STATISTICAL ANALYSIS PLAN

ABLYNX NV
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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

Clinical Study Protocol No. ALX-0681-2.1/10

Prepared by

[redacted]

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Protocol 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

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The signature below acknowledges that the Statistical Analysis Plan prepared by inVentiv Health Clinical for Ablynx NV is fully acceptable in its current form, thus authorizing the start of programming activities.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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
AUC0-t	Area under the plasma concentration vs. time curve up to time t
AUC0-24	Area under the plasma concentration vs. time curve up to 24 hour
AUCextra	Extrapolated AUC obtained from Ct/Lambda z
AUCinf	Area under the plasma concentration vs. time curve up to infinite
AUC0-ι	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
BU/mL	Bethesda units per milliletre
BUN	Blood urea nitrogen
Ca	Calcium
Cl	Chloride
CL	Clearance
Cmax	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
CTCAE	Common terminology criteria for adverse events
CV	Coefficient of variation
d	Day
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
GGT	Gamma-glutamyl transferase

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
HEENT	Head, eyes, ears, nose and throat
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
IgA	Immunoglobin A antibody
IgG	Immunoglobin G antibody
IgM	Immunoglobin M antibody
i.m.	Intramuscular
IMPD	Investigational medicinal product dossier
IND	Investigational new drug application
INR	International normalised ratio
IRB	Institutional review board
ITP	Immune thrombocytopenic purpura
IU	International unit
i.v.	Intravenous(ly)
K	Potassium
kg	Kilogram
λz	Elimination rate constant
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LMWH	Low molecular weight heparin
m	Month
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MD	Multiple dose
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
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
t1/2	Terminal phase half-life
tmax	Time to reach Cmax
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
vWF:Ag	von Willebrand factor antigen
Vz	Volume of distribution
WLL/SR	Word list learning and selective reminding
WBC	White blood cells
WFI	Water for injection
WHO	World health organisation
WLL/DR	Word list learning and delayed recall
WMEM	Working memory

INTRODUCTION

This is a multicentre, multinational study in which it is anticipated to include 110 adult subjects with acquired thrombotic thrombocytopenic purpura (TTP) from approximately 50 participating sites across approximately 13 countries in Europe, Middle East and Northern America. This population includes symptomatic patients with acute episodes of acquired TTP, requiring treatment with plasma exchange (PE). In a limited number of sites, the trial allows inclusion of adolescent subjects (age 12 - < 18 years) as per EMA PIP (EMEA-001160-PIP01-11).

TTP is a rare and life-threatening disorder of the blood coagulation system, in which accumulation of Ultra large von Willebrand factor (ULvWF) multimers has been implicated, leading to an increased risk of thrombus formation in small blood vessels due to excessive platelet aggregation and is associated with profound thrombocytopenia and erythrocyte fragmentation. The condition is characterized by systemic platelet aggregation in the microcirculation, producing fluctuating ischaemia in many organs. If sustained, this may cause tissue infarction.

ALX-0081 is a bivalent Nanobody, consisting of two identical monovalent building blocks, that target von Willebrand factor (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).

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.

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 subjects with TTP. Through its inhibition of ULvWF-mediated platelet aggregation and resulting antithrombotic effect ALX-0081 may permit more rapid control of acute episodes of TTP when used in combination with PE. This would potentially reduce the risk of organ ischaemia and a more rapid normalization of the platelet count could also reduce the risk of haemorrhagic complications. Its use may also result in improved outcomes in poorly responsive subjects, 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.

1.1 Study Objectives

The objectives of this study are as follows:

Primary

- Reduction of time-to-response, defined by the achievement of laboratory blood marker response (platelets), confirmed at 48 hours after the initial reporting of this response (platelets and LDH).

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)

- Improvement of cognitive level at steady state post acute phase (adults only)
- 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 subjects with acquired TTP

1.2 Study Design

This is a Phase II multicentre, single-blinded, parallel design, randomised, placebo-controlled study. After confirmation of eligibility to study participation, adult subjects will be randomised in a ratio of 1:1 to either receive ALX-0081 or placebo as adjunctive therapy to PE. Adolescent subjects will not be randomised and will be treated with ALX-0081.

Adult 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). This first PE on study is followed by subcutaneous (s.c.) administration of 10 mg study drug. Adolescent subjects will receive weight-based doses according to the same administration schedule as adults.

Subsequently daily s.c. administrations of 10 mg ALX-0081 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 last PE. 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 period following last PE. 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 (longer-term) 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.

1.3 Study Timepoints

The subjects will be followed in 3 different phases during this study:

- Screening (≤ 12 hours prior to first PE on study and study drug) and baseline (15 minutes-6 hours prior to first PE on study and study drug)
- Treatment Phase:
  - Daily PE adjunctive s.c. treatment phase
  - Day 1 after the last daily PE
  - Post daily PE s.c. treatment phase (including PE tapering)
- Follow-up Phase (after completion of study drug treatment):
  - Day 3 (+/- 1 day)
  - Day 7 (+/- 1 day)
  - Month 1 (+/- 3 days)
  - Month 2 (+/- 7 days)
  - Month 3 (+/- 15 days)
  - Month 6 (+/- 15 days)
  - Month 12 (+/- 15 days)

Subjects enrolled into the study under earlier versions of the protocol will also be followed up at Days 1, 2, 4, 5 and 6 of the Follow-Up Phase. Data for these time points will be included in summary tables and listings only for those subjects where the data was collected. Due to the lack of meaningful interpretation of a percentage based on the number of subjects in the population, the percentage for these time points will not be presented.

Figure 1 displays a schematic overview of the different study phases and Appendix I contains the general schedule of assessments for this study.

