drug accountability and reconciliation check.

Used study medication can be destroyed per institution policy after drug accountability has been checked.

The pharmacist or his/her designee will be responsible for the inventory of all clinical supplies, exercising accepted pharmaceutical practices. An accurate, timely record of the clinical study supply will be maintained. The original Drug Preparation Log and Drug Dispensing and Accountability Log are considered as source data and will be archived at the site.

6.5 Drug Accountability

Supplies of ALX-0081 will be shipped deep frozen at -20°C (± 5°C) to the hospital at appropriate intervals, depending on subject accrual. The Investigator at the study site is responsible for keeping accurate drug accountability records throughout the study regarding the receipt of study drug, the dispensing to the subjects and the return of all used and unused study drug.
A Drug Preparation Log as well as a Drug Dispensing and Accountability and temperature Log must be kept current and should contain the following information:

- In hospital use:
  - Vial number
  - Subject number for whom the drug was prepared
  - Number of injections prepared
  - Date on which drug was dispensed
  - Quantity of the drug administered

- Use at home by the subject:
  - Subject number to whom the drug was dispensed
  - Information on vials dispensed
    - Number of vials dispensed
    - Vial identification numbers dispensed
    - Date of thawing
    - Date of dispension
    - Vials returned by the subject
  - Name of the person who administered the study drug
  - Date and time of study drug administration
  - Quantity of the drug administered

The inventory must be available for inspection by the monitor.
Generally, at study termination, all unused study medication must be returned to the Sponsor accompanied by the appropriate documentation. Upon permission/request of the Sponsor, and if allowed by local procedures and regulations, unused study drug may be destroyed on site. The destruction has to be clearly documented, and can only occur after drug accountability and reconciliation check. Used study medication can be destroyed per institution policy after drug accountability has been checked.

7. TREATMENT

7.1 Treatments to be Administered

Subjects will receive best medical care and treatment judged appropriate by the Investigator at each site and according to site guidelines for treatment of TTP. The principal treatment for acquired TTP is daily PE. Discontinuation of daily PE depends on normalisation of platelet count, neurological status and other clinical and laboratory parameters. The frequency of PE is occasionally reduced ('tapered') rather than stopping completely at time of response, however this is not based on randomised clinical trial data and is not recommended per this protocol (although it is allowed if considered necessary by the Investigator).
Additional treatment may include one or more of the following: adjunctive immunosuppressive treatment (e.g. corticosteroids, rituximab), antiplatelet agents (e.g. aspirin), supportive therapy with red cell transfusion or folate supplementation, treatment with vincristine or cyclosporin in case of refractory TTP.[13] After platelet counts have partially recovered, LMWH may be used prophylactically in patients at high risk for venous thromboembolism. In this case heparin will be administered according to local institutional guidelines, or in the absence of these, after a platelet count of at least 100,000/µL has been reached.

7.2 Treatment and Dosing Regimen for Study Drug

The study drug will be administered as adjunctive treatment at specific times relative to the PE procedures. The study drug consists of 10 mg of ALX-0081 or placebo, once or twice daily as explained below (Table 8).

Subjects will receive a first i.v. bolus of 10 mg ALX-0081 or placebo via push injection within 6h, but not later than 15 min prior to the initiation of PE on study (i.e., the very first PE session, if the subject was randomised prior to the initiation of PE, or the second PE session, if the subject was randomised after one, single PE session; see section 4.2). This first PE on study is followed by s.c. administration of 10 mg study drug within 30 minutes after the end of the PE procedure.

During the complete PE treatment period (including tapering and PE given for exacerbations), study drug will be administered daily via s.c. injections.

- If 1 PE per day is scheduled, 10 mg of study drug will be administered within 30 minutes after the end of the PE procedure.
- If 2 PEs per day are scheduled, 10 mg of study drug will be administered within 30 minutes after the end of each PE procedure. The maximum total daily dose of study drug is hence 20 mg.
- If less than 1 PE per day is scheduled (i.e. during a tapering regimen), 10 mg of study drug will be administered daily. On days with a PE, study drug administration should be within 30 minutes after the end of the PE procedure; on days without PE, study drug administration should be 24 h (± 1 h) after previous administration

Daily s.c. study drug administration of 10 mg will continue for 30 days after the very last PE (including tapering).

Maximum treatment duration with study drug will be limited to 90 days after first administration of study drug.

In case of exacerbation of TTP (after ≥ 1 day but ≤ 30 days after the last daily PE), standard treatment (PE) should be re-initiated and daily s.c. administration of study drug continued.[a] The "study drug post-PE" period (for 30 days after the very last PE, see Figure 5 further below) will re-commence once PE is again stopped. Maximum treatment duration with study drug will be limited to 90 days after first administration of study drug.

Re-initiation of study drug treatment as an adjunctive treatment to PE in case of on-study TTP relapse is not permitted. Relapse of TTP is defined as *de novo* event of TTP that occurs later than 30 days after the last daily PE. Tapering will prolong study drug administration and delay the start of the "study drug post-PE" period (see Figure 5 further below). It is therefore possible that a relapse would occur ≥ 30 days after the last daily PE, but before the end of the 30-day period of study drug administration post-PE. In this case, the study drug is to be discontinued at the restart of the PE treatment.

The s.c. injections will be performed on the abdomen according to a written instruction manual. At each administration, subjects will receive two s.c. injections of 1 mL ALX-0081 solution for injection (5 mg/mL) or placebo solution at different abdominal locations. The site

[a] Note that, in case of re-initiation of daily PE due to exacerbation, no i.v. bolus injection has to be administered prior to the first new PE session; daily s.c. study drug administration will continue per protocol.

of the injections will be recorded and will be changed from day to day. The time of administration of study drug and the initials of the person performing the administration will be recorded in the source documents. All injections of study drug will be performed by medical or paramedical personnel.

7.3 Dose modification due to treatment related AE – clinically relevant bleeding

Clinically relevant bleeding is the main potential risk based on the pharmacological action of ALX-0081. It is defined as moderate to severe (including life-threatening) bleeding requiring urgent medical and/or surgical intervention. In case of clinically relevant bleeding, appropriate treatment for bleeding according to standard practice should be initiated and treatment with study drug must be interrupted. In addition, plasma levels of vWF:Ag and FVIII chromogene should be determined. If FVIII < 10%, assess for anti-FVIII antibodies and if presence is confirmed, permanently discontinue study drug. If either or both vWF and FVIII are at clinically significant low levels, administration of vWF and FVIII through commercially available combination preparations, such as Haemate-P or equivalent antihaemophilic factor/vWF complex should be initiated and continued until the bleeding stops. Study drug should only be restarted when the bleeding has stopped and vWF > 50% and FVIII level is within normal range. The PE treatment, if applicable, should continue as clinically indicated.

Dosage, method of administration and duration of treatment are summarised in Table 8.

Table 8: Dosage, method of administration and treatment duration.

First study drug administration is 10 mg as an i.v. bolus, administered by a push injection, 15 minutes to 6 hours prior to initiation of PE on study.* This first PE on study is followed by subcutaneous (s.c.) administration of 10 mg study drug.

* As discussed in section 4.2, one PE session prior to randomisation is allowed. In such case, the second PE session will be the first PE on study.

S.c. study drug administration **during treatment phase with PE**	
Frequency of PE	*Treatment administration - daily*
1 PE/day	Administer 10 mg study drug within 30 min after end of PE
2 PEs/day	• For subjects receiving anti-vWF Nanobody: administer 10 mg study drug within 30 min after each PE • For subjects receiving placebo, maintain a once daily dosing regimen
Tapering (< 1 PE/day)	Daily administration of 10 mg study drug. On days with PE: within 30 min after end of PE; on days without PE at 24 h (± 1 h) after previous administration

S.c. study drug administration (in hospital and at home) for **30 days after the very last PE** (including tapering and PE given for exacerbations)*: 10 mg study drug once daily.

* As discussed in section 7.2, in case of exacerbation of TTP, standard treatment (PE) should be re-initiated and daily administration of study drug continued. The “study drug post-PE” period (for 30 days after the very last PE) will recommence once PE is again stopped. Maximum treatment duration with study drug will be limited to 90 days after first administration of study drug.

If **clinically relevant bleeding*** occurs
• Stop study drug administration and continue PE if clinically indicated and applicable • Assess vWF:Ag and Factor VIII (FVIII) levels**. If FVIII < 10%, assess for anti-FVIII antibodies and if presence is confirmed, permanently discontinue study drug. • If vWF:Ag and/or FVIII levels are at a clinically significant low level, initiate i.v. Haemate-P 50 U/kg (or equivalent antihaemophilic factor/vWF complex) • i.v. Haemate-P treatment should be discontinued when bleeding has clearly stopped and when vWF > 50% • Restart study medication at 10 mg daily when bleeding has clearly stopped and when vWF > 50% and FVIII levels are within normal range

* Clinically relevant bleeding is defined as moderate to severe (including life-threatening) bleeding requiring urgent medical and/or surgical intervention.

** FVIII chromogene or other measure of FVIII activity

7.4 Prior / Concomitant Medication

Upon inclusion in the study, chronic treatment with anticoagulant treatment such as vitamin K antagonists, heparin (or LMWH) and non-acetyl salicylic acid non-steroidal anti-inflammatory molecules should be discontinued. If recommended by local guidelines, aspirin can be continued. Heparin can be administered according to local institutional guidelines, or in the absence of these, after a platelet count of at least 100,000/µL has been reached. Re-initiation of anticoagulant treatment is allowed whenever required to ensure the safety of the

subject. (Re-)initiation of anticoagulant treatment should be guided upon balancing the risk for thrombosis versus the risk for bleeding and should be based upon local guidelines. For example, LMWH can be used prophylactically in subjects at high risk for venous thromboembolism whenever platelet counts have partially recovered. Anticoagulant treatment prescribed as part of the local PE procedure is allowed.

Concomitant medication administered specifically as part of the PE procedure and during the course of the PE session will be recorded separately. Other concomitant and adjunctive medication, such as methylprednisone, rituximab and other immunosuppressives will be reported in the concomitant medication other than PE-related medication.

Medication given in response to a PE-related AE (i.e. antibiotic administration due to a central line infection) will be reported in the concomitant medication other than PE-related medication.

Any concomitant medication taken during the study must be recorded in the CRF. Items to be recorded concerning concomitant medication include: dose and units of dose, modification of dose, start time and date, end time and date, administration frequency, route of administration, therapeutic indication.

Desmopressin should be considered as prohibited medication.

7.5 Assignment to Treatment

Subjects will be assigned to one of the two treatments according to a computerised randomisation schedule. When the randomisation number and treatment assignment are obtained, the randomisation number will be recorded on the CRF. This is a single blinded study. The Investigator will be informed of the treatment at the time of randomisation.

Randomisation is performed via an interactive web-based system.

7.6 Management of Overdose

In case of suspected or actual overdose, there is an increased risk of bleeding based on the pharmacological action of study drug. Subjects should therefore be monitored closely for signs and symptoms of clinically relevant bleeding, defined as moderate to severe (including life-threatening) bleeding requiring urgent medical and/or surgical intervention (see Section 7.3). In case of clinically relevant bleeding associated with (suspected) overdose, appropriate treatment for bleeding according to standard practice should be initiated and treatment with study drug must be interrupted. In addition, plasma levels of vWF:Ag and FVIII should be determined. If FVIII < 10%, assess for anti-FVIII antibodies and if presence is confirmed, permanently discontinue study drug. If either or both vWF and FVIII are at clinically

significant low levels, administration of vWF and FVIII through commercially available combination preparations, such as Haemate-P or equivalent antihaemophilic factor/vWF complex should be initiated and continued until the bleeding stops. Treatment with study drug should only be restarted when the bleeding has stopped and when vWF > 50% and FVIII levels are within normal range. 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 with the next PE or next daily dose as applicable and as per protocol.

7.7 Management of Hypersensitivity Reactions

In the case of immediate or late allergic or immunogenic reaction to ALX-0081 - manifesting as itching, rash, hives, or in severe cases as anaphylactic reaction or even shock - appropriate standard medical care measurements will be initiated by the responsible Investigator involving the intensive care unit when necessary.

7.8 Restrictions

Males who can father children and women of childbearing potential, must use double-barrier contraception during the study and during the first 3 months after last dosing. This is the use of a condom with spermicidal paste or the use of oral contraception combined with male condom or vaginal condom or other adequate combination of 2 contraceptive methods.
Subjects should refrain from potentially dangerous activities or contact sports during the treatment phase of the study and until 7 days after last administration of study drug.

7.9 Treatment Compliance

Records of study drug used, dosages administered and intervals between visits are kept during the study. Study drug accountability is performed on an ongoing basis by the study staff and checked by the monitor during site visits and at the completion of the study.
The administration of the study medication will be performed by the Investigator or Sub-Investigator or medically trained personnel and will be documented accordingly.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Description of Study Days and Schedules of Assessments

The subjects will be followed in different phases during this study:

- Screening and baseline measurements after admission to hospital
- Treatment phase
  - Single i.v. bolus study drug administered via push injection
  - Daily PE adjunctive s.c. treatment phase
  - Post-daily PE s.c. treatment phase (including PE tapering if applicable, and study drug post-PE for 30 days after the very last PE)
- Follow-up phase

Please see Figure 5 for a schematic overview of the different study phases. A general overview of study assessment is shown in Table 9.
Time intervals and follow-up window details are provided in Table 10, Table 11 and Table 13.