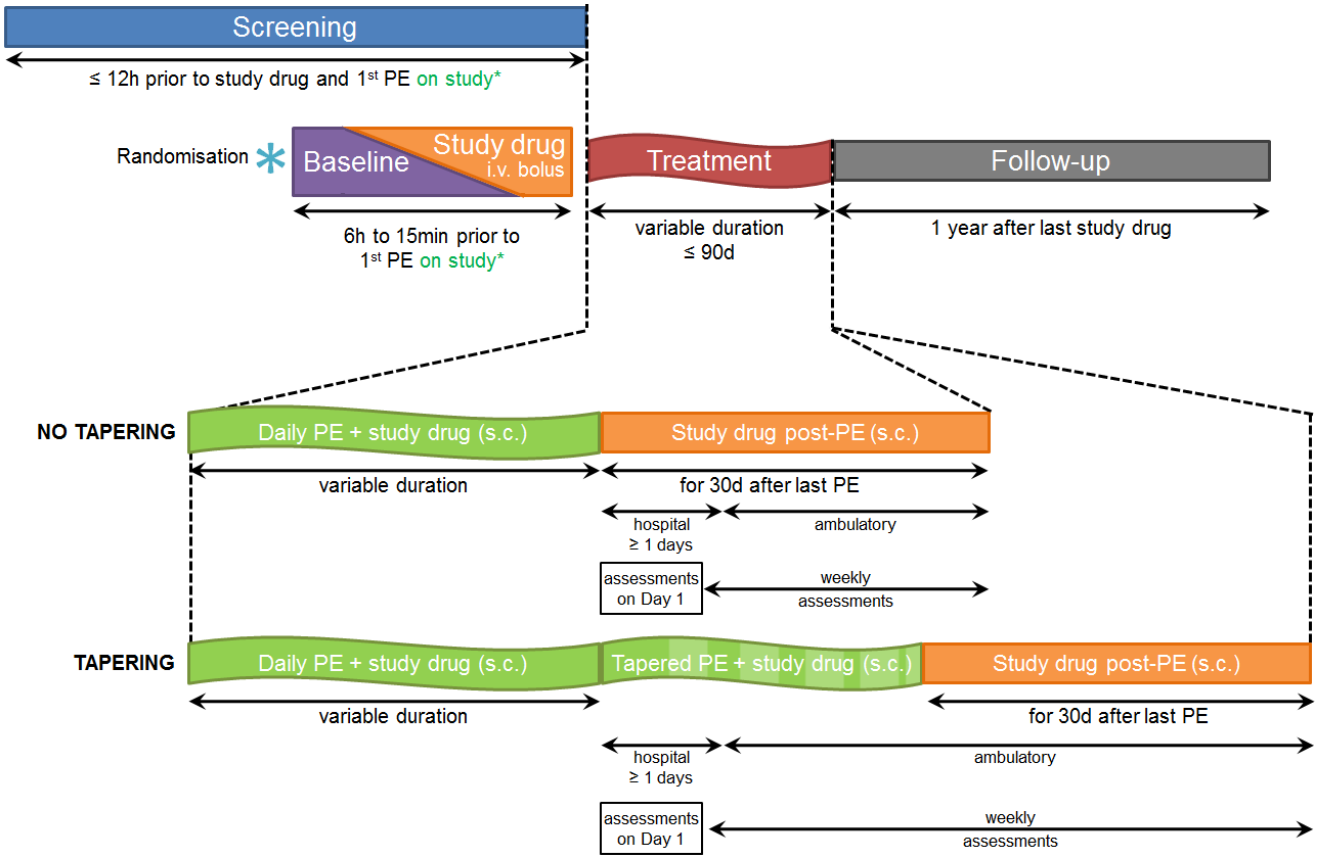

Figure 1: Schematic overview of pre-treatment, treatment and follow-up phases.

* 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 very first PE, and will be considered the first PE on study.

2. STUDY POPULATIONS

Four subject populations will provide the basis for all statistical analyses, data evaluations and summaries of the adult subjects.

Safety Population: The safety population includes all subjects who received at least one dose or partial dose of study drug, with treatment assignment designated according to actual treatment received.

Actual treatment received is not collected in the study database. [redacted] will record the details of any subject receiving treatment that does not correspond to their randomised treatment assignment. Actual treatment received will be defined as being equal to randomised treatment assignment for a particular subject unless the incorrect treatment was administered for the majority of the subject's time on treatment.

Intent-to-Treat (ITT) Population: The intent-to-treat population includes all randomised subjects, according to the randomised treatment assignment. The ITT population will be the primary population of interest for efficacy analyses.

Per-Protocol (PP) Population: The per-protocol population includes all randomised subjects, according to the randomised treatment assignments who have no major protocol deviations (see Appendix II) and satisfactorily complete the study. The PP population will be a subset of the ITT population and will be the secondary population of interest for efficacy analyses.

Subjects to be excluded from the PP Population will be defined prior to the database lock according to criteria as per Appendix II without regard to study drug assignment. Appendix II describes the major protocol deviations affecting the statistical analysis of the study and their derivation; an extensive tracker of all clinical protocol deviations is maintained separately by [redacted].

Pharmacokinetic (PK) Population: The PK population will consist of all subjects who received the study drug and for whom the primary PK data are considered to be sufficient and interpretable. The PK analysis will utilize the PK population.

Adolescent subject data will be described separately from the adult subjects. There will be no formal statistical analysis of adolescent data, only listings. Data for adolescent subjects will be grouped separately from adult subject data within the listings.

3. DEFINITIONS AND DERIVED VARIABLES

Study Completion: To complete treatment study phase including the 30 days after last study drug administration.

Follow-up Completion: To complete the follow-up study phase up to and including the 12 month assessment.

Age: Age will be calculated as:
[Date of Informed Consent – Date of Birth] / 365.25 rounded down to the nearest integer.
In cases where the Date of Birth is only partially known, for the purposes of calculating age the 15th of the month (where the month and year are known), or the 1st of July (where the year is known) will be used.

Temperature (°C): Temperature in °F multiplied by 9, divided by 5, plus 32.

Weight (kg): Weight in lb will be multiplied by 0.454 to convert to kg.

Height (cm): Height in inches will be multiplied by 2.54 to convert to cm.

BMI (kg/m^2): BMI will be calculated as:
Weight (kg) / [Height (m) x Height (m)]

Prior medications: Prior medications are defined as medication that started and stopped before the first date of study treatment. Only medications where the stop date is prior to the date of informed consent will be considered prior. If the stop date is unknown or incomplete and the medications cannot definitely be considered as stopped prior to first date of study treatment then the medications will be considered as concomitant medications.

Concomitant medications: Concomitant medications are defined as medications that either started before the first date of study treatment and continued into the study

treatment phase, or medications that started during the study treatment phase. This includes medications that were started after the first date of study treatment and discontinued during the study treatment phase.

Concomitant medications during follow-up: Concomitant medications during follow-up are defined as medications that either start before the last date of study treatment and continue into the follow-up phase, or medications that start during the follow-up phase.

Baseline: Baseline will be defined as the last assessment available prior to first administration of study drug.

Change: Change will be defined as a given post-baseline value minus the baseline value, taken at baseline or screening, whichever is applicable.

Percentage Change: Percentage change will be defined as [(post-baseline value minus baseline value) / baseline value] x 100.

Complete remission: Complete remission is defined as recovery of platelets (confirmed by platelets $\geq$ 150,000/µL and LDH $\leq$ 2 x ULN at 48 hrs after initial platelet response) and absence of exacerbation.

Initial platelet recovery: Date of initial platelet recovery is defined as the first occurrence of platelets $\geq$ 150,000/µL which is **confirmed** 48 hours later by platelets $\geq$ 150,000/µL and LDH $\leq$ 2 x ULN. For example, if platelets reach $\geq$ 150,000/µL on Day 5, are not confirmed at Day 7, reach $\geq$ 150,000/µL again on Day 10 and are confirmed at Day 12, the initial platelet recovery occurs on Day 10. Initial platelet recovery and confirmation dates will be determined using the actual lab results, following standardisation to consistent units.

Time to Response: Time to response will be calculated as the number of days, hours and minutes (represented by number of days with two significant digits after the decimal point) from study drug administration to initial platelet recovery, as defined above. An

observation is censored if the observation does not meet the defined time interval of 30 days, due to any cause of loss-to follow-up (including death), or endpoint not being reached.
Subjects that attain confirmed platelet response:
Time-to-Response = [Date and time (hrs, min) of initial platelet recovery] – [Date and time (hrs, min) of first study drug administration]

Exacerbation: Exacerbation of TTP is defined as recurrent thrombocytopenia following a confirmed platelet response and requiring a re-initiation of daily PE treatment ≥ 1 day but ≤ 30 days after the last daily PE.

Relapse: Defined as de novo event of TTP that occurs later than 30 days after the last daily PE.

First PE: Defined as start of PE.

First on-study PE: Defined as first PE received after randomisation.
In case first on-study PE is not first PE, then first on-study PE should be started within 24 hours (after the end) of the first PE. If not it is considered major protocol deviation.