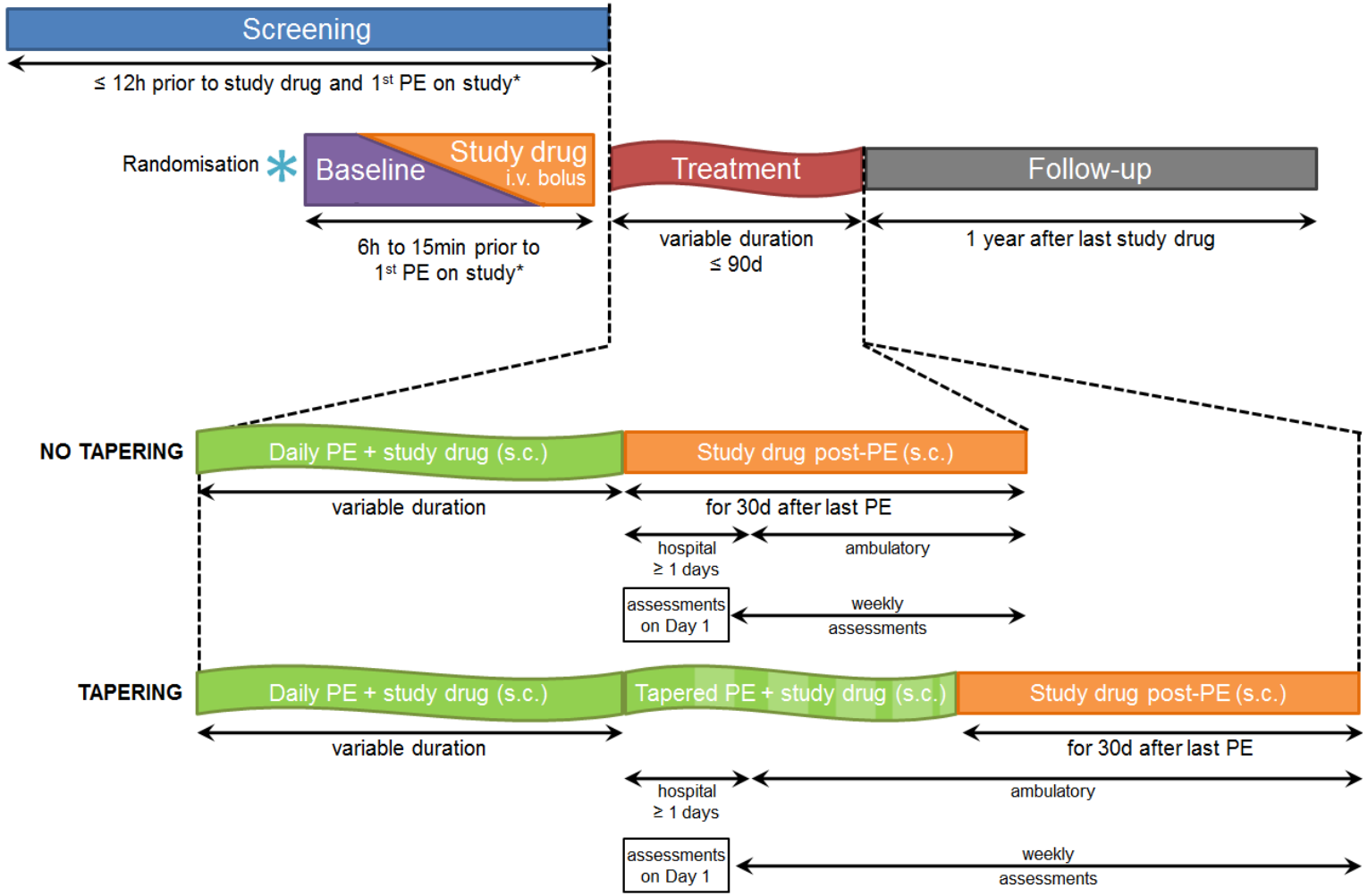


Figure 5: Schematic overview of pre-treatment, treatment and follow-up phase.

* Subjects will be randomised prior to the start of PE treatment. In exceptional cases however (due to need or ability to start PE in a time frame which does not allow all required screening and/or baseline study procedures to be performed), a subject may be randomised after the first, single PE session, but prior to the start of the second PE session. This overall second PE session should be started within 24 hours of the end of the very first PE session, and will be considered the first PE on study.

Table 9: General schedule of study assessments.

	Screening	Baseline	Treatment phase				Follow-up							AE and unsche-duled visit
			Study drug i.v. bolus	Daily PE treatment phase	Day 1 after last daily PE	Post daily PE (including PE tapering)	30 day post last PE (including tapering)- stop study drug	Day 3	Day 7	1m	2m	3m	6m	12m	
Time interval	≤12h prior to first PE on study and study drug	15min-6h prior to first PE on study and study drug		see Table 11	1 day	see Table 11		±1d	±1d	±3d	±7d	±15d	±15d	±15d	as needed
Assessment/Activity															
Treatment with study drug				X	X	X									
PK (central lab)		X		X	X	X		X	X	X					X
RICO (central lab)		X		X	X	X		X	X	X					X
ADA (central lab)		X		X	X	X				X	X	X	X	X	X
vWF (central lab)		X		X	X	X		X	X	X	X	X	X	X	X
FVIII chromogene (central lab)		X		X	X	X		X	X	X	X	X	X	X	X
Blood type (ABO and Rh) and direct antiglobulin test (DAT) (local lab)	X														
Blood chemistry (local lab)	X	X		X	X	X		X	X	X	X	X	X	X	X
Haematology (local lab)	X	X		X	X	X		X	X	X	X	X	X	X	X
Coagulation (local lab)	X	X		X	X	X		X	X	X	X	X	X	X	X
Urine pregnancy test (local lab)	X									X		X			
Urinalysis (local lab)	X														
HIV1/2, HBV, HCV (local lab)	X														
Cardiac marker (TnT or TnI) (local lab)		X		X	X	X				X				X	X
BNP or NT proBNP (local lab)		X		X	X	X				X				X	X
Brain damage markers (NSE, Sβ100) (central lab)		X		X	X	X				X				X	X
ADAMTS13 & anti-ADAMTS13-antibodies (central lab)	X				X	X				X				X	X
12-lead ECG		X		X	X	X				X	X	X	X	X	X
Informed consent	X														
Inclusion/exclusion criteria	X														
Medical history and demographics	X														

	Screening	Baseline	Treatment phase			Follow-up							AE and unsche-duled visit
			Daily PE treatment phase	Day 1 after last daily PE	Post daily PE (including PE tapering)	Day 3	Day 7	1m	2m	3m	6m	12m	
Time interval	≤12h prior to first PE on study and study drug	15min-6h prior to first PE on study and study drug	see Table 11	1 day	see Table 11	±1d	±1d	±3d	±7d	±15d	±15d	±15d	as needed
Physical examination and vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Spent plasma retrieval			X										
Modified ITP bleeding score		X	X	X	X			X					X
Clinically relevant bleeding	X	X	X	X	X			X					X
Glasgow Coma Score	X	X[c]	X	X	X								
Neurocognitive battery		X	X			X						X	
Recuperate nurse sheet and/ or AE diary					X	X	X	X	X	X	X	X	X
PE details[a]			X[a]	X[a]	X[a]								
Prior/concomitant medication recording other than PE related treatment[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]
AE recording		X	X	X	X	X	X	X	X	X	X	X	X

First PE on study: see section 4.2.

[a] Including RBC transfusion details

[b] Including concomitant medication related and simultaneous to PE.

[c] If abnormal at screening

8.1.1 Screening and Baseline Measurements

In a window of time defined by less than 12 hours prior to initiation of first PE on study (as detailed in section 4.2) and study drug, all subjects will undergo a thorough examination to investigate their suitability for participation in the study. Inclusion and exclusion criteria will be checked. A screening log should be maintained, recording the reason when subjects are screened but not included in the study. If the subject satisfies the inclusion and exclusion criteria, informed consent will be obtained prior to randomisation and additional assessments will be performed within 15 minutes to 6 hours prior to initiation of the first PE on study and study drug. If done within 6 hours of starting study drug, the chemistry, haematology and coagulation assessments can be considered baseline and do not need to be repeated (see Table 10).

The following screening procedures must be performed prior to randomisation (see Table 10):

- Check in/exclusion criteria
- Demographic data (e.g. age, height, weight, body mass index (BMI), ethnic origin and number of years of formal education completed). The balance should have a precision of at least 0.5 kg. Body weight will be recorded in kg with 1 decimal. The BMI will be calculated from the weight and height: BMI (kg/m^2) = weight (kg) / height (m) x height (m).
- Medical history
- Prior and concomitant medication taken during the 30 days prior to the screening examination are to be documented. Concomitant medication from the 30 days prior to screening until follow-up or started during the course of the study will be recorded on the Concomitant Medications page of the CRF. Concomitant medications initiated, stopped, up-titrated or down-titrated for an AE will also be recorded on a specific Concomitant Medications page of the CRF.
- Clinical assessment will include physical examination and vital signs (blood pressure and heart rate at rest, body temperature),
- Obtain signed and dated informed consent
- The Glasgow Coma Score will be determined using the Glasgow Coma Scale (original scale), which is a neurological scale that measures the conscious state of the subject. The best eye, verbal and motor responses will be scored according to the scale and the separate scores added up to obtain the final score, ranging from 3 to 15.
- Assessment of clinically relevant bleeding

- Urinalysis (local laboratory)
- Urine pregnancy test for female subjects (Human chorionic gonadotropin (hCG) only) (local laboratory)
- Blood typing (ABO, Rh) and direct antiglobulin test (DAT) (local laboratory)
- Blood sampling for chemistry will include the following: glucose, bilirubin (total), AP, AST, ALT, LDH, C-reactive protein (CRP), hCG (for women, only if urine pregnancy test not feasible or inconclusive), haptoglobin, rheumatoid factor, antinucleic acid, iron, ferritin, transferrin, creatinine, urea (blood urea nitrogen (BUN)), uric acid, protein, albumin, sodium (Na), potassium (K), calcium (Ca), magnesium (Mg) and chloride (Cl) (local laboratory)
- Blood sampling for haematology will include the following: haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), full blood count including red blood cells (RBC), white blood cells (WBC), differential, reticulocytes, optical platelet count and immature platelet fraction (local laboratory). In case optical platelet counts are not available, they can be replaced by measurements based upon impedance. If not available in the local laboratory, immature platelet fraction measurements can be omitted
- Blood sampling for coagulation variables will include: fibrinogen, aPTT, PT, international normalised ratio (INR), vWF:Ag, FVIII chromogene, lupus anticoagulant, anticardiolipin antibodies (antiphospholipid) (local laboratory). In case FVIII chromogene is not available in the local laboratory, it can be replaced by an alternative method (e.g. one stage clotting assay)
- Blood sampling for viral serology (hepatitis B virus (HBV), hepatitis C virus (HCV), HIV subtype-1 and -2 [HIV-1 and HIV-2]) (local laboratory)
- Blood sampling for ADAMTS13 and anti-ADAMTS13 antibody titre (central laboratory).

The following procedures must be performed after randomisation, as baseline assessments (see Table 10):

- Prior and concomitant medication taken during the 30 days prior to the screening examination are to be documented. Concomitant medication from the 30 days prior to screening until follow-up or started during the course of the study will be recorded on the Concomitant Medications page of the CRF. Concomitant medications initiated, stopped, up-titrated or down-titrated for an AE will also be recorded on a specific Concomitant Medications page of the CRF.

- Clinical assessment will include physical examination and vital signs (blood pressure and heart rate at rest, body temperature),
- AE recording
- Glasgow Coma Score (if abnormal at screening)
- The neurocognitive battery, only if level of consciousness and attentiveness of the subject permits and environmental factors are appropriate to support neurocognitive testing (e.g., subject is able to sit upright and interact with computer touch screen; subjects have eyeglasses used for reading and hearing devices, if applicable; testing area is quiet and relatively free of distracting stimuli)
- Bleeding score according to the modified ITP bleeding score
- Assessment of clinically relevant bleeding
- 12-lead ECG
- Blood sampling for chemistry (local laboratory) (only if sampling for screening was done more than 6 h prior to first PE on study and first study drug administration)[b]
- Blood sampling for haematology (local laboratory) (only if sampling for screening was done more than 6 h prior to first PE on study and first study drug administration)[b]
- Blood sampling for coagulation variables (local laboratory) (only if sampling for screening was done more than 6 h prior to first PE on study and first study drug administration)[b]
- Blood sampling for markers for cardiac cell death: Troponin T (local laboratory). In case Troponin T is not available in the local laboratory, it can be replaced by Troponin I
- Blood sampling for markers for heart failure: BNP (brain natriuretic peptide) or N-terminal pro brain natriuretic peptide (NT-proBNP) (local laboratory)
- Blood sampling for markers for brain damage: NSE (neuron specific enolase), protein S100 beta (Sβ100) (central laboratory)
- Blood sampling for PK (central laboratory). This sample needs to be drawn within 1 hour prior to the first administration of study drug
- Blood sampling for PD assessments. This sample needs to be drawn within 1 hour prior to the first administration of study drug. The PD assessments include RICO, vWF (vWF:Ag and vWF propeptide) and FVIII chromogene (central laboratory).
- Blood sampling for ADA (central laboratory). This sample needs to be drawn within 1 hour prior to the first administration of study drug

[b] Not to be repeated if screening assessment occurred within 6 hours of starting study drug.