Overall duration of study treatment exposure (days): Defined as date of last dose of study treatment – date of first dose of study treatment + 1

Duration of study treatment exposure during daily PE (days): Defined as date of last dose of study treatment during the daily PE period – date of first dose of study treatment during the daily PE period + 1

Duration of study treatment exposure post daily PE (days): Defined as date of last dose of study treatment – date of first dose of study treatment after the daily PE period + 1

RR interval for electrocardiogram (ECG): Defined as 60,000 / Heart Rate

4. EFFICACY PARAMETERS

Clinical Outcomes:

- 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 and percentage of subjects with confirmed platelet response
- Number and percentage of subjects with complete remission
- Number and percentage of (subjects with) exacerbations of TTP and time to first exacerbation of TTP
- Daily PE data (total volume of plasma units administered and number of days of PE), including serious adverse events (SAEs) related to PE treatment
- Total mortality within the daily PE treatment period and within the subsequent study drug treatment period (including tapering). Note that tapering of PE is considered to be part of the subsequent study drug period rather than as part of the daily PE period.
- Number and percentage of subjects relapsing of TTP for a maximum of 1 year and time to first relapse of TTP
- Number and percentage of subjects with platelets ≥ 150,000/µL at day 30 of study drug administration (last treatment day visit) and at 1 month follow-up time point
- Neurocognitive function (adults only), as measured by a neurocognitive test battery, at complete remission and at 1 year follow-up. Remission is defined as the absence of need for PE treatment ≥ 30 days. [3,4] In adults, this test will be preceded by the Glasgow Coma Score to measure the state of consciousness of the subject. For adolescents, neurocognitive function is not measured by a neurocognitive test battery; only the Glasgow Coma Score will be assessed.
- The Glasgow Coma Score which indicates the degree of consciousness, is sum of the Eye Opening, Verbal and Motor Response scores.
- Improvement of organ dysfunction and improvement of TTP related signs and symptoms
- Determination of biomarkers of TTP including but not limited to disintegrin-like and metalloprotease with thrombospondin repeats 13 (ADAMTS13) activity levels, including baseline functional inhibitors (see also PD assessments)

Clinical Outcome of Special Interest parameters:

- Plasma exchange (PE)
- Transfusion of red blood cells (RBC)
- Peripheral and/or central blood line placement and replacement for PE
- Concomitant medication other than PE, i.e. for treatment of TTP, e.g. corticosteroids, rituximab
- Modified Immune Thrombocytopenic Purpura (ITP) bleeding score
- Neurocognitive battery which is comprised of the Computerised neuropsychological test battery (CNTB), the Category Fluency Test and the Letter Fluency Test

Laboratory Markers of Disease:

- Platelets
- ADAMTS13 activity, including baseline functional inhibitors (central laboratory)
- Cardiac marker (Troponin T [TnT] or Troponin I [TnI])
- Brain natriuretic peptide or B-type natriuretic peptide (BNP); N-terminal pro B-type natriuretic peptide or N-terminal pro brain natriuretic peptide (NT–proBNP)
- Brain damage markers (Neuron specific enolase [NSE], Protein S-100 beta [Sβ100]) (central laboratory)
- PD: Ristocetin cofactor activity (RICO) (central lab), von Willebrand factor antigen (vWF Ag) and propeptide (central lab), coagulation factor VIII (FVIII) chromogene (central lab)

5. SAFETY PARAMETERS

Laboratory parameters:

- Haematology
  - Full blood count, including red blood cells (RBC), haemoglobin, haematocrit, mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), white blood cells (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
- Haptoglobin
- Gamma-glutamyl transferase (GGT) (screening only)
- Bilirubin (total) (screening and baseline only)
- Alkaline phosphatase (AP) (screening and baseline only)
- Aspartate transaminase (AST)
- Alanine transaminase (ALT)
- Lactate dehydrogenase (LDH)
- C-reactive protein (CRP)
- Human chorionic gonadotropin (hCG) (for women, only if urine pregnancy test is not feasible or inconclusive) (baseline only)
- Rheumatoid factor (baseline only)
- Antinucleic acid (baseline only)
- Iron, ferritin, transferrin (baseline only)
- Creatinine, blood urea nitrogen (BUN), uric acid
- Protein, albumin
- Sodium (Na), Potassium (K), Calcium (Ca), Magnesium (Mg), Chloride (Cl)

• Urinanalysis

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocytes

• Urine pregnancy test for female subjects (hCG only)

• Virus serology

- Human immunodeficiency virus type 1 and type 2 (HIV1 and HIV2) antibodies at screening
- Surface antigen of hepatitis B virus (HBV HbsAg) and hepatitis C virus (HCV) antibodies at screening

• Coagulation variables (local lab)

- Activated partial thromboplastin time (aPTT)
- Prothrombin time (PT)
- International normalized ratio (INR)
- Fibrinogen
- vWF Ag
- FVIII chromogenic or alternative method (e.g. one stage clot test) if not available in the local lab
- Lupus anticoagulant
- Anticardiolipin antibodies (antiphospholipid):
    - Immunoglobin G (IgG), Immunoglobin M (IgM) and Immunoglobin A (IgA)

• Blood typing (ABO and Rhesus factor [Rh]) and direct antiglobulin test (DAT)

Physical Examination

• Dermatologic

• Immunological / Allergies (other than to medication)

• Head, Eyes, Ears, Nose and Throat (HEENT)

• Endrocrine

• Respiratory

• Cardiovascular

• Genitourinary / Reproductive

• Musculoskeletal

• Neurological

• Psychological / Psychiatric

• Other Symptoms

Vital Signs

• Systolic and Diastolic Blood Pressure

• Heart Rate

• Body Temperature

• Height (screening only)

• Weight

Bleeding Events:

• Clinically relevant bleeding

• Modified ITP bleeding score

Cardiovascular Monitoring:

• 12-lead electrocardiogram (ECG) parameters:

- • Heart rate
- • PR
- • QRS
- • QT
- • QTc (Bazett)
- • RR

Glasgow Coma Score, which indicates the degree of consciousness, is sum of the Eye Opening, Verbal and Motor Response scores

Adverse Events, which are defined as any untoward medical occurrence which does not necessarily have a causal relationship with study treatment

Immunogenicity

Anti-drug antibodies (ADA) in serum as determined by an appropriate assay technique

6. STATISTICAL METHODOLOGY

6.1 Statistical and Analytical Issues

6.1.1 Statistical Methods

All data will be summarised by treatment group. In addition, where appropriate, a total overall group column will be included to summarise all subjects. Where appropriate, data will be summarised by treatment group and visit or whenever the assessment is done (e.g. the 1 and 3 week post-last day PE sampling may be done at the weekly visit, even if not at exactly 1 or 3 weeks).

All data will be listed and some selected variables will be tabulated or presented graphically, and will be noted where appropriate.

In summary and analysis tables of continuous variables, the minimum and maximum statistics will be presented to the same number of decimal places as the original data. The mean, median, quartiles, Least Squares mean (LS mean), and 95% Confidence Interval (CI) will be presented to one more decimal place than the original data, the standard deviation (SD) and standard error (SE) will be presented to two more decimal places than the original data. Standard descriptive statistics (number of subjects with data available [n], mean, SD, median, minimum and maximum) will be presented in summary tables. The LS mean, SE and 95% CI will be presented in the statistical analysis outputs as appropriate.

In summary tables of categorical variables, the number of non-missing observations and percentages will be presented. The denominator for each percentage will be the number of subjects within the population of interest [N] (unless otherwise specified).