The procedures to be performed at screening and/or baseline are also listed in Table 10.

Table 10: Schedule of assessments at screening and baseline measurements.

Assessment/Activity	**Screening less than 12 h prior to first PE on study**	**Baseline less than 6 h prior to first PE on study**
Informed consent	X	
In/exclusion criteria	X	
Medical history and demographic data	X	
Blood typing (ABO and Rh) and DAT (local lab)	X	
Physical examination and vital signs	X	X
Serology (HIV1/2, HBV and HCV) (local lab)	X	
Urinalysis (local lab)	X	
Urine or blood pregnancy test for female subjects (hCG only) (local lab)	X	
12-lead ECG		X
Blood chemistry (local lab)[a]	X	X[a]
Haematology (local lab)[a]	X	X[a]
Coagulation variables (local lab)[a]	X	X[a]
Prior and concomitant medication other than PE related treatment	X	X
ADAMTS13 and anti-ADAMTS13 antibody titre (central lab)	X	
PK (central lab)[b]		X[b]
RICO (central lab)[b]		X[b]
vWF (central lab)[b]		X[b]
FVIII chromogene (central lab)[b]		X[b]
ADA (central lab)[b]		X[b]
Cardiac marker (TnT or TnI) (local lab)		X
BNP or NT proBNP (local lab)		X
Brain damage markers (NSE, Sβ100) (central laboratory)		X
Modified ITP bleeding score		X
Clinically relevant bleeding	X	X
Glasgow Coma Score[c]	X	X[c]
Neurocognitive battery[d]		X[d]
AE recording		X

First PE on study: see section 4.2.

[a] values determined at screening can be used as baseline values to avoid additional blood sampling, if screening assessment occurred within 6 hours of starting study drug.

[b] ≤ 1h prior to first study drug administration

[c] if abnormal at screening

[d] if possible

Blood chemistry includes glucose, bilirubin (total), AP, AST, ALT, LDH, CRP, hCG (for women, to be performed as soon as possible, if urine pregnancy test is not feasible or inconclusive), haptoglobin, rheumatoid factor, antinucleic acid, iron, ferritin, transferrin, creatinine, urea (BUN), uric acid, protein, albumin, Na, K, Ca, Mg and Cl.
Haematology includes haemoglobin, haematocrit, MCV, MCH, MCHC, full blood count including RBC, WBC, differential, reticulocytes, platelet count and, if available, immature platelet fraction.
Coagulation variables include fibrinogen, aPTT, PT, INR, vWF:Ag, FVIII (chromogene or alternative method), lupus anticoagulant, anticardiolipin antibodies (antiphospholipid).

8.1.2 Treatment Phase

The treatment phase commences with the first study drug administration (i.v. bolus by a push injection) in hospital, continues with the daily s.c. study drug administration in addition to the PE sessions (including PE as part of a tapering regimen) and continues for 30 days after the last PE procedure, both in hospital and ambulatory after hospital discharge. There is a maximum possible treatment duration of 90 days after first administration of the study drug.
For details on adjunctive treatment with the study drug, please refer to Section 7.1.

The following procedures must be recorded or performed:

- Concomitant medication taken since the screening and baseline must be recorded on the Concomitant Medications page of the CRF. Concomitant medications initiated, stopped, up-titrated or down-titrated for an AE will also be recorded on a specific Concomitant Medications page of the CRF. This must be performed daily during daily PE period, on the first day after the daily PE period and then weekly for the subsequent time interval until the last day of study drug administration.
- Transfusion of RBC units will be recorded according to Section 8.2.1.1. This will be done for each transfusion. Data will be recorded as concomitant medication.
- PE information will be recorded according to Section 8.2.1.1. This will be done for each and all PE sessions. This includes concomitant medication specific to the PE session.
- Peripheral and central blood line placement and replacement for PE will be recorded according to Section 8.2.1.1. This will be done for each blood line placement and replacement.
- Clinical assessment will include physical examination and vital signs (blood pressure and heart rate at rest, body temperature). This must be performed daily during daily PE period, on the first day after the daily PE period and then weekly for the subsequent time interval until the last day of study drug administration.
- AE recording will be performed daily during daily PE period, on the first day after the daily PE period and then weekly for the subsequent time interval until the last day of study drug administration. All AEs will be recorded.
- The Glasgow Coma Score will be determined using the Glasgow Coma Scale (original scale). This score will be obtained weekly if the Glasgow coma score was abnormal at screening and as long as the subject is hospitalised in the investigative centre.

- The neurocognitive battery, if NOT performed at baseline, will be administered once as soon as possible, i.e., when level of consciousness and attentiveness of the subject permits and environmental factors are appropriate to support neurocognitive testing (e.g., subject is able to sit upright and interact with computer touch screen; subjects have eyeglasses used for reading and hearing devices, if applicable; testing area is quiet and relatively free of distracting stimuli).
- The bleeding score according to the modified ITP bleeding score will be performed daily during daily PE period, on the first day after the daily PE period and then weekly for the subsequent time interval until the last day of study drug administration.
- Assessment of clinically relevant bleeding will be performed daily during daily PE period, on the first day after the daily PE period and then weekly for the subsequent time interval until the last day of study drug administration.
- 12-lead ECG daily during the hospitalisation if it was abnormal at baseline. In addition, an ECG will be taken on day 1 and day 4, 4-6 hours post-study drug even when ECG was normal at baseline. The ECG will also be performed at pre-discharge and weekly after discharge until the last day of study drug administration.

Sampling for local laboratory:

- Blood sampling for chemistry will include the following: glucose, AST, ALT, LDH, CRP, creatinine, urea (BUN), uric acid, protein, albumin, haptoglobin, Na, K, Ca, Mg and Cl (local laboratory). The blood sample will be drawn daily during daily PE period, on the first day after the daily PE period and then weekly until the last day of study drug administration.
- Blood sampling for haematology will include the following: haemoglobin, haematocrit, MCV, MCH, MCHC, full blood count including RBC, WBC, differential, reticulocytes, optical platelet count and immature platelet fraction (local laboratory). In case optical platelet counts are not available, they can be replaced by measurements based upon impedance. If not available in the local laboratory, immature platelet fraction measurements can be omitted; The blood sample will be drawn daily during daily PE period, on the first day after the daily PE period and then weekly until the last day of study drug administration.
- Blood sampling for coagulation variables will include: fibrinogen, aPTT, PT, INR, vWF Ag and FVIII chromogene (local laboratory). In case FVIII chromogene is not available in the local laboratory, it can be replaced by an alternative method (e.g. one stage clotting assay). The blood samples will be drawn on Mondays, Wednesdays,

and Fridays during daily PE period, on the first day after the daily PE period and then weekly until the last day of study drug administration.

- Blood sampling for markers for cardiac cell death: Troponin T (local laboratory). Daily during daily PE period, on the first day after the daily PE period and then weekly until the last day of study drug administration. In case the two initial measurements indicate that values are < ULN, all subsequent tests can be omitted. In case Troponin T is not available in the local laboratory, it can be replaced by Troponin I.
- Blood sampling for markers for heart failure: BNP or NT-proBNP (local laboratory). The blood samples will be drawn on Mondays, Wednesdays, and Fridays during daily PE period, on the first day after the daily PE period and then weekly until the last day of study drug administration. In case the two initial measurements indicate that values are <ULN, all subsequent tests can be omitted.

Sampling for central laboratory:

- Blood sampling for markers for brain damage: NSE, Sβ100 (central laboratory). The blood samples will be drawn Mondays, Wednesdays, and Fridays during daily PE period, on the first day after the daily PE period and then weekly until the last day of study drug administration.
- Blood sampling for RICO (central laboratory). Daily during daily PE period (pre-PE), on the first day after the daily PE period and then weekly until the last day of study drug administration.
- Blood sampling for PK, vWF and FVIII assessments (all central laboratory) need to be taken at the following time points or time intervals:
    - During daily PE period:
        - 3 samples on day 1: at 5-10 min, 3-6 h, and 8-24 h post- i.v. administration of study drug, but prior to the second PE
        - 4 samples on day 2: after PE, but prior to s.c. study drug, and at 1-6 h, 6-12 h, and 18-24 h post-study drug, but prior to the next PE
        - 1 sample on last day of PE: after PE, but prior to s.c. study drug
    - On first day after the daily PE period:
        - 4 samples: prior to study drug and at 1-6 h, 6-12 h, 18-24 h post-study drug, but prior to next administration of study drug or before next PE (in case of tapering)
    - Subsequent time interval until the last day of study drug administration:
        - 2 samples once-weekly: prior to study drug administration (but after PE, in case of tapering) and 4-8 h post-study drug. Of note, for each day that a follow-up at the investigational site is planned, the

administration of 10 mg study drug will be performed during the follow-up visit in the investigational site.

- Blood samples for ADA (central lab) need to be taken on day 14, and then weekly until the last day of study drug administration.
- Blood sampling for ADAMTS13 and anti-ADAMTS13 antibody titre (central laboratory). This blood sampling needs to be performed on the first day after the daily PE period and 1 week post last day of PE (including tapering) and at 3 weeks post last day of PE (including tapering); the 1 week and 3 weeks after the very last PE (including tapering) sampling may be done at the weekly visit, even if not exactly 1 or 3 weeks.
- Retrieval of 30 mL from the first bag of pathological spent plasma resulting from the first PE procedure on study. This will be divided in aliquots of 5 mL each for storage at -70°C. The retrieved spent plasma, obtained from the first plasma exchange on study, and the first spent bag will be used for following purposes.
    - As matrix for development and validation of ADA, biomarker assays that will be used in TITAN trial.
    - For further characterisation of possible immunogenicity findings.
    - For additional measurement of vWF and ALX-0081 concentrations under R&D conditions and subsequent PK/PD modelling to assess extent of removal of these components upon plasma exchange.

- Recuperate nurse sheet and/or AE diary at each post discharge visit.

An overview of assessments performed during the treatment phase of this trial is provided in Table 11.

Assessments scheduled in case of TTP exacerbation

In case of TTP exacerbation, defined as recurrent thrombocytopenia following a response and requiring a re-initiation of daily PE treatment after ≥ 1 day but ≤ 30 days after the last daily PE, the assessments scheduled for “Day 1 after last daily PE” are not performed after completion of the exacerbation treatment, instead, the “post-daily PE (including tapering)” assessments are continued. A dedicated schedule of assessments is provided in Table 12.

Assessments scheduled in case of TTP relapse

Assessments scheduled in case of TTP relapse are discussed in section 8.1.3 (Table 14).

Table 11: Schedule of assessments during treatment phase.