All hypothesis testing will be 2-sided unless otherwise specified and carried out at the 5% significance level and designed to evaluate the superiority of ALX-0081 to placebo.

P-values will be rounded to three decimal places. P-values less than 0.001 will be reported as <0.001. P-values greater than 0.999 will be reported as >0.999.

Should any of the statistical methods (other than the primary endpoint analysis) proposed prove unsuitable during the final analysis, more appropriate methods will be used, and any changes documented in the CSR, including the rationale for use.

All statistical analysis will be performed using SAS® v9.2 or higher.

6.1.2 Handling of Dropouts and Missing Data

The primary, secondary and longer term endpoint analyses will be based on available data. No imputations will be made for missing data unless otherwise specified.

If a subject had a PE prior to being randomised then there will be no replacement of missing baseline values by screening values. If a subject did not have a PE prior to being randomised then missing baseline values will be replaced by screening values. Missing data post-baseline will not be estimated or imputed for any of the parameters.

6.1.3 Pooling of Investigator Sites

Data will be pooled from multiple sites for this analysis. The justification for pooling is made on a clinical basis (Meinert, 1986). The basis for pooling comes from three critical factors. The study sites must implement one common protocol. The sponsor must provide very close monitoring of study site compliance, and the study sites must use common data collection procedures.

6.1.4 Determination of Sample Size

The primary endpoint of time-to-response of blood markers (defined as time-to-response) is monitored in a survival setting. The time-to-response of blood markers comprises recovery of platelets ≥ 150,000/μL. Accrual period was taken as 1.5 years. Actual accrual time is longer than 1.5 years; however there is no impact on the sample size. 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*. [2]). 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 ratio of control versus experimental (ALX-0081) treatment thus equaling 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 (time of first study drug administration to time to event) only

equals 30 days. Based on the above described assumptions a sample size of 110 adult subjects is required. As subjects can be replaced, the ITT population may be larger than 110 subjects.

6.1.5 Changes to Planned Analyses from the Protocol

- Section 4.1.2 of the protocol describes the following secondary endpoint:
  Resolution or improvement (improvement of ≥ 1 grade in the CTCAE v4.0 scale) of TTP-related signs and symptoms as captured on the physical examination and as adverse events.
  At the time of writing this Statistical Analysis Plan, it is apparent from the design of the CRF that the CTCAE grade is recorded only once per event. Therefore it is not possible to determine if or when the CTCAE grade of a particular event has improved by ≥ 1 grade. As a consequence, for the adverse events part of this endpoint only resolution of events (defined as having a stop date and an outcome of either 'resolved' or 'resolved with sequelae') will be considered.

- Section 4.1.2 of the protocol describes the following secondary endpoint:
  Resolution of non-focal neurological symptoms as defined by neurocognitive function at complete remission, measured by a neurocognitive test battery.
  The intention was to define neurocognitive function as having a CNTB average summary score immediately post hospital discharge that is equal to or higher than at Baseline. At the time of writing this Statistical Analysis Plan, it is apparent from the data for the CNTB that the majority of subjects do not have their first CNTB assessment until after they have received study treatment. The time from first treatment to first CNTB assessment is not consistent across subjects, such that a homogeneous Baseline time point cannot be defined. It is therefore not appropriate to derive this endpoint based on change from Baseline because the resulting data will have no meaningful interpretation. It has been agreed that the CNTB will be summarised by descriptive statistics at each time point for actual results only; change from Baseline will not be calculated.

- Section 4.1.3 of the protocol describes the following secondary endpoint:
  Resolution of non-focal neurological symptoms as defined by neurocognitive function at one year follow-up, measured by a neurocognitive test battery.
  The intention was to define neurocognitive function as having a CNTB average summary score 12 months post hospital discharge that is equal to or higher than at Baseline. As explained in the previous bullet, a homogeneous Baseline time point cannot be defined and it is therefore not appropriate to derive this endpoint based on change from Baseline; it has been agreed that the CNTB will be summarised by descriptive statistics at each time point for actual results only; change from Baseline will not be calculated.

6.2 Subject Characteristics

6.2.1 Subject Disposition

Complete accounting of subject participation (from entrance into the study through to final visit) in the study is presented in the summary table for subject disposition.

Subject disposition will be summarised by treatment group and overall for all subjects. The number of subjects screened and the number of subjects who failed screening will be presented. In addition, the number of subjects randomised and the number and percentage of randomised subjects who complete the study, discontinue the study, and reasons for discontinuation from the study will be summarised. The number and percentage of randomised subjects within each population by treatment and overall will also be summarised.

Subjects who discontinued the study early and were replaced will be included in the disposition listing.

6.2.2 Protocol Deviations

A protocol deviation is defined as failure to fully comply with the study protocol. The deviation can be classified further as:

- Minor Protocol Deviation – does not have an impact on the subject's rights, safety or wellbeing, or the completeness, accuracy and reliability of the study data
- Major Protocol Deviation – may affect the subject's rights, safety or well being and/or the completeness accuracy and reliability of the study data

The sponsor will make any decisions regarding whether any subjects or any individual parameters pertaining to a subject will be excluded from the safety and efficacy evaluations when the protocol deviation is considered to have a negative impact on scientific aspects and interpretation of the study results.

Major protocol deviations will be excluded from the PP population.

All major protocol deviations will be listed. Major protocol deviations will be summarised by treatment group and overall for the ITT population.

6.2.3 Background and Demographic Characteristics

Demographic data presented will be age, gender, ethnicity/race, years of formal education and Baseline BMI completed for the safety, ITT and PP populations by treatment group and overall.

Body measurements collected at the baseline are weight and height, from which a BMI is calculated. These are summarised for the safety population within Vital Signs section.

Background data (blood type and DAT, HIV1/2, HBV and HCV) will be listed and summarised for the safety population using summary statistics for continuous variables (number of subjects [n], mean, standard deviation [SD], median, minimum and maximum) or by way of group frequencies and percentages for categorical variables, as appropriate.

6.2.4 Baseline Disease Characteristics

Baseline disease characteristics presented will be platelets, LDH, ADAMTS13 activity (subdivided into < 5% and ≥ 5%), ADAMTS13 functional inhibitors (categorised as <0.5 BU/mL, ≥0.5 BU/mL and ≤2 BU/mL, >2 BU/mL, >>2 BU/mL), vWF:Ag levels, initial

or recurrent episode (where an episode is considered to be recurrent for subjects with one or more occurrences of MedDRA preferred term "THROMBOTIC THROMOCYTOPENIC PURPURA" at latest, the month preceding the month of first dosing within the Medical History data), PE prior to randomisation (Yes/No) and exploratory markers of disease such as cardiac markers (TnT or TnI, BNP or NT-proBNP) and brain damage markers (NSE, Sβ100) for ITT and PP populations. ADAMTS13 activity will also be summarised separately for subjects having or not having received one PE prior to randomisation.

Baseline disease characteristic data will be listed and summarised using summary statistics for continuous variables (number of subjects [n], mean, standard deviation [SD], median, minimum and maximum) or by way of group frequencies and percentages for categorical variables, as appropriate.

6.2.5 Treatment Exposure and Compliance

Subjects are followed during three separate phases of the study. Treatments only occur during the treatment phase of the study as adjunctive treatment, with treatment times relative to the PE procedures. The study drug consists of 10mg of ALX-0081 or placebo administered during the treatment phase either once or twice daily. Subjects receive a first i.v. bolus of 10mg of ALX-0081 or placebo via push injection within 6 hours 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). The first PE on study is followed by s.c. administration of 10mg of study drug.