Assessment/ Activity	Daily PE treatment phase	Day 1 after last daily PE	Post daily PE (including PE tapering)
Treatment with study drug	Once daily or twice daily (only if twice daily PE)[a]	once daily	once daily ± 2 hours
Concomitant medication recording other than PE-related treatment	all	all	weekly ± 2 days
PE details[b]	all	NA	NA or all in case of tapering
Patient review/clinical assessment, including vital signs	daily	yes	weekly ± 2 days
AE recording	daily (all)	yes	weekly ± 2 days (all)
Glasgow Coma Score	weekly if abnormal at screening	if abnormal at screening	weekly if abnormal at screening and if subject hospitalised
Neurocognitive battery[c]	once, ASAP[c]	no	no
Modified ITP bleeding score	daily	yes	weekly ± 2 days
Clinically relevant bleeding	daily	yes	weekly ± 2 days
12-lead ECG	daily if abnormal at baseline. on day 1 and day 4, 4-6 h post-study drug	yes	weekly ± 2 days
Blood chemistry (local lab)	daily pre-PE	yes	weekly ± 2 days
Haematology (local lab)	daily pre-PE	yes	weekly ± 2 days
Coagulation variables (local lab)	Mon, Wed, Fridays	yes	weekly ± 2 days
Cardiac marker (TnT or TnI) (local lab)	daily pre-PE if value > ULN in baseline or at day 1	if value > ULN in baseline or at day 1	weekly ± 2 days if value > ULN in baseline or at day 1
BNP or NT proBNP (local lab)	Mon, Wed, Fridays pre-PE if value > ULN in baseline or at day 1	if value > ULN in baseline or at day 1	weekly ± 2 days if value > ULN in baseline or at day 1

Assessment/ Activity	Daily PE treatment phase	Day 1 after last daily PE	Post daily PE (including PE tapering)
Brain damage markers (NSE, Sβ100) (central lab)	Mon, Wed, Fridays pre-PE	yes	weekly ± 2 days
PK (central lab)	• 3 samples on day 1: at 5-10 min, 3-6 h, 8-24 h post-i.v. administration, but prior to second PE; • 4 samples on day 2: after PE, but prior to study drug, and at 1-6 h, 6-12 h, 18-24 h post-study drug, but prior to next PE; • 1 sample on last day of PE: after PE, but prior to study drug	4 samples: • prior to study drug • 1-6 h post study drug • 6-12 h post study drug • 18-24 h post-study drug, but prior to next administration of study drug, or before next PE (in case of tapering)	2 samples weekly: • prior to study drug, but after PE (in case of tapering) • 4-8 h post-study drug
RICO (central lab)	daily pre-PE	yes	weekly ± 2 days (pre-PE in case of tapering)
vWF (central lab)	coupled to PK above	coupled to PK above	coupled to PK above
FVIII chromogene (central lab)	coupled to PK above	coupled to PK above	coupled to PK above
ADA (central lab)	only on day 14 (when at least 14 days of PE would be needed)	only on Day 14 (if not performed previously).	weekly until the last day of study drug administration
ADAMTS13 and anti-ADAMTS13 antibody titre (central lab)	no	yes	1 week and 3 weeks after the very last PE, including tapering[e]
Spent plasma retrieval	once, first PE on study, first spent bag	no	no
Recuperate nurse sheet and/or AE diary	NA	NA	Post-hospital discharge: weekly ± 2 days[d]

First PE on study: see section 4.2

[a] Once or twice daily as detailed in the Treatment and Dosing Regimen for study drug Section 7.2 (Table 8).

[b] Including concomitant medication related and simultaneous to PE procedure.

[c] As soon as level of consciousness and attentiveness of the subject permits and environmental factors are appropriate to support neurocognitive testing

[d] Post-discharge bleeding and any other AEs will be recorded daily by the medically trained person administering the study drug. The medically trained person will be instructed to contact the investigator in case of unexpected or clinically relevant findings

[e] The 1-week and 3-weeks after the last day of PE (including tapering) sampling may be done at the weekly visit, even if not exactly 1 or 3 weeks

Blood chemistry includes glucose, AST, ALT, LDH, CRP, creatinine, urea (BUN), uric acid, protein, albumin, haptoglobin, Na, K, Ca, Mg and Cl.

Haematology includes haemoglobin, haematocrit, MCV, MCH, MCHC, full blood count including RBC, WBC, differential, reticulocytes, optical platelet count and immature platelet fraction. Coagulation variables include fibrinogen, aPTT, PT, INR, vWF:Ag and FVIII (chromogene or alternative method).

Table 12: Schedule of assessments during treatment phase in case of exacerbation.

Assessment/ Activity	**Daily PE treatment phase**	**Post daily PE (including PE tapering)**
Treatment with study drug	Once daily or twice daily (only if twice daily PE)[a]	once daily ± 2 hours
Concomitant medication recording other than PE-related treatment	all	weekly ± 2 days
PE details[b]	all	NA or all in case of tapering
Patient review/clinical assessment, including vital signs	daily	weekly ± 2 days
AE recording	daily (all)	weekly ± 2 days (all)
Glasgow Coma Score	weekly if abnormal at screening	weekly if abnormal at screening and if subject hospitalised
Neurocognitive battery	no	no
Modified ITP bleeding score	daily	weekly ± 2 days
Clinically relevant bleeding	daily	weekly ± 2 days
12-lead ECG	daily if abnormal at baseline. on day 1 and day 4, 4-6 h post-study drug	weekly ± 2 days
Blood chemistry (local lab)	daily pre-PE	weekly ± 2 days
Haematology (local lab)	daily pre-PE	weekly ± 2 days
Coagulation variables (local lab)	Mon, Wed, Fridays	weekly ± 2 days
Cardiac marker (TnT or TnI) (local lab)	daily pre-PE if value > ULN in baseline or at day 1	weekly ± 2 days if value > ULN in baseline or at day 1
BNP or NT proBNP (local lab)	Mon, Wed, Fridays pre-PE if value > ULN in baseline or at day 1	weekly ± 2 days if value > ULN in baseline or at day 1
Brain damage markers (NSE, Sβ100) (central lab)	Mon, Wed, Fridays pre-PE	weekly ± 2 days
PK (central lab)	No	2 samples weekly: • prior to study drug, but after PE (in case of tapering) • 4-8 h post-study drug

Assessment/ Activity	**Daily PE treatment phase**	**Post daily PE (including PE tapering)**
RICO (central lab)	daily pre-PE	weekly ± 2 days (pre-PE in case of tapering)
vWF (central lab)	No	coupled to PK above
FVIII chromogene (central lab)	No	coupled to PK above
ADA (central lab)	No	weekly until the last day of study drug administration
ADAMTS13 and anti-ADAMTS13 antibody titre (central lab)	No	1 week and 3 weeks after the very last PE, including tapering[e]
Spent plasma retrieval	No	no
Recuperate nurse sheet and/or AE diary	NA	Post-hospital discharge: weekly ± 2 days[d]

[a] Once or twice daily as detailed in the Treatment and Dosing Regimen for study drug Section 7.2 (Table 8).
[b] Including concomitant medication related and simultaneous to PE procedure.
[c] As soon as level of consciousness and attentiveness of the subject permits and environmental factors are appropriate to support neurocognitive testing
[d] Post-discharge bleeding and any other AEs will be recorded daily by the medically trained person administering the study drug. The medically trained person will be instructed to contact the investigator in case of unexpected or clinically relevant findings
[e] The 1-week and 3-weeks after the last day of PE (including tapering) sampling may be done at the weekly visit, even if not exactly 1 or 3 weeks
Blood chemistry includes glucose, AST, ALT, LDH, CRP, creatinine, urea (BUN), uric acid, protein, albumin, haptoglobin, Na, K, Ca, Mg and Cl.
Haematology includes haemoglobin, haematocrit, MCV, MCH, MCHC, full blood count including RBC, WBC, differential, reticulocytes, optical platelet count and immature platelet fraction. Coagulation variables include fibrinogen, aPTT, PT, INR, vWF:Ag and FVIII (chromogene or alternative method).

8.1.3 Follow-up

The following procedures have to be performed at scheduled follow-up visits counted in days and months after last study drug administration (3 days ± 1 day, 7 days ± 1 day,1 month ± 3 days, 2 months ± 7 days, 3 months ± 15 days, 6 months ± 15 days, and 12 months ± 15 days). Unless stated otherwise, a given action is to be performed at all scheduled follow-up visits:

- Concomitant medication taken since the previous visit must be recorded on the Concomitant Medications page of the CRF. Concomitant medications initiated, stopped, up-titrated or down-titrated for an AE will also be recorded on a specific Concomitant Medications page of the CRF. Transfusion of RBC units will be recorded according to Section 8.2.1.1. This will be done for each transfusion. Data will be recorded as concomitant medication
- Clinical assessment will include physical examination and vital signs (blood pressure and heart rate at rest, body temperature)
- AE recording
- The neurocognitive battery will be administered at the day 3±1 and 1 year follow-up visits only
- Bleeding score according to the modified ITP bleeding score will be performed at the 1 month follow-up visit
- Assessment of clinically relevant bleeding will be performed at the 1 month follow-up visit
- 12-lead ECG at 1 m follow-up (± 3 days), 2 m follow-up (± 7 days), 3 m follow-up(± 15 days), 6 m follow-up (± 15 days), and 12 m follow-up (± 15 days)
- Urine pregnancy testing at 1 m follow-up (± 3 day) and 3 m follow-up (± 3 day) visits (local)
- Blood sampling for chemistry will include the following: glucose, AST, ALT, LDH, CRP, creatinine, urea (BUN), uric acid, protein, albumin, haptoglobin, Na, K, Ca, Mg and Cl (local laboratory)
- Blood sampling for haematology will include the following: haemoglobin, haematocrit, MCV, MCH, MCHC, full blood count including RBC, WBC, differential, reticulocytes, optical platelet count and immature platelet fraction (local laboratory). In case optical platelet counts are not available, they can be replaced by measurements based upon impedance. If not available in the local laboratory, immature platelet fraction measurements can be omitted.
- Blood sampling for coagulation variables will include: fibrinogen, aPTT, PT, INR, vWF:Ag and FVIII chromogene (local laboratory) In case FVIII chromogene is not

available in the local laboratory, it can be replaced by an alternative method (e.g. one stage clotting assay)

- Blood sampling for markers for cardiac cell death: Troponin T (local laboratory) will be taken at the 1 m follow-up (± 3 day) and 12 m follow-up (± 3 day) visits. In case the two initial measurements indicate that values are <ULN, all subsequent tests can be omitted. In case Troponin T is not available in the local laboratory, it can be replaced by Troponin I
- Blood sampling for markers for heart failure: BNP or NT-proBNP (local laboratory). The blood samples will be drawn at the 1 m follow-up (± 3 day) and 12 m follow-up (± 3 day) visits. In case the two initial measurements indicate that values are <ULN, all subsequent tests can be omitted
- Blood sampling for markers for brain damage: NSE, Sβ100 (central laboratory). The blood samples will be drawn at the 1 m follow-up (± 3 day) and 12 m follow-up (± 3 day) visits.
- Blood sampling for PK and PD assessments (PD assessments include RICO, vWF, FVIII chromogene) (all central laboratory) need to be taken at the following time points or time intervals:
    - day 3 ± 1 day
    - day 7 ± 1 day
    - 1m follow-up ± 3 day

  In addition, blood samples for vWF (central lab) and for FVIII chromogene (central lab) need to be taken at 2m, 3m, 6m and 12m follow-up visits
- Blood sampling for ADA needs to be taken at 1m, 2m, 3m, 6m and 12m follow-up visits (central lab).
- Blood sampling for ADAMTS13 and anti-ADAMTS13 antibody titre (central laboratory) needs to be taken at 1m and 12m follow-up visits
- Recuperate the nurse sheet and/or AE diary card

An overview of assessments performed during the follow-up phase of this trial is provided in Table 13.

During this follow-up phase, there will be no administration of study drug.

Table 13: Schedule of assessments during follow-up.

Assessment/ Activity	Day 3 (± 1 d)	Day 7 (± 1 d)	1m follow-up (± 3 d)	2m follow-up (± 7 d)	3m follow-up (± 15 d)	6m follow-up (± 15 d)	12m follow-up (± 15 d)	AE and unscheduled visit
Concomitant medication recording other than PE related treatment	X	X	X	X	X	X	X	X
Physical examination and vital signs	X	X	X	X	X	X	X	X
AE recording	X	X	X	X	X	X	X	X
Neurocognitive battery	X						X	
Modified ITP bleeding score			X					X
Assessment for clinically relevant bleeding			X					X
12-lead ECG			X	X	X	X	X	X
Urine pregnancy test (local lab)			X		X			
Blood chemistry (local lab)	X	X	X	X	X	X	X	X
Haematology (local lab)	X	X	X	X	X	X	X	X
Coagulation variables (local lab)	X	X	X	X	X	X	X	X
Cardiac marker (TnT or TnI) (local lab)			X				X	X
BNP or NT proBNP (local lab)			X				X	X
Brain damage markers (NSE, Sβ100) (central lab)			X				X	X
PK (central lab)	X	X	X					If applicable[a]
RICO (central lab)	X	X	X					If applicable[a]
vWF (central lab)	X	X	X	X	X	X	X	X
FVIII chromogene (central lab)	X	X	X	X	X	X	X	X
ADA (central lab)			X	X	X	X	X	X
ADAMTS13 and anti-ADAMTS13 antibody titre (central lab)			X				X	X
Recuperate AE diary	X	X	X	X	X	X	X	If applicable[b]

[a] i.e. during treatment phase with study drug.
[b] i.e. post-hospital discharge
Blood chemistry includes glucose, AST, ALT, LDH, CRP, creatinine, urea (BUN), uric acid, protein, albumin, haptoglobin, Na, K, Ca, Mg and Cl. Haematology includes haemoglobin, haematocrit, MCV, MCH, MCHC, full blood count including RBC, WBC, differential, reticulocytes, platelet count and, if available, immature platelet fraction. Coagulation variables include fibrinogen, aPTT, PT, INR, vWF:Ag and FVIII (chromogene or alternative method)

Precaution to be taken for cessation of study drug administration:

As described in section 8.1.2, ADAMTS13 and anti-ADAMTS13 antibody titre will be measured from blood sampling at 1-week and 3-weeks after the last day of PE (including tapering). Note that the 1-week and 3-weeks after the last day of PE (including tapering) sampling may be done at the weekly visit, even if not exactly 1 or 3 weeks.