Daily s.c. study drug administration of 10 mg will continue for 30 days after the last PE with a maximum treatment duration of 90 days after the first administration of study drug.

Adolescent subjects will receive weight-based doses according to the same administration schedule as adults.

Treatment exposure overall, during daily PE and post daily PE will be summarised by length of exposure in days for the safety population with the details provided in a listing. Compliance is not an issue due to the administration of the study drugs via s.c. methods.

6.2.6 Prior and Concomitant Medications and Therapies

Any prior or concomitant medication taken during the study must be recorded in the CRF. Prior and concomitant medication will be recorded in the CRF separately for medication related to PE versus medication not related to PE.

All medications will be classified using the World Health Organization Drug Dictionary (WHODD) September 2010 Q3 (or later). The Anatomical Therapeutic Chemical (ATC) Classification levels 2 and 4 will be used to list and summarise the data.

Not related to PE: Prior and concomitant medication not related to PE such as methylprednisone, rituximab and other immunosuppressives, will be reported as concomitant medication other than PE-related medication.

Related to PE: Prior and concomitant medication related to PE will be reported as related to the PE. Anticoagulant treatment prescribed as part of the local PE procedure is allowed and considered related to PE. Medication given in response to a PE-related AE (i.e. antibiotic administration due to a central line infection) will be reported in the PE-related concomitant medication section.

The number and percentage of subjects reporting the use of any prior medications by ATC level 2 and ATC level 4 will be summarised for the safety population and for the ITT population by treatment and overall and by relationship to PE.

The number and percentage of subjects reporting the use of any concomitant medications related to PE will be summarised by ATC level 2 and ATC level 4 for the safety population and for the ITT population by treatment and overall.

The number and percentage of subjects reporting the use of any concomitant medications not related to PE will be summarised by ATC level 2 and ATC level 4 for the ITT population by treatment and overall.

The number and percentage of subjects reporting the use of any concomitant medications during follow-up will be summarised by ATC level 2 and ATC level 4 for the ITT population by treatment and overall and by relationship to PE.

Prior and concomitant medications will also be listed and will include reported and ATC terms (levels 2 and 4), indication, dosage, start and stop dates, whether the medication was related to PE and whether the medication was given for an adverse event.

6.2.7 Medical Histories

Medical history will be summarised for the safety population. The number and percentage of subjects for those who had any pre-study medical history and any pre-study medical history within each body system will be summarised by treatment group and overall. Those conditions that are reported as the underlying cause of TTP will be summarised separately. Subjects reporting more than one condition in a category will be counted only once for that category.

Medical history will be listed and will include reported body system, reported medical history term, date of onset, date of resolution, and ongoing status. An asterix or an extra Y/N column indicating each line of medical history that is checked off as TTP related equal to Y will be placed.

6.2.8 Plasma Exchange Histories

PE history (including the one PE within 24 hours prior to randomisation) will be summarised for the ITT population. The number and percentage of subjects who had any pre-study PE history will be summarised by treatment group and overall. The total number of days for pre-study PE per subject will be summarised with descriptive

statistics: [n], arithmetic mean, standard deviation [SD], median, range (*i.e.* minimum and maximum values), and 95% confidence intervals for the mean.

PE history will be listed and will include date of TTP diagnosis, whether the subject has a history of PE (Yes or No), date of PE, number of days for PE, and plasma product. An asterix will be placed indicating the PE which is given within 24 hours prior to randomisation.

6.3 Efficacy Analysis

6.3.1 Primary Efficacy Variable

Primary endpoint

Time-to-response, as defined in Section 3, 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")

Time-to-response will be measured in days, hours and minutes from date of first study drug administration. A Kaplan-Meier (KM) analysis with time-to-response as the end point 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 medication, due to any cause of loss-to follow-up (including death), or endpoint not being reached. The resulting survival estimates will be presented graphically. The median, 25th and 75th percentile time-to-event data will be presented in a table with 95% CIs (if they exist). ALX-0081 will be compared to placebo using a one-sided log-rank test in order to assess superiority at 2.5% significance level. The log-rank test is one-sided because a reduction in time-to-response by ALX-0081 is expected compared to placebo due to an inhibition of vWF by ALX-0081 (based on pre-clinical data).

Subgroup analyses

In addition to the KM estimates, the corresponding Cox proportional hazard regression model with baseline disease characteristics (ADAMTS13 activity < 5% versus ≥ 5%, vWF level (continuous), first episode versus recurrent disease (as described in Section 6.2.4), presence or absence of RICO suppression of < 20% throughout treatment period, one PE prior to randomisation or not) will be used to estimate the hazard ratio (HR) and associated 95% CIs for the HR for ALX-0081 and placebo group. This will be represented by means of Forest plots.

The trial was not sized to test for the presence of treatment by subset interactions. Thus true treatment by subset interactions would likely be missed, unless they are substantial. Conversely, should any particular subset of subjects seem to benefit more or less from therapy than the total population, this would not be taken as evidence of a true treatment by subset interaction, given the likelihood that such an observation could be due to chance alone.

Underlying model assumptions will be investigated for the survival analysis using diagnostic statistics and graphical methods, and if necessary, an alternative analysis technique may be used. Any changes in methodology will be documented in the clinical study report (CSR, to be produced by [redacted]), including the rationale for use. The proportional hazards assumption will be assessed by graphical display of the log-log survival distribution function versus the log event time for each treatment group.

In order to accommodate tied time-to-event data, the EXACT option within SAS PROC PHREG shall be used. This method assumes that there is a true but unknown ordering for the tied event times, and that the ties are merely the results of imprecise measurements of time.

Censoring and event plan

The primary endpoint in this trial is time to (initial) response. The event or response is defined as confirmed recovery of platelets above or equal to 150,000/µL.

- Confirmed response means that 48 hours after the initial response, platelets remain above or equal to this cut-off (*de novo* measurement), and lactate dehydrogenase (LDH) ≤ 2 x upper limit of normal (ULN).

- 'Time to' is defined as time in days, hours and minutes between the event and the first administration of study drug. The initial time of reaching platelets above or equal to 150,000/µL is considered as the time of recovery of platelets, and must occur within 30 days after first administration of study drug. However, this initial recovery of platelets must be confirmed at 48 hours after initial reporting, implying that time of confirmation may be 48 hours later than 30 days after first administration.

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 population (all randomised subjects).

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. Only right censoring is applicable to this trial. In **Table 1**, different potential response (censoring/event) scenarios are presented.

Table 1: Censoring/event scenarios (for ITT and PP analysis of confirmed platelet response)

Case	Description	Time at risk/ Time to recovery of platelets (days)	Responder	Censored (No = 0; Yes = 1)
1	No event in 30 days of continuous daily PE[a]	30	No	1
2	At day 30, confirmed recovery of platelets (per protocol)	30	Yes	0

Case	Description	Time at risk/ Time to recovery of platelets (days)	Responder	Censored (No = 0; Yes = 1)
3	At day x[b] (1st measurement of platelet recovery), confirmed recovery of platelets, ideal case (per protocol)	x	Yes	0
4	No event occurred and subject is no longer in trial at day x[b] (including replaced subjects who are dosed)	x	No	1
5	At day x[b] (1st measurement of platelet recovery), subject has recovery of platelets, however, missing data at 48 hours later, and no subsequent confirmation on platelet count during daily PE (no more daily platelet measurements)[c]	x	No	1
6	No recovery of platelets, however, daily PE stopped (daily PE considered surrogate for response[d]). Except if PE stopped due to AE[e] (then idem case 4)	Time of last daily PE	No	1
7	Subject not dosed (after randomisation)	1	No	1

[a] PE = plasma exchange.
[b] At day x within 30 days assessment period.
[c] No subsequent confirmation during daily PE, since daily PE has been stopped by Investigator for clinical response which does not meet protocol definition of response.
[d] Certain subject's platelet counts 'hover' around 150,000/µL, and in clinical practice, PE is stopped.
[e] Start and stop dates of adverse events related to PE will need to be compared to PE stop dates in order to identify PE stopped due to AE.