The resulting data will be provided to the Investigator for information at the end of the study. In case an investigator has no access to similar assays and availability of ADAMTS13 and anti-ADAMTS13 antibody titre are considered essential for clinical decision making, an ad hoc determination of the results can be organised (under supervision of the country coordinator).

Platelets and LDH will be measured from blood sampling on days 3 and 7 following the conclusion of study drug administration. If at any time the platelet count falls below 70% of the last platelet count prior to cessation of study drug administration, with concomitant LDH > 1.5 X ULN: the subject will be considered at risk of a relapse and she/he will need to be closely monitored by the site staff.

When practical and logistical circumstances prevail, the Investigator can decide to hospitalise a subject for observation in order to facilitate the follow up during these 7 days post-study drug treatment period. Such a hospitalisation, organised only for practical and logistic reasons and not triggered by clinical significant altered laboratory values nor by clinical signs or symptoms, should be considered as an elective hospitalisation to be captured as an additional visit, and not as an AE or SAE (please refer to section 9.1.1).

Assessments scheduled in case of TTP relapse

In case of TTP relapse, defined as *de novo* event of TTP that occurs later than 30 days after the last daily PE, the assessments described under “daily PE for the treatment of relapse” are scheduled (see Table 14). Note that there are no “post-daily PE (including tapering)” assessments, instead, follow-up should continue per protocol. In case a follow-up visit was scheduled during the daily PE period, this visit is omitted.

Table 14: Schedule of assessments during daily PE for the treatment of a relapse.

Assessment/Activity	Daily PE for the treatment of a relapse
Treatment with study drug	No
Concomitant medication recording other than PE-related treatment	all
PE details[a]	all
Patient review/clinical assessment, including vital signs	daily
AE recording	daily (all)
Glasgow Coma Score	No
Neurocognitive battery	no
Modified ITP bleeding score	daily
Clinically relevant bleeding	No
12-lead ECG	daily if abnormal at baseline. on day 1 and day 4
Blood chemistry (local lab)	daily pre-PE
Haematology (local lab)	daily pre-PE
Coagulation variables (local lab)	Mon, Wed, Fridays
Cardiac marker (TnT or TnI) (local lab)	daily pre-PE if value > ULN in baseline or at day 1
BNP or NT proBNP (local lab)	Mon, Wed, Fridays pre-PE if value > ULN in baseline or at day 1
Brain damage markers (NSE, Sβ100) (central lab)	No
PK (central lab)	No
RICO (central lab)	No
vWF (central lab)	No
FVIII chromogene (central lab)	No
ADA (central lab)	No
ADAMTS13 and anti-ADAMTS13 antibody titre (central lab)	No
Spent plasma retrieval	No

Assessment/Activity	Daily PE for the treatment of a relapse
Recuperate nurse sheet and/or AE diary	NA

[a] Including concomitant medication related and simultaneous to PE procedure.
Blood chemistry includes glucose, AST, ALT, LDH, CRP, creatinine, urea (BUN), uric acid, protein, albumin, haptoglobin, Na, K, Ca, Mg and Cl.
Haematology includes haemoglobin, haematocrit, MCV, MCH, MCHC, full blood count including RBC, WBC, differential, reticulocytes, optical platelet count and immature platelet fraction. Coagulation variables include fibrinogen, aPTT, PT, INR, vWF:Ag and FVIII (chromogene or alternative method).

8.1.4 Unscheduled Additional Visit

In case of unscheduled additional visits, the following assessments will be performed at a minimum (Table 13):

- Concomitant medication taken since the previous visit must be recorded on the Concomitant Medications page of the CRF. Concomitant medications initiated, stopped, up-titrated or down-titrated for an AE will also be recorded on a specific Concomitant Medications page of the CRF. Transfusion of RBC units will be recorded as concomitant medication
- Clinical assessment will include physical examination and vital signs (blood pressure and heart rate at rest, body temperature)
- Bleeding score according to the modified ITP bleeding score
- Assessment of clinically relevant bleeding
- AE recording
- 12-lead ECG
- Blood sampling for chemistry will include the following: glucose, AST, ALT, LDH, CRP, creatinine, urea (BUN), uric acid, protein, albumin, Na, K, Ca, Mg and Cl (local laboratory)
- Blood sampling for haematology will include the following: haemoglobin, haematocrit, MCV, MCH, MCHC, full blood count including RBC, WBC, differential, reticulocytes, optical platelet count and immature platelet fraction (local laboratory). In case optical platelet counts are not available, they can be replaced by measurements based upon impedance. If not available in the local laboratory, immature platelet fraction measurements can be omitted
- Blood sampling for coagulation variables will include: fibrinogen, aPTT, PT, INR, vWF:Ag and FVIII chromogene (local laboratory). In case FVIII chromogene is not available in the local laboratory, it can be replaced by an alternative method (e.g. one stage clotting assay)
- Blood sampling for markers for cardiac cell death: Troponin T (local laboratory). In case Troponin T is not available in the local laboratory, it can be replaced by Troponin I
- Blood sampling for markers for heart failure: BNP or NT-proBNP (local laboratory)
- Blood sampling for markers for brain damage: NSE, Sβ100 (central laboratory)
- Blood sampling for PK and RICO, if applicable (additional visit during period of administration of study drug (central laboratory)
- Blood sampling for vWF, FVIII chromogene, and for ADA (central laboratory)

- Blood sampling for ADAMTS13 and anti-ADAMTS13 antibody titre (central laboratory)
- Recuperate the nurse sheet and/or AE diary, if applicable (additional visit post-hospital discharge)

8.1.5 Exacerbation and relapse visits

Additional information on the assessments performed during TTP exacerbation and relapse is included in sections 8.1.2 and 8.1.3 respectively.

8.2 Assessment of Efficacy

8.2.1 Clinical Outcome

- Time-to-response of treatment, defined by a recovery of platelets ≥ 150,000/µL. This response must be confirmed at 48 hours after the initial reporting of platelet recovery above 150,000/µL by a *de novo* measure of platelets ≥ 150,000/µL and LDH ≤ 2 X ULN
- Number of subjects with complete remission
- Number of (subjects with) exacerbations of TTP and time to first exacerbation of TTP. Exacerbation is defined as recurrent thrombocytopenia following a response and requiring a re-initiation of daily PE treatment after ≥ 1 day but ≤ 30 days after the last daily PE.[1]
- Number of subjects relapsing of TTP (defined as *de novo* event of TTP that occurs later than 30 days after the last daily PE) for a maximum of 1 year, and time to first relapse of TTP
- Daily PE data, including serious adverse events (SAEs) related to daily PE treatment
- Neurocognitive function, as measured by a neurocognitive test battery, at complete remission and at 1 year follow up. This test will be preceded by the Glasgow Coma Score to measure the state of consciousness of the subject
- Improvement of organ dysfunction and improvement of TTP related signs and symptoms
- Total mortality within the daily PE treatment period and within the subsequent study drug treatment period (including tapering)
- Determination of biomarkers of TTP including but not limited to disintegrin-like and metalloprotease with thrombospondin repeats 13 (ADAMTS13) levels and anti-ADAMTS13 antibody titres (see also PD assessments)

8.2.1.1 Outcomes of Special Interest

8.2.1.1.1 Plasma exchange

PE is the principal therapy of this pathology. PE will be described and recorded in detail throughout the study. This includes the initial series of PE sessions, as well as any further PE sessions that may be administered after interruption of the previous session. All PE sessions arising prior to remission and ultimately within 1 year after inclusion into the study will be recorded.

The following minimum details will be required, for each PE session:

1. Start date/time and end date/time of each procedure
2. Completion as planned or interruption needed and reason thereof
3. Plasma replacement
    a. Type of plasma product used
    b. ABO group used
    c. Total number of units used during the PE session
    d. Total volume used for plasma replacement during the PE session
4. Anticoagulant administered, if any, for the PE session
5. Concomitant medication administered specifically as part of the PE procedure and during the course of the PE session will be recorded separately. Other concomitant medication, such as methylprednisone will be reported in the concomitant medication other than PE-related medication.

    Medication given in response to a PE-related AE (i.e. antibiotic administration due to a central line infection) will be reported in the concomitant medication other than PE-related medication. This also includes immunosuppressive and other treatments adjunctive to PE (i.e. methylprednisone, rituximab).

8.2.1.1.2 Transfusion of RBC

Transfusion of RBC will be described by:

- Number of RBC units
- Date/time of administration
- This data is entered in the concomitant medication other than PE.

8.2.1.1.3 Peripheral and/or central blood line placement and replacement for daily PE

Each placement and replacement will be described for:

- Central or peripheral access
- Implant date/time and removal date/time of each central access
- Material used and anatomical point of entry
- Results of culture after removal

8.2.1.1.4 Supportive measures

Supportive measures will be described in concomitant medication other than PE.

8.2.1.1.5 Modified ITP bleeding score

This bleeding score is described in Section 8.3.3.

8.2.1.1.6 Neurocognitive battery

This test battery is described in the Section 8.3.6.

8.2.2 Pharmacodynamics

Sampling

Pharmacodynamic parameters listed below will be assessed by a central laboratory. Blood samples for laboratory parameters will be collected as scheduled in Table 10 (screening and baseline), Table 11 (treatment phase) and Table 13 (follow-up).

- RICO (conducted at central lab)
- vWF, including vWF:Ag and vWF propeptide (conducted at central lab)
- FVIII chromogene (conducted at central lab)

Instructions for the handling of laboratory samples are in a separate Laboratory Manual.

Labelling and shipping procedures for PD samples

Sites will receive required material for sampling before the start of the study. The tubes will be labelled and will carry the following information:

- Type of sample, e.g., blood, urine, etc.

- Study number
- Subject number
- Sample number
- Scheduled time of sampling

Instructions for the handling of laboratory samples are in a separate Laboratory Manual.

8.2.3 Laboratory Markers of Disease

Disease markers listed below will be assessed by a central or local laboratory. Blood samples will be collected as scheduled in Table 10 (screening and baseline), Table 11 (treatment phase) and Table 13 (follow-up).

- ADAMTS13 and anti-ADAMTS13 antibody titre (central laboratory)
- Cardiac marker (TnT or TnI)
- BNP or NT proBNP
- Brain damage markers (NSE, Sβ100) (central laboratory)
- PD (see Section 8.2.2 above)

8.3 Assessment of Safety

8.3.1 Safety Laboratory Monitoring

Blood samples for laboratory parameters will be collected as scheduled in Table 10 (screening and baseline), Table 11 (treatment phase) and Table 13 (follow-up).

All safety laboratory parameters will be performed at each local site laboratory. For each local laboratory, the Investigator will provide Ablynx with the name, professional degree and curriculum vitae of the laboratory director, a copy of the laboratory's certification- and the normal ranges for each parameter being evaluated in the study. These laboratory references must be forwarded to Ablynx before study start and updated whenever necessary. However, the Investigator will request that the clinical laboratory does not change any normal range during the course of the study.

Instructions for the handling of laboratory samples are in a separate Laboratory Manual.

Virus serology will be measured at screening only. The samples will be sent to the local laboratory as soon as possible after blood sampling.

Laboratory data will be transmitted electronically from the laboratory, to the study site. A print-out of the laboratory results will be added to the source documents. Each parameter outside the normal range will be assigned as H (high) or L (low) on the laboratory sheet. The

Investigator has to interpret each “outside the normal range” value as n.c.s. (not clinically significant) or c.s. (clinically significant). In the latter case the Investigator has to give a comment and the deviation is judged as an AE or SAE as appropriate.

Laboratory parameters

For all the items below the name of the laboratory, units of each parameter and normal range (lower limit of normal (LLN) and ULN) must be specified.

- Haematology
  - Full blood count, including haemoglobin, haematocrit, MCV, MCH, MCHC, full blood count including: RBC, WBC and differential blood count
  - Reticulocytes
  - Optical platelet count (if not available, can be replaced by measurement based upon impedance)
  - Immature platelet fraction (can be omitted)
- Blood chemistry
  - Glucose
  - Bilirubin (total)
  - AP
  - AST
  - ALT
  - LDH
  - CRP
  - hCG (for women, only if urine pregnancy test is not feasible or inconclusive)
  - Rheumatoid factor
  - Antinucleic acid
  - Iron, ferritin, transferrin
  - Creatinine, urea (BUN), uric acid
  - Protein, albumin
  - Na, K, Ca, Mg, Cl
- Urinanalysis
  - pH
  - Specific gravity
  - Protein
  - Glucose
  - Ketones
  - Bilirubin
  - Blood

  - Nitrite
  - Urobilinogen
  - Leukocytes
- Urine pregnancy test for female subjects (hCG only)
- Virus serology
  - HIV1 and HIV2 antibodies at screening
  - Surface antigen of HBV (HbsAg) and HCV antibodies at screening
- Coagulation variables
  - aPTT
  - PT
  - INR
  - Fibrinogen
  - vWF:Ag
  - FVIII chromogenic or alternative method (e.g. one stage clot test)
  - Lupus anticoagulant
  - Anticardiolipin antibodies (antiphospholipid)
- Blood typing (ABO and Rh) and DAT

8.3.2 Physical Examination and Vital Signs

A complete patient review and clinical assessment including vital signs will be performed at screening, during treatment phase and during follow-up, as indicated in Table 10, Table 11 and Table 13, respectively.

Blood pressure (systolic and diastolic) shall always be measured on the same arm (preferentially on the left arm). Heart rate measurements will be performed manually. Body temperature will be measured by the standard means of the investigational site. Measurements shall be recorded from the subject in the lying position after having rested for a 5-minute period.

After drug administration, inspections for vascular effects will focus on checks for bruising, haematomas, bleeding at injection and puncture sites and shaving nicks, gingival haemorrhage after brushing teeth, epistaxis and urinary blood loss or any other unusual bleeding. Specific questioning will be performed on whether subjects have experienced bleeding or bruises since the last examination.

8.3.3 Bleeding Events

Clinically relevant bleeding

Incidence of clinically relevant bleeding will be reported. Clinically relevant bleeding is defined as moderate to severe (including life-threatening) bleeding requiring urgent medical and/or surgical intervention.

Modified ITP bleeding score

Bleeding will also be measured using a modified version of the immune thrombocytopenic purpura (ITP) bleeding score. The rationale for using a modified version of the ITP bleeding score is the following. Both the WHO bleeding scale and other bleeding scales used in the frame of cardiac intervention or treatment of venous thromboembolism include bleeding or blood loss requiring transfusion of packed RBC or whole blood as a severity factor. It is common for subjects undergoing PE to need transfusions, even without apparent bleeding. The ITP bleeding score[27] does not include transfusion data. It is expected to be more sensitive than the other bleeding scales mentioned above. The modified ITP bleeding score is the sum of the scores for each line (Table 15).

Table 15: Modified ITP bleeding score.

Grade	0	1	2
Skin: petechiae	None	Scattered petechiae	Diffuse petechiae
Skin: ecchymosis	None	1-5 bruises	>5 bruises with size > 2cm
Oral	None	1 blood blister or >5 petechiae or gum bleeding <5 min	Multiple blood blisters or gum bleeding >5 min
Epistaxis	None	Blood when blowing nose or epistaxis <5 min (per episode)	Epistaxis >5 min (per episode)
Ocular	None	Subconjunctival haemorrhage	
Intracranial	None		Haemorrhage
Gastrointestinal	None	Blood when wiping	Blood present on stool
Urinary	None	Dipstick greater than trace	Macroscopic
Gynaecological	Normal period	Spotting outside of normal period	Bleeding greater than spotting outside of normal period, or very heavy period
Pulmonary	None	Haemoptysis	Haemorrhage

Clinically relevant findings that are observed prior to study drug initiation must be recorded on the relevant Medical History source documents page. Abnormalities in local tolerability will be reported via AE reporting throughout the trial. Clinically relevant findings found after study

drug initiation and meeting the definition of an AE (new AE or worsening of previously existing condition) must be recorded on an AE page of the source documents.

8.3.4 Cardiovascular Monitoring

12-lead ECGs will be performed at the time points specified in Table 10 (baseline), Table 11 (treatment phase) and Table 13 (follow-up). ECGs will be conducted with respect to the following procedure. Subjects will be in horizontal position during the measurements. ECGs will be evaluated and classified as normal/abnormal. In case of “abnormal”, the abnormality has to be described. Heart rate, PR, QRS, QT and QTc (Bazett) will be entered into the database. Bazett is automatically calculated by the ECG apparatus and provided on the print-out. Fridericia and RR will be calculated from the available data. For the baseline ECG, one recording will be made. The 12-lead ECGs will be recorded after the subjects have rested for at least five minutes in supine position. Six limb leads, as specified by Einthoven (I, II and III) and Goldberger (aVR, aVL, aVF), and six precordial leads (V1–V6), according to Wilson, will be used. The ECG will be recorded at a paper speed of 25 mm/s and a standard calibration of 1 mV (= 10 mm). Each ECG will include the following information: identification of each lead, study number, subject number, paper speed, voltage calibration as well as date and time of the recording. This procedure will also be followed for unscheduled visits.

8.3.5 Glasgow Coma Score

The Glasgow Coma Score will be determined using the Glasgow Coma Scale (original scale), which is a neurological scale that measures the conscious state of the subject. The best eye, verbal and motor responses will be scored according to the scale, and the separate scores added up to obtain the final score, ranging from 3 to 15.

8.3.6 Neurocognitive Battery

The neurocognitive battery, consisting of the CNTB and two manually-administered, pencil-and-paper tests (Category Fluency and Letter Fluency), will be administered at the following time points:

- Baseline (only if the level of consciousness and attentiveness of the subject permits and environmental factors are appropriate to support neurocognitive testing)
- Treatment phase
    - Once as soon as possible during the PE treatment phase (i.e., as soon as the level of consciousness and attentiveness of the subject permits and

environmental factors are appropriate to support neurocognitive testing) and only if the subject's condition did not allow to perform the CNTB at baseline

- Follow-up
  - At 3 days ± 1 days
  - At 12 months ± 15 days

Only appropriately trained and Sponsor-approved testers may administer the neurocognitive battery to study subjects. The Principal Investigator will be responsible for ensuring that his/her staff conduct the testing according to the protocol and any training guidelines provided for the battery. When testing occurs in the clinic setting, subjects should be tested in the same room under constant environmental conditions such as lighting, heating and noise. When testing occurs outside of the clinic setting, e.g., at bedside, the tester should ensure that the subject is able to sit upright and interact with computer touch screen and the testing area is quiet and relatively free of extraneous, distracting stimuli. Subjects who wear hearing devices or eyeglasses for reading will wear them when completing the neurocognitive assessments.

8.3.6.1 CNTB

The CNTB is an assessment tool for the computerised testing of neuropsychological function. The standard CNTB has 15 modules that can be combined in a customised manner to measure specific cognitive domains of interest. The customised set of modules is administered in a standardised order and with standardised stimulus durations. In this study, 6 CNTB modules will be administered (with approximate time to administer) in the sequence that follows:

Word List Learning and Selective Reminding (WLL/SR)	approx. 7 minutes
Choice Reaction Time (CRT)	approx. 2.5 minutes
Visual Memory (VMEM)	approx. 5 minutes
Simple Reaction Time (SRT)	approx. 2 minutes
Working Memory (WMEM)	approx. 2.5 minutes
Word List Learning and Delayed Recall (WLL/DR)	approx. 2 minutes

A word list learning test will be administered to evaluate verbal learning and memory (verbal rote memorisation). It has 2 components: an initial learning component utilising selective reminding (WLL/SR) and a delayed recall component (WLL/DR). A test requiring memory of novel shapes (VMEM) will be given to evaluate visual learning and memory (visual rote

memorisation). Information processing speed will be measured by tests of SRT and CRT. The CRT, together with a WMEM test, will be used to measure complex attention and concentration. This customised CNTB battery will take approximately 21 minutes to complete.

8.3.6.2 Category Fluency Test

In this test, subjects are required to produce as many examples of a given category (e.g., animals, vegetables) as quickly as possible within a specified time period. A higher number indicates better performance. The category fluency test assesses rapid language generation and depends on sustained attention, verbal intelligence, cognitive flexibility and efficiency of semantic processing. The category fluency test takes approximately 2-3 minutes to administer.

8.3.6.3 Letter Fluency Test

This test measures the number of correct words generated by the subject within one minute, where the generated words are required to begin with three predefined letters (which differ, depending on the language in which the scale is being used). A higher number indicates a better performance. The letter fluency test assesses rapid language generation and depends on sustained attention, verbal intelligence, cognitive flexibility and efficiency of semantic processing. The letter fluency test takes approximately 5-6 minutes to administer.

8.3.7 Adverse Events

It is the responsibility of the Investigator to document all AEs which occur during the entire study period, up to the last follow-up visit.
All AEs occurring after the start of the study must be reported. Subjects entry into the study is defined as the time at which informed consent is obtained. All subsequent AEs, irrespective of whether no drug, active drug or placebo has been administered, must be recorded regardless of whether or not they are considered to be drug related.
At each assessment, all AEs either observed by the Investigator or one of his clinical collaborators, or reported by the subject spontaneously or in a response to a direct question must be evaluated by the Investigator and noted in the AE sections of the subject's CRF.
Any clinically significant changes in laboratory parameters and all deviations of coagulation parameters outside normal range will be recorded as (an) AE(s) in the relevant section of the CRF.

The non-leading question "Have you felt different in any way over the last few days?" will be asked at baseline and the question "Do you feel different in any way since starting the new treatment/the last assessment?" will be asked at regular intervals throughout the study. The responses will be recorded in the subject's CRF.
The nature of each event, date and time of onset, duration, severity and relationship to treatment should be established. Details of changes to the dosage schedule or any corrective treatment should be recorded on the appropriate pages of the CRF.
The Investigator should follow-up subjects with AEs until the event has subsided (disappeared) or until the condition has stabilised. Reports relative to the subject's subsequent course must be submitted to the clinical study monitor.
For more details, refer to section 9.

8.3.8 Immunogenicity

ADA in serum will be determined by an appropriate assay technique. Immunogenicity testing will be performed on the timepoints indicated in Table 10 (screening and baseline), Table 11 (treatment phase) and Table 13 (follow-up). The sample analysis will be done by Ablynx NV.
A full description of the ADA assay is provided in the separate Laboratory Manual.
A separate immunogenicity report will be prepared and presented as an Appendix to the Final Clinical Study Report.

8.4 Pharmacokinetic Assessment

8.4.1 Sampling

Blood sampling for PK assessment will take approximately 1 minute. A detailed overview for the sampling times is presented in Table 10 (screening and baseline), Table 11 (treatment phase) and Table 13 (follow-up).
In case several study procedures are scheduled at the same time point, the following sequence should be followed: asking for AEs, ECG, vital signs, PK blood sampling and blood sampling for clinical laboratory tests. Enough time should be reserved for all assessments to be performed so that the administration of study drug and the PK blood sampling is done at the scheduled time point.
All assessments have to be scheduled in a way that the time point of PK sampling is strictly kept as displayed in Table 10, Table 11 and Table 13.
Instructions for the handling of laboratory samples are in a separate Laboratory Manual.

8.4.2 Labelling and Shipping Procedures for PK Samples

Sites will receive required material for sampling before the start of the study. The tubes will be labelled and will carry the following information:

- Type of sample, e.g., blood, urine, etc.
- Study number
- Subject number
- Sample number
- Scheduled time of sampling

Instructions for the handling of laboratory samples are in a separate Laboratory Manual.

8.4.3 Analytical Assays

The concentrations of ALX-0081 in plasma will be determined using a validated assay. Concentrations will be calculated by interpolation from a calibration curve. Quality control samples will be analysed throughout the study. Their measured concentrations will be used to determine between-run, overall precision and accuracy of the analyses.

8.4.4 Pharmacokinetics

Predose plasma concentrations against time will be plotted to demonstrate attainment of steady state.

A separate PK-report will be written and presented as an Appendix to the final Clinical Study Report.

The plasma concentration-time data of ALX-0081 will be analysed using population PK modeling. Typical population values of basic PK parameters will be estimated together with the inter-individual variability. Effects of subject demographics, laboratory parameter values, and other covariates on the pharmacokinetics of ALX-0081 will be explored. The results of the population PK analysis will be reported in an independent Modeling and Simulation report.

9. SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

9.1 Adverse Events

9.1.1 Definitions of Adverse Events

An AE is “any untoward medical occurrence in a patient or clinical investigation subject administered a study drug and which does not necessarily have a causal relationship with this treatment”. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not related to the study drug.

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

AEs include:

- Exacerbation of a pre-existing disease
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study
- Continuous persistent disease or symptoms present at baseline that worsen following the start of the study
- Lack of efficacy in the acute treatment of a life-threatening disease
- Events considered by the Investigator to be related to study-mandated procedures
- Abnormal assessments, e.g., ECG, vital signs or physical examination findings, must be reported as AEs if they represent a clinically significant finding that was not present at baseline or worsened during the course of the study
- Laboratory test abnormalities must be reported as AEs if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the study

AEs do not include:

- Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative
- Pre-existing disease or medical condition that does not worsen
- Situations in which an adverse change did not occur, e.g., hospitalisations for cosmetic elective surgery or for social and/or convenience reasons, or elective

hospitalisation for observation in order to facilitate the follow-up when practical and logistical circumstances exist.

- Overdose of either study drug or concomitant medication without any signs or symptoms. However, overdose must be mentioned in the Study Drug Log

9.1.2 Definition of Adverse Reaction (AR)

An AR is a noxious and unintended response to a study drug irrespective of the dose administered.
All ARs are judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to the study drug. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.
An unexpected adverse reaction is an AR, the nature or severity of which is not consistent with the information available on the study drug (i.e. the current Investigator's Brochure).

9.1.3 Intensity of Adverse Events

The intensity of clinical AEs is graded on a three-point scale: mild, moderate, severe and reported on specific AE pages of the source documents.
If the intensity of an AE worsens during study drug administration, the AE will be closed and a new AE with enhanced severity will be generated in the source documents. If the AE lessens in intensity, no change in the severity is required.
If an AE occurs during a washout or placebo run-in phase and afterwards worsens during the treatment phase, a new AE page must be filled in with the intensity observed during study drug administration.