Sensitivity analyses with regards to primary (and secondary) efficacy endpoints

Sensitivity analyses comprise the following aspects:

1) For efficacy endpoints (EPs) (primary and secondary), analyses performed on per protocol (PP) populations. Details on major deviations are specified in Appendix II.

2) Analysis of treatment effect adjusted for the following covariates:
   a. ADAMTS13 activity at baseline: < 5% vs. ≥ 5%,
   b. von Willebrand Factor (vWF) level (continuous),
   c. first episode vs. recurrent disease (as described in Section 6.2.4),
   d. Ristocetin Cofactor (RICO) suppression < 20% throughout treatment period: yes vs. no,
   e. absence/presence of one PE session prior to randomisation.

A Cox proportional hazards model is fit to the data, and in addition to treatment, significant (5% significance level; SL) covariates are retained. This will be represented by means of Forest plots for the covariates found to be significant.

3) Analysis of non-confirmed and confirmed platelet response (instead of confirmed platelet response only) for the ITT population: see **Table 2**, with changes to

4) **Table 1** indicated in **bold green**.

5) Assessment of impact (potential bias) of use of rituximab during daily PE: log rank analysis of primary endpoint with subjects censored at time they start using rituximab for the ITT population. Use of rituximab will be determined by using the Concomitant Medications data (both PE related and not PE related) with ATC code "L01XC*"* (coded term "RITUXIMAB").

Table 2: Censoring/event scenarios (for ITT and PP analysis of non-confirmed and confirmed platelet response; changes to Table 1 indicated in bold green)

Case	Description	Time at risk/ Time to recovery of platelets (days)	Responder	Censored (No = 0; Yes = 1)
1	No event in 30 days of continuous daily PE[a]	30	No	1
2	At day 30, confirmed recovery of platelets (per protocol)	30	Yes	0
3	At day x[b] (1st measurement of platelet recovery), confirmed recovery of platelets, ideal case (per protocol)	x	Yes	0
4	No event occurred and subject is no longer in trial at day x[b] (including replaced subjects who are dosed)	x	No	1
5	**At day x[b] (1st measurement of platelet recovery), subject has recovery of platelets, however, missing data at 48 hours later, and no subsequent confirmation on platelet count during daily PE (no more daily platelet measurements)[c]**	**x**	**Yes**	**0**
6	**No recovery of platelets, however daily PE stopped (daily PE considered surrogate for response[d]). Except if PE stopped due to AE[e] (then idem case 4)**	**Time of last daily PE**	**Yes**	**0**
7	Subject not dosed (after randomisation)	1	No	1

[a] PE = plasma exchange.
[b] At day x within 30 days assessment period.

[c] No subsequent confirmation during daily PE, since daily PE has been stopped by Investigator for clinical response which does not meet protocol definition of response.
[d] Certain subject's platelet counts 'hover' around 150,000/µL and in clinical practice PE is stopped.
[e] Start and stop dates of adverse events related to PE will need to be compared to PE stop dates in order to identify PE stopped due to AE.

6.3.2 Secondary Efficacy Variables

Secondary Endpoints

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

- Number and percentage of subjects with complete remission (defined as confirmed platelet response and absence of exacerbation)
- Number and percentage 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 daily PE sessions, number of total volume of plasma administered and number of days of daily PE
- Total mortality within the PE treatment period and within the subsequent study drug treatment period (including tapering)
- Number and percentage of subjects relapsing of TTP (defined as *de novo* event of TTP that occurs later than 30 days after the last daily PE)
- Number and percentage of subjects with platelets ≥ 150,000/µL at day 30 of study drug administration (last treatment day visit) and one month follow-up time point
- 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)
- 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

This study has been statistically powered for the primary endpoint. No adjustment for multiplicity has been applied to the exploratory analysis for the secondary variables. All analysis will be performed on the ITT and PP populations and any p-values presented for secondary efficacy variables are purely exploratory (e.g. comparison of the number and percent of subjects with complete remission, exacerbations, relapse and daily PEs).

The number and percentage of subjects with complete remission at one month post first administration of study treatment, along with the exact binomial CI of the percentage will be presented by treatment group, overall and by ADAMTS13 activity < 5% vs. ≥ 5% at baseline.

The number and percentage of (subjects with) exacerbations of TTP at one month post first administration of study treatment, along with the exact binomial CI of the percentage will be presented by treatment group, overall and by ADAMTS13 activity < 5% vs. ≥ 5% both at baseline and after last PE (measured on day 1 after last daily PE). The time to first exacerbation of TTP, from first study drug administration, will follow the same analysis method as the primary efficacy endpoint and will be presented graphically.

The number and percentage of subjects relapsing of TTP at one month post first administration of study treatment, along with the exact binomial CI of the percentage will be presented by treatment group, overall and by ADAMTS13 activity < 5% vs. ≥ 5% both at baseline and after last PE (measured on day 1 after last daily PE). The time to first relapse of TTP, from first study drug administration, will be presented graphically.

The number and percentage of subjects with exacerbation and/or relapse, along with the exact binomial CI of the percentage will be presented by treatment group, overall and by ADAMTS13 activity < 5% vs. ≥ 5% both at baseline and after last PE (measured on day 1 after last daily PE). The time to first exacerbation or relapse (whichever occurs first), for first study drug administration, will be presented graphically.

The number of daily PE sessions (all PE sessions during the daily PE period, which may include more than one PE per day), total volume of plasma administered, number of days

of PE (number of days with at least one PE administration) and number of consecutive days of PE (maximum number of days per subject where there was no interruption of PE) will be summarised descriptively by treatment group, overall, by ADAMTS13 activity < 5% vs. ≥ 5% at baseline and by having received first PE before randomisation or not.

The number and percentage of unique subjects with resolved or improved TTP-related signs and symptoms as captured on physical examination and as adverse events within the PE treatment period, within the ensuing 30 days and at the one month follow-up will be summarised by treatment and overall along with the exact binomial CI of the percentage. Improvement of physical examination is defined as progressing from an abnormal to a normal result for a particular system at a given time point. Resolution of physical examination is defined as having normal results for all systems at a given time point. Resolution of an adverse event is defined as having a stop date present and an outcome of either 'resolved' or 'resolved with sequelae' within the given period. Both physical examination systems and adverse events flagged as being related to TTP will be considered.

The number and percentage of deaths within the PE treatment period, within the ensuing 30 days (study treatment period) and within the period from the end of the study treatment period up to and including the one month follow-up will be presented for each treatment group and overall for the ITT population only. Each death will be categorised into one of the distinct periods identified above, such that the death is counted only once in the table.