- **Mild**
  Event may be noticeable to subject; does not influence daily activities; usually does not require intervention
- **Moderate**
  Event may make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed
- **Severe**
  Event may cause noticeable discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or intervention is usually needed

A mild, moderate or severe AE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction).

However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39°C that is not considered severe may become serious if it prolongs hospital discharge by a day (see Section 9.2.1.1). Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

9.1.4 Classification according to CTCAE

AEs will be classified by the Investigator according to CTCAE v4.0 in addition to severity.

9.1.5 Relationship to Study Drug

AEs should be assessed by the Investigators as to whether or not there is a reasonable possibility of causal relationship to the study drug and reported as either related or unrelated.

- **Related to study drug**
  This category applies to any AE (serious or not) with a causal relationship to the use of the study drug such as:
  - The event occurred in close temporal relationship to study drug administration
  - The event abated (diminished) or disappeared when treatment with the study drug was down-titrated, interrupted or discontinued
  - The event re-occurred when treatment was re-introduced
  - Cannot be explained by known features of the subject's clinical condition

- **Possibly related to study drug**
  This category applies to any AE (serious or not) that appears to have a reasonable possibility of causal relationship to the use of the study drug (i.e., a relationship cannot be ruled out). Guidelines to determine whether an event might be considered possibly related include (but are not limited to) the following:
  - Is a clinical event, including laboratory test with clinically significant abnormalities, within a reasonable time sequence to administration of the study drug
  - Environmental factors such as clinical state and other treatments could equally have caused the event
  - Information on study drug withdrawal may be lacking or unclear

- **Unlikely/Not related to study drug**
  This category applies to any AE (serious or not) that does not appear to have a reasonable relationship to the use of study drug (see above guidelines).
  According to current knowledge, the likelihood of a causal connection with the study drug is minimal.

9.1.6 Reporting of Adverse Events

All AEs occurring after the start of the study must be recorded until end of follow-up (1y), or until subject withdrawal. Subjects entry into the study is defined as the time at which informed consent is obtained. All subsequent AEs, irrespective of whether no drug, study drug or placebo was administered, must be recorded on specific AE pages of the respective CRF, regardless of whether or not they are considered to be study drug related. AEs occurring from study drug initiation until 30 days post study drug discontinuation (inclusive) are defined as treatment emergent.

9.1.7 Follow-up of Adverse Events

AEs still ongoing at the follow-up visit must be followed until resolution if possible.

9.2 Serious Adverse Events/Serious Adverse Reaction

9.2.1 Definitions

9.2.1.1 Serious Adverse Events/Serious Adverse Reaction (SAE/SAR)

An SAE or SAR is defined by the International Conference on Harmonisation (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- Fatal
- Life-threatening
- Requiring subject's hospitalisation or prolongation of existing hospitalisation
- Resulting in persistent or significant disability or incapacity
- Congenital anomaly or birth defect
- Medically significant or requires intervention to prevent at least one of the outcomes listed above

Life-threatening refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

Important medical events that may not immediately result in death, be life-threatening or require hospitalisation may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The reference safety document to assess whether or not an SAE should be reported by the Sponsor to Health Authorities, Ethics Committees (ECs)/IRBs and Investigators in an expedited fashion, is the Investigator's Brochure.

9.2.1.2 Hospitalisation and Prolongation of Existing Hospitalisation

Hospitalisation is defined as an overnight stay in a hospital unit and/or emergency room.

An additional overnight stay defines a prolongation of existing hospitalisation.

The following is not considered an SAE and should be reported as an AE only:

- Treatment on an emergency or outpatient basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalisation

The following reasons for hospitalisations are not considered AEs and therefore not SAEs:

- Hospitalisations for cosmetic elective surgery, social and/or convenience reasons
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, including elective hospitalisation for observation in order to facilitate the follow-up when practical and logistical circumstances exist
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., hospitalisation for chemotherapy for cancer, elective hip replacement for arthritis

9.2.1.3 Serious Adverse Events Related to Study-mandated Procedures

SAEs related to study-mandated procedures are defined as SAEs that appear to have a reasonable possibility of causal relationship (i.e., a relationship cannot be ruled out) to study-mandated procedures (excluding administration of study drug) such as discontinuation of subject's previous treatment during a washout period or complication of a mandated invasive procedure (e.g., blood sampling, heart catheterisation) or car accident on the way to the hospital for a study visit, etc.

9.2.1.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

All suspected ARs related to a study drug which occur in the concerned study, and that are both unexpected and serious are classified as suspected unexpected serious adverse reactions (SUSARs).

9.2.2 Reporting of Serious Adverse Events

9.2.2.1 Before Study Drug Initiation

SAEs occurring after signature of the Informed Consent and up to study drug initiation must be reported on SAE forms and on the AE pages of the respective CRF.

9.2.2.2 During Study Drug Administration

All SAEs regardless of causal relationship must be reported, including those related to study-mandated procedures. These SAEs occurring during study drug administration, i.e., between study drug initiation and follow-up after study drug discontinuation (as per Section 9.2.2.3), are defined as treatment emergent SAEs. Elective hospitalisation should be considered as non-reportable events and should only be recorded as clinical finding.

These SAEs are reported on SAE forms and on the AE pages of the respective CRF.

9.2.2.3 After Study Drug Discontinuation

All SAEs occurring within and including 30 days after study drug discontinuation must be recorded and reported on an SAE form and on the AE pages of the respective CRF. These SAEs are defined as treatment emergent.
SAEs occurring after 30 days post last administration of study drug are reported until end of follow-up (1y), or until subject withdrawal (as per section 5.4.2).

9.2.2.4 Reporting Procedures by the Investigator

All SAEs as defined above must be reported by the Investigator to the CRO's Drug Safety department within 24 hours of the Investigator's knowledge of the event.
These SAE forms must be faxed to the CRO's Drug Safety responsible (see contact details Page 5). The Investigator must complete the SAE form in English (unless otherwise

specified) and assess the relationship to study drug. Such preliminary reports will be followed by detailed descriptions that should include copies of hospital case reports, autopsy reports, hospital discharge summaries and other documents when requested and applicable. Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The CRO's Drug Safety department may contact the Investigator to obtain further information.

Suspected (considered related to the study drug) and Unexpected (not previously described in the reference safety document), SUSARs will be expedited by the CRO to Health Authorities, ECs/IRBs, as appropriate.

9.2.3 Follow-up of Serious Adverse Events

SAEs must be followed until resolution or death, including those still ongoing at the End-of-Study visit.

9.2.4 Reporting Procedures by the CRO on behalf of the Sponsor

All SUSARs will be reported to the competent Regulatory Authority concerned and to the competent IEC (or IRB) concerned as soon as possible but within a maximum of 15 days (fatal or life-threatening SUSARs within a maximum of 7 days) of first knowledge by the CRO or Sponsor.
Relevant follow-up information of fatal or life-threatening SUSARs will be communicated subsequently within an additional eight days.
Once a year throughout the clinical study, a listing of all suspected SARs (expected and unexpected) which have occurred and a report on the safety of the participating subjects (Annual Safety Report) will be provided to the competent Regulatory Authority and the competent IEC (or IRB).

10. STATISTICAL PROCEDURES

An SAP will be written to provide details of all statistical analyses. The SAP will be finalised before database lock and will comprise all methods and tests applied for analysis of the data The different study populations defined for endpoint analysis are described below.

10.1 Study Populations

Populations for the primary and secondary endpoint analyses

The primary analysis population will be the intent-to-treat (ITT) population, which will consist of all randomised subjects according to the randomised treatment assignment. In addition, for the efficacy analyses, the per protocol population (PP) will be used. The PP population will be a subset of the ITT population and will consist of all randomised subjects, according to the randomised treatment assignment, with exclusion of all major protocol violators.

Population for the safety analysis

The safety population will consist of all subjects who received at least one dose of study drug, with treatment assignment designated according to actual treatment received.

Population for the PK analyses

The PK analyses will be performed on the PK population, which will consist of all subjets who have received study drug and for whom the primary PK data are considered to be sufficient and interpretable.

10.2 Statistical and Analytical Plan for Pharmacokinetic Evaluation

For the sparse sampling, descriptive statistics (mean, median, min, max, standard deviation and % coefficient of variation (CV)) will be calculated per sampling day and sample collection interval. A separate Data Analysis Plan (DAP) will be prepared prior to the population PK analysis.

10.3 Evaluation of Safety and Tolerability Parameters

All safety parameters (physical examination, vital signs, bleeding, ECG-parameter, biochemistry/haematology and ADA evaluations, concomitant medications (including PE characteristics) and AEs) will be summarised descriptively by treatment. Quantitative variables will be described by n, mean, standard deviation, median, minimum and maximum. Qualitative variables will be described by frequency tables containing counts and percentages. Additionally, shift tables will be provided for the safety laboratory parameters (within, below or above normal range) from pre-study to post-dose.
The AEs will be coded according to MedDRA and tabulated by system organ class, preferred term and lower level term. An AE will be referred to by the treatment and time point after which it occurred, i.e. any AE occurring before the dosing will be counted as a baseline AE and will be considered as a treatment-emergent AE only if the severity or relation to drug changes.
No formal statistical testing will be performed on the safety data.

10.4 Determination of Sample Size

For the sample size calculation SAS version 9.2 has been used.
The primary endpoint of time-to-response of blood markers (defined as time-to-response) is monitored in a survival setting.

Sample Size Calculation The time-to-response of blood markers is monitored in a survival setting. The primary endpoint time-to-response of blood markers comprises recovery of platelets ≥ 150,000/µL. Accrual period is taken as 1.5 years. Zero to time-to-event period is set at 30 days. As median time-to-response for the control group we take 6 days (this information is calculated based upon Bandarenko et al.[28]). For the treated group with ALX-0081 we assume a 44% risk reduction corresponding to a reduction in median time to event of 2.64 days, and ultimately resulting in a time-to-response of 3.36 days. The hazard ratio is defined in the SAS code as the hazard of control versus experimental (ALX-0081) treatment thus equalling to 6/3.36=1.786. The sample size calculations are performed based on a log-rank test, aiming for a power of 80%, tested 1-sided at 2.5% significance level with 1:1 randomisation. Note that we assume that 15% of subjects would be lost-to-follow-up. The latter is justifiable because the active follow-up period only equals 30 days. Based on the above described assumptions a sample size of 110 subjects is required.

10.5 Assessment of Primary Endpoint

The primary endpoint (i.e. time-to-response of blood markers comprising recovery of platelets ≥ 150,000/µL) will be formally assessed by means of a survival analysis. An SAP will be prepared before closing the database and will comprise all methods and tests applied for analysis of the data.

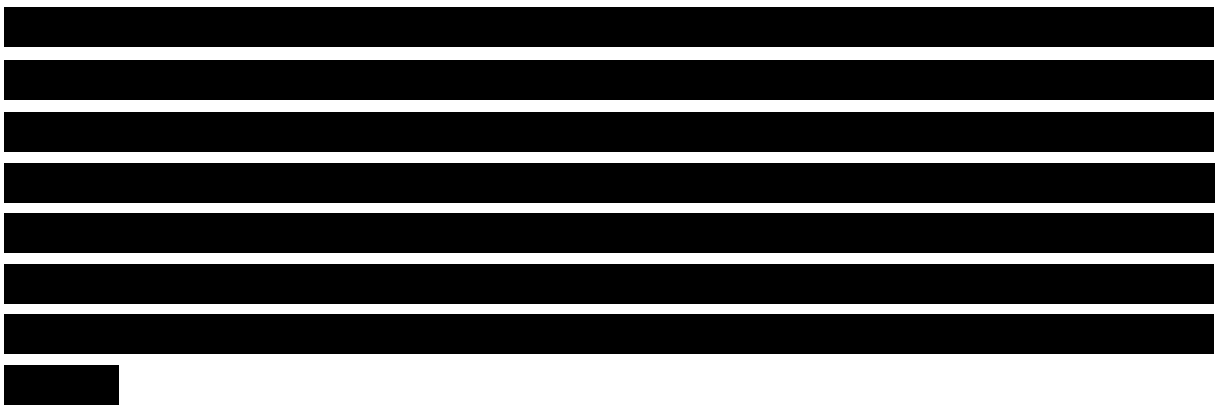
Assessment of the primary endpoint is performed by using a one-sided log-rank test at 2.5% significance level. A Kaplan-Meier (KM) analysis with time-to-response as the endpoint and treatment group as the independent variable, and stratified for absence/presence of one PE session prior to randomisation, will be performed on the ITT and PP populations. An observation is censored if the observation does not meet the defined time interval of 30 days after first administration of study drug medication, due to any cause of loss-to follow-up (including death), or endpoint not being reached within the defined time interval.

The log-rank test is one-sided because inhibition by ALX-0081 of vWF is expected for all subjects. Indeed, as described in section 2.4.2, 100% of subjects receiving a SD s.c. injection of 8 mg already had inhibition of RICO up to a minimum of 18 hours.

10.6 Analysis of Efficacy Parameters and Secondary Endpoints

Descriptive statistics for efficacy parameters and secondary endpoints, including PD parameters, will be presented for all available data using either the ITT population, the safety population, or the PP population. The descriptive statistics will include (but not limited to) the number of observations, mean, standard deviation, median, minimum and maximum for continuous variables and number of observations and their percentages for categorical parameters. An SAP will be prepared before closing the database and will comprise all methods and tests applied for analysis of the data.

10.7 Analysis of Tertiary and Exploratory Endpoints



11. ETHICAL ISSUES AND INSURANCE

11.1 Independent Ethics Committee

The study protocol (including all substantial amendments) together with the written informed consent form and informed consent updates, subject recruitment procedures (e.g. advertisements), any other written information to be provided to subjects, and any other documents needed by the IEC will be submitted for approval to the IEC which according to local regulatory requirements is in charge. Written approval of the study needs to be obtained from the IEC prior to the start of the study.
The Sponsor should submit written reports of the clinical study status to the IEC annually, or more frequently if requested by the IEC. A final study notification will be forwarded to the IEC within 90 days after the study has been completed or in the event of premature termination of the study within 15 days.
The IEC will be informed of all subsequent protocol amendments and of all SUSARs occurring during the study and all other events that have an impact on the safety of the subjects or the conduct of the study.

11.2 Ethical Conduct of the Study

The study will be conducted in accordance with the EU Clinical Trial Directive 2001/20/EC, the ICH guideline for GCP dated July 1996 and the ethical principles laid down in the Declaration of Helsinki (Appendix 1). Current national regulations and guidelines will also be followed.

11.3 Patient Information and Consent

The subjects or in case that the subject is physically or mentally incapable, their legal representatives according to local law will be informed about the nature and importance of the study. They will receive a detailed description of the foreseeable risks and discomforts and of the procedures to be followed. They will be informed that they are free to withdraw from the study at any time without any disadvantages. The consent form must be approved (along with the protocol) by the IEC and be acceptable to the Sponsor. The consent form must be in a language fully comprehensible to the prospective subject/representative.
In first intention, voluntary informed consent will be signed and dated by each subject and the person who conducted the informed consent discussion at screening prior to any study-

related procedures. All subjects will be fully informed about the meaning, aim and conduct of the study. This will take place under conditions where the participant has adequate time to consider the risks and benefits associated with his participation in the study. The subjects will have the possibility to ask all of their questions. By dating and signing the informed consent form, the subjects will agree to their participation in the study.

In second intention, in the expected case where subjects cannot provide informed consent due to physical or mental incapacity, a legal representative of the subject will be able to provide consent according to local requirements, and regulations and IEC approval. In the clinical setting of this trial investigating the acute phase of TTP, this occurrence is expected to be more frequent, with a more severe intensity of physical and/or mental incapacity. If local requirements, regulations and ethical committees allow, the study can be initiated prior to obtaining the informed consent, in case of physical or mental incapacity to consent and absence of a legal representative.

As soon as possible, voluntary informed consent must be sought and obtained from these physically or mentally incapacitated subject, or legal representative, as applicable.

It is the responsibility of the Investigator to assure that informed consent is obtained for each participant in accordance with Section 4.8 of the ICH consolidated guideline for GCP from July 1996, and local regulations. The signed informed consent will be retained with the study records. Each participant will receive a copy of the signed informed consent.

The Investigator should maintain a log of all subjects who sign the informed consent form and indicate if the subject received study drug or, if not, the reason why. The subject's medical records should also document that the informed consent form was signed and dated prior to any study-related procedures being performed.

11.4 Insurance/Liability

All subjects who have given their written consent to the clinical study will be protected in accordance with local Law. The policies regarding compensation for injury for subjects are described in the compensation information leaflet and are available upon request. A copy of the compensation information leaflet will be given to the subject upon request in accordance with the country specific requirements.

12. GENERAL REGULATIONS, AGREEMENTS AND ORGANISATIONAL PROCEDURES

12.1 Legal Aspects/Declaration of Helsinki

This study follows the Declaration of Helsinki (sixth revision, 2008) (Appendix 1), the appropriate local regulations and the ICH-GCP Note for Guidance.

12.2 Investigator's Brochure

The Investigator will be informed about current knowledge concerning the study medication through the Investigator's Brochure. Any substantial new information will be provided with no delay to all parties concerned.

12.3 Data Protection

During this clinical study, all clinical data will be identified only through an ID number and the subject's initials.

The Investigator ensures that the appointed monitor, the project manager, the auditor or representatives of the competent authorities and ECs may examine all parts of the documentation associated directly with this study (including, but not limited to, laboratory test results, admission/discharge reports of hospitalisations during participation in the clinical study and autopsy reports for deaths occurring during the clinical study).

12.4 Monitoring

During the study initiation visit the monitor explains to the Investigator all the documents and procedures relating to this study.

Tight monitoring by the appointed monitor is carried out in order to ensure the study's high quality standards.

A detailed description of monitoring is defined in the standard operating procedures (SOPs).

Regular monitoring visits are carried out at appropriate intervals in order to clarify questions that may crop up and to review all CRFs in terms of completeness and plausibility. This also involves source data verification.

The above includes a 100% review of subject numbers, initials, consent forms, demographic data, visit data, inclusion/exclusion criteria - as far as possible - as well as all AEs. The Investigator has to maintain these data up-to-date and well documented in the medical files.
Source data verification is done by direct inspection of the original medical files by authorised persons.
Personnel changes at the Investigator's site and changes in responsibilities must be notified by him/her immediately.
The following is also constantly monitored: the study's logistic workflow, compliance with regulations and the study medication's handling.
The monitor is the Investigator's permanent contact person. Unusual incidents will be documented immediately and forwarded to the project director.
The remaining study medication and the CRFs will be retrieved on the clinical study's completion.

12.5 Audits and Inspections

In the interests of quality assurance, the Sponsor or appointed independent experts may carry out audits during the clinical study's implementation phase and after its completion. In conjunction with the audit it may also be examined whether the planning, implementation and analysis of the clinical study meets the relevant statutory regulations and the requirements of GCP. This includes a review of data maintenance and organisation at the study site and at the Sponsor's, inspection of equipment and laboratories and of the source documents.

12.6 Storage of Study Records in the Investigator's File

The Investigator will be provided with an Investigator's file. The Investigator will store those documents necessary for the clinical study. As part of the monitoring, the Investigator's file will be inspected for up-to-date information and completeness in accordance with the national and international regulations.
The Investigator records in the subject identification log the following details for all persons giving their consent to participate in the study: name (first and surname), date of birth, sex, subject initials (first and surname) and the assigned subject number. The date of recruitment into the study must also be documented.
This subject identification log serves for later identification and remains with the Investigator.
After the study's completion or termination, all study documentation, including the subject identification log, will be properly archived in accordance with the Sponsor's instructions.

12.7 Costs

Agreement will be reached between PRA and the Principal Investigator, on incurred costs. These relate to the number of subjects recruited for the study plus the costs of control visits and other study related procedures. This agreement applies to payment for protocol-compliant, fully completed and documented subjects. The payment for subjects withdrawing from the study prematurely will be paid proportionally.

12.8 Confidentiality

The objectives and contents of this clinical study as well as its results are to be treated as confidential and may not be made accessible to third parties. Employees participating in the study are bound by this agreement.

12.9 The Clinical Study's Approval and General Obligation of Notification

All documents associated with the study will be submitted to the competent Regulatory Authority for approval.
Additionally all notifications to local authorities as laid down in the relevant national regulations will be made.
The Investigator will receive a copy of the notification for information.

12.10 Final Report and Publication

An integrated study report in accordance with the ICH Harmonised Tripartite Guideline (E3) (Structure and content of clinical study reports) will be prepared. The main clinical study report (CSR) will be generated once the last subject has completed the 1-month follow-up visit, and will describe the complete data set/results for the primary and secondary endpoints of all subjects in the trial. The data set/results on the 12-month follow-up period will be included in a longer term (disease outcome) addendum to the CSR.

All data and records provided by the Sponsor or generated during the study (other than subject's medical records) and all data and inventions discovered 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 any 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 written agreement of the Sponsor.

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14. APPENDICES

14.1 Appendix 1: Declaration of Helsinki

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI (Sixth revision, 2008)

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53th WMA General Assembly, Washington 2002 (Note of Clarification on Paragraph 29 added)

55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)

59th WMA General Assembly, Seoul, October 2008

A. INTRODUCTION

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should not be applied without consideration of all other relevant paragraphs.

2. Although the Declaration is addressed primarily to physicians, the WMA encourages other participants in medical research involving human subjects to adopt these principles.

3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

4. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

5. Medical progress is based on research that ultimately must include studies involving human subjects. Populations that are underrepresented in medical research should be provided appropriate access to participation in research.

6. In medical research involving human subjects, the well-being of the individual research subject must take precedence over all other interests.

7. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
8. In medical practice and in medical research, most interventions involve risks and burdens.
9. Medical research is subject to ethical standards that promote respect for all human subjects and protect their health and rights. Some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves and those who may be vulnerable to coercion or undue influence.
10. Physicians should consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

11. It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects.
12. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
13. Appropriate caution must be exercised in the conduct of medical research that may harm the environment.
14. The design and performance of each research study involving human subjects must be clearly described in a research protocol. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.
15. The research protocol must be submitted for consideration, comment, guidance and approval to a research ethics committee before the study begins. This committee must be independent of the researcher, the sponsor and any other undue influence. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration. The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No change to the protocol may be made without consideration and approval by the committee.
16. Medical research involving human subjects must be conducted only by individuals with the appropriate scientific training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional. The responsibility for the protection of research subjects must always rest with the physician or other health care professional and never the research subjects, even though they have given consent.

17. Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research.
18. Every medical research study involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and communities involved in the research in comparison with foreseeable benefits to them and to other individuals or communities affected by the condition under investigation.
19. Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject.
20. Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians must immediately stop a study when the risks are found to outweigh the potential benefits or when there is conclusive proof of positive and beneficial results.
21. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects.
22. Participation by competent individuals as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no competent individual may be enrolled in a research study unless he or she freely agrees.
23. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information and to minimize the impact of the study on their physical, mental and social integrity.
24. In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information. After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.
25. For medical research using identifiable human material or data, physicians must normally seek consent for the collection, analysis, storage and/or reuse. There may be situations where consent would be impossible or impractical to obtain for such research or would pose a threat to the validity of the research. In such situations the research may be done only after consideration and approval of a research ethics committee.
26. When seeking informed consent for participation in a research study the physician should be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent should be sought by an appropriately qualified individual who is completely independent of this relationship.
27. For a potential research subject who is incompetent, the physician must seek informed consent from the legally authorized representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the population represented by the potential subject, the research cannot instead be performed with competent persons, and the research entails only minimal risk and minimal burden.

28. When a potential research subject who is deemed incompetent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorized representative. The potential subject's dissent should be respected.
29. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research population. In such circumstances the physician should seek informed consent from the legally authorized representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research should be obtained as soon as possible from the subject or a legally authorized representative.
30. Authors, editors and publishers all have ethical obligations with regard to the publication of the results of research. Authors have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. They should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results should be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest should be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

31. The physician may combine medical research with medical care only to the extent that the research is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
32. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention, except in the following circumstances:

- The use of placebo, or no treatment, is acceptable in studies where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

33. At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.
34. The physician must fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never interfere with the patient-physician relationship.
35. In the treatment of a patient, where proven interventions do not exist or have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorized representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, this intervention should be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information should be recorded and, where appropriate, made publicly available.

22.10.2008

14.2 Appendix 2: Common Terminology for Adverse Events v4.0 (CTCAE)

National Cancer Institute (NCI) CTCAE Version 4.0
See http://ctep.cancer.gov/reporting/ctc.html.

14.3 Appendix 3: Elements of Informed Consent

The following elements of Informed Consent are compatible with the ICH, GCP and country-specific regulations. The Informed Consent Form should address each issue listed.

1. The trial involves research.
2. The purpose of the trial.
3. The trial treatment(s) and the probability for random assignment to each treatment.
4. The trial procedures to be followed, including all invasive procedures.
5. The subject's responsibilities.
6. Those aspects of the trial that are experimental.
7. The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, foetus, or nursing infant.
8. The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
9. The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important benefits and risks.
10. The compensation and/or treatment available to the subject in the event of a trial-related injury.
11. The anticipated prorated payment, if any, to the subject for participating in the trial.
12. The anticipated expenses, if any, to the subject for participating in the trial.
13. The subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
14. The monitors, the auditors, the IRB/IEC and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by applicable laws and regulations and that, by signing an ICF, the subject or the subject's legally acceptable representatives authorise such access.
15. Records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

16. The subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
17. The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
18. The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
19. The expected duration of the subject's participation in the trial.
20. The approximate number of subjects involved in the trial.

Signature Page

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