The incidence of PE treatment-related AEs, such as, but not restricted to: hemorrhage from catheter insertion, sepsis, catheter thrombosis, pneumothorax, fluid overload, hypoxia, hypotension, anaphylactoid reactions and transfusion related acute lung injury (TRALI) will be summarised by system organ class, preferred term, treatment group and overall. The summary will be repeated for PE treatment-related SAEs for the ITT population only.

Frequency tables (with accompanying Chi-square p-values) will be made for the following characteristics: use of corticosteroids during daily PE, use of rituximab during daily PE and tapering. Use of corticosteroids will be determined by using the Concomitant Medications data (both PE related and not PE related) with ATC codes beginning with "H02" (systemic corticosteroids). Use of rituximab will be determined by using the Concomitant Medications data (both PE related and not PE related) with ATC code "L01XC*"* (coded term "RITUXIMAB").

The number and percentage of subjects with platelets ≥ 150,000/µL (regardless of confirmation) at Day 30 of study drug administration (i.e. the last administration of study drug) and at the one month follow-up will be summarised by treatment and overall along with the exact binomial CI of the percentage.

6.3.3 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 opening, 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. Scores will be summarised within each system (eye opening, verbal and motor) and final score by treatment group and visit for the ITT and PP populations.

6.3.4 Neurocognitive Battery

The neurocognitive battery, consisting of the CNTB and two manually-administered, pencil and paper tests (Category Fluency and Letter Fluency), administered at the baseline and during the treatment phase. The CNTB has 6 modules: word list learning and selective reminding (WLL/SR), choice reaction time (CRT), visual memory (VMEM), simple reaction time (SRT), working memory (WMEM), and word list learning and delayed recall (WLL/DR).

The average summary score for CNTB, the total score and the change from baseline total score for Category Fluency and Letter Fluency (Trials 1, 2 and 3 respectively) will be

summarised by treatment group and visit using summary statistics for continuous variables for the ITT population.

6.3.5 Longer-Term Variables

[redacted]

6.3.6 Other exploratory analyses

[redacted]

[redacted]

6.4 Safety Analysis

Analysis of all safety data will be performed on the safety analysis population.

6.4.1 Adverse Events

All AEs will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary version 15.0 or higher.

Events will be classified as *treatment-emergent* if they started on or after date of first dose of study drug. Treatment-emergent adverse events are therefore a subset of all adverse events. If an event start date is partial, then the start month, year or stop date will be used to determine if the event is treatment-emergent. If the classification of the AE cannot be determined from the data available, then the event will be considered treatment-emergent.

The following presentations will be produced by treatment group and overall:

Treatment-emergent events:

- A general summary table reporting the number of events and the number and percentage of subjects with events will be presented by treatment group. The following categories will be included in this general summary table:
    - The number of subjects having any adverse event.
    - The number of subjects having at least one treatment-emergent adverse event.
    - The number of subjects having at least one TTP-related treatment-emergent adverse event.
    - The number of subjects having at least one PE-related treatment-emergent adverse event.

- The number of subjects having at least one drug-related treatment-emergent adverse event (defined as related or possibly related to study treatment).
- The number of subjects having at least one treatment-emergent adverse event leading to discontinuation of study drug (defined as having study treatment action taken recorded as "study drug discontinued").
- The number of subjects having at least one treatment-emergent adverse event leading to interruption of study drug (defined as having study treatment action taken recorded as "study drug interrupted").
- The number of subjects having at least one treatment-emergent adverse event leading to interruption or discontinuation of study drug (defined as having study treatment action taken recorded as either "study drug interrupted" or "study drug discontinued").
- The number of subjects having treatment-emergent adverse events with death as outcome.
- The number of subjects having at least one serious adverse event.
- The number of subjects having at least one serious treatment-emergent adverse event.
- The number of subjects having at least one serious treatment-emergent drug-related adverse event.

- Treatment-emergent AEs and SAEs will be summarised by system organ class and preferred term. The number of events and the number and percentage of subjects having each event will be presented.
- Treatment-emergent AEs and SAEs will be summarised by system organ class, preferred term and severity. The number of events and the number and percentage of subjects having each event will be presented for the maximum severity reported for each event. The maximum severity per preferred term will be evaluated for each subject and the resulting dataset will be used to present the summary. Any missing severity will be left as missing and categorised as such.

- Treatment-emergent AEs and SAEs will be summarised by system organ class, preferred term and relationship to study drug. The number of events and the number and percentage of subjects having each event will be presented for the most conservative relationship to study drug reported for each event. For example, if a subject has both a related and a possibly related event in the same preferred term, the related event will be taken for summary. The most conservative relationship per preferred term will be evaluated for each subject and the resulting dataset will be used to present the summary. Any missing relationship will be left as missing and categorised as such.
- Treatment-emergent AEs that lead to discontinuation of study drug will be summarised by system organ class and preferred term. The number of events and the number and percentage of subjects having each event will be presented.
- Treatment-emergent AEs that lead to interruption of study drug will be summarised by system organ class and preferred term. The number of events and the number and percentage of subjects having each event will be presented.
- Treatment-emergent AEs that lead to interruption or discontinuation of study drug will be summarised by system organ class and preferred term. The number of events and the number and percentage of subjects having each event will be presented.

Note: If a subject records multiple AEs with the same preferred term, these shall be summarised once within the count for n (%) of subjects, yet each event will be counted within the number of reports n* of each AE. AEs that have grade changes reported in the CRF shall be counted once, at the maximum severity reported.

All adverse events:

All recorded adverse events will be listed.

6.4.2 Physical Examination

Physical examinations recorded at screening, baseline, all treatment visits, and all follow-up visits, will include examination of the following body systems: Dermatologic, Immunological/Allergies (other than to medication), HEENT, Endocrine, Respiratory, Cardiovascular, Genitourunary/Reproductive, Musculoskeletal, Neurological,

Psychological/Psychiatric and Other. All findings for 'Other' systems for the same subject at the same visit will be grouped together for summary and labelled as "Other".

The number and percentage of subjects with results recorded as normal, abnormal not clinically significant, abnormal clinically significant, related to TTP and not done will be summarised by treatment and visit for each body system.

6.4.3 Vital Signs

Vital signs, performed at every visit, will include temperature, supine heart rate and supine diastolic and systolic blood pressures. Supine recordings will be made after the subject has been recumbent for 5 minutes. The CRF allows a selection of units in which to record temperature, but measurements will be converted to consistent units for summarisation. Temperature will be summarised in degrees Celsius. See Section 3 for unit conversion.

Weight, height and BMI will also be summarised within the Vital Signs table. The CRF allows a selection of units in which to record these parameters, but measurements will be converted to consistent units for summarisation. Weight will be summarised in kg, height will be summarised in cm. See Section 3 for unit conversions.

The absolute values of temperature, supine heart rate, supine systolic and diastolic blood pressures, weight (screening and baseline only), BMI (screening and baseline only) and height (screening only) will be summarised at each visit by treatment using the summary statistics for continuous variables. Change from baseline values will also be presented for post baseline visits.

6.4.4 Electrocardiogram

A 12-lead ECG will be recorded after at least 5 minutes in the supine position at baseline (15minutes – 6 hours prior to PE and study drug), day 1 (4 – 6 hours post study drug), day 4 (4 – 6 hours post study drug), pre-discharge, weekly (+/- 2 days) post-discharge (during continued study drug administration), 1 month (+/- 3 days) follow-up, 2 month (+/- 7 days) follow-up, 3 month (+/- 15 days) follow-up, 6 (+/- 15 days) month follow-up, 12 (+/- 15 days) month follow-up and at any AE occurrence or other unscheduled visits.

If ECG is abnormal at baseline, additional ECG measurements will be taken daily during hospitalisation.

The absolute values of heart rate, PR, QRS, QT, QTc (Bazett) and RR will be summarised at baseline and each post-drug visit by treatment using the summary statistics for continuous variables. Change from baseline values will also be presented for post baseline visits.

The number and percentage of the subjects with Normal / Abnormal Not Clinically Significant / Abnormal Clinically Significant categorical ECG results will be summarised by treatment and visit.

The shifts in Normal / Abnormal Not Clinically Significant / Abnormal Clinically Significant results from baseline to all subsequent ECG readings will also be summarised by treatment and visit.

6.4.5 Laboratory Parameters

Normal ranges as provided by Ablynx will be presented in the data listings. 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. If the units are written into the CRF they will be converted to the preferred (standard, SI) units as specified in the CRF for each parameter.

The following laboratory tests are to be performed at the times indicated in the Schedule of Assessments (Appendix I):

- Hematology: hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular haemoglobin (MCHC), mean corpuscular volume (MCV), optical platelet count (if not available, can be replaced by measurement based upon impedance),

immature platelet fraction (can be omitted), RBC, reticulocytes, WBC (neutrophils, lymphocytes, monocytes, basophils, eosinophils)

- Coagulation: fibrinogen, aPTT, PT, INR, vWF:Ag, factor VIII chromogenic or alternative method (e.g. one stage clot test), lupus anticoagulant, anticardiolipin antibodies (IgG, GPL; IgM, MPL; IgA, APL)
- Chemistry: glucose, haptoglobin, GGT, total bilirubin, alkaline phosphatase, AST, ALT, LDH, hCG (for women, only if urine pregnancy test is not feasible or inconclusive), c-reactive protein (CRP), rheumatoid factor, antinucleic acid, iron, feritin, transferrin, creatinine, urea (BUN), uric acid, protein, albumin, sodium, potassium, calcium, magnesium, chloride
- Urinalysis: pH, specific gravity, protein, glucose, ketones, bilirubin, blood, nitrite, urobilinogen, leukocytes, RBC, RBC casts, WBC, WBC casts
- Pregnancy test (urine or blood): females only at baseline
- Blood Typing (ABO), Rhesus factor in Blood (Rh), Direct Antiglobulin Test (DAT)

Continuous laboratory variables (hematology, coagulation, and chemistry parameters) will be summarised as actual result, change from baseline and percentage change from baseline for all available visits by treatment group. Urinalysis is collected at screening only and selected urinalysis parameters will be summarised for the actual result only.

Summary tables presenting the shift in result (low, normal, high) from baseline to Day 1 after last PE and from baseline to last day of treatment phase will be presented for each laboratory parameter for hematology, coagulation and chemistry parameters.

The number and percentage of subjects with abnormal laboratory results will be presented by treatment and visit for all tests and visits with at least one abnormal result. In the event that a subject has multiple abnormal values for the same test at the same visit, they will be counted only once in the summary.

The number and percentage of subjects within each blood typing, Rh and DAT status will be presented by treatment. This summary is provided as part of the background characteristics described in Section 6.2.3.

6.4.6 Bleeding Events

Clinically relevant bleeding is the main potential risk based on the pharmacological action of ALX-0081. Clinically relevant bleeding is assessed daily during daily PE period, on the first day after the daily PE period and then weekly for the subsequent time interval until 30 days after the last PE session and during any unscheduled visits. The number of subjects who experience clinically relevant bleeding and the number of subjects requiring surgical and/or medical intervention will be tabulated by treatment group and summarised by visit using counts and percentages.

Bleeding according to the modified ITP bleeding score is assessed daily during daily PE period, on the first day after the daily PE period and then weekly for the subsequent time interval until 30 days after the last PE session and during any unscheduled visits. Modified ITP bleeding score will be summarised for each parameter by treatment group and visit using counts and percentages. The sum of the parameter scores for each subject at each time point will be summarised using descriptive statistics for continuous variables.

6.4.7 Immunogenicity

ADA in serum will be determined by an immuno assay and processed at GLP Pharma. Immunogenicity testing will be performed on the timepoints indicated in Appendix I. A separate immunogenicity report will be prepared and presented as an Appendix to the Final Clinical Study Report.

The number and percentage of subjects who developed anti-drug antibodies (ADA) $\leq$ 30 days post-last study drug treatment will be presented by treatment group and overall.

The number and percentage of subjects who developed ADA > 30 days post-last study drug treatment will be presented by treatment group and overall.

6.4.8 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 opening, 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. Scores will be summarised within each system (eye opening, verbal and motor) and final score by treatment group and visit for the Safety population.

6.5 PK/PD Analysis

6.5.1 Pharmacokinetics

The plasma concentration-time profiles and summary statistics per treatment and overall will be presented for the PK population. Summary statistics will include: arithmetic mean, SD, coefficient of variation (CV) of the arithmetic mean, geometric mean, CV of the geometric mean, median, minimum and maximum.

A non-linear mixed effects pharmacokinetic/pharmacodynamic model will be used to describe the observed data. A separate Data Analysis Plan will describe the main objectives, steps and rules of the analysis. The results are outside the scope of this SAP and will be performed by the PK modelling group within Ablynx. The results will be reported in a separate study report.

6.5.2 Pharmacodynamics

The following assessments were taken at baseline and throughout the treatment phase for the pharmacodynamic (PD) analysis:

- RICO (conducted at central lab), presented as the number of subjects and days with RICO < and ≥ 20% during study drug treatment and in one month follow-up.
- vWF, including vWF:Ag and vWF propeptide (conducted at central lab)
- FVIII chromogene (conducted at central lab)
- Platelet count

Of the above, tables will be made using the safety population. Subject profile plots and summary statistics by parameter and treatment will be presented for the Safety population.

6.6 Interim Analysis

An interim analysis for safety with formal stopping rules will be done when 28 of the ALX-0081 treated subjects have been treated and assessed. Upon review of the interim safety analysis, DSMB will then make a recommendation on study continuation or discontinuation.
Since no efficacy analyses will be conducted at the interim, no alpha adjustment is made. This DSMB review is covered separately in a DSMB SAP and Charter.

The formal statistical analysis is conducted once all data for the one month follow-up is clean and locked. There will be a second formal analysis at the end of the study, when the outputs including data up to the one year follow-up will be delivered.

6.7 Data Monitoring Committee Charter

An independent DSMB monitors 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 makes recommendations on continuation of the study. After recruitment of 56 subjects a formal safety review of the data is foreseen using a safety stopping rule. More details on this review and safety stopping rule can be found in the DSMB charter and SAP. No review of efficacy data by the DSMB is foreseen.

The members of the DSMB will be experts who are independent from the sponsor and the contract research organization (CRO). The procedures and responsibilities for the collection, analysis, and review of the data by the DSMB as well as communication and documentation of their opinions and recommendations are defined in the DSMB charter.

DSMB reviews are handled by IDDI, with no involvement from inVentiv Health Clinical Biostatistics.

7. TABLES, LISTINGS, AND FIGURES

The default tables, listings and figures (TLF) layout will be as follows.

Orientation	Landscape
Paper Size	A4
Margins	Top: 3.2 cm Bottom: 2.5 cm Left: 2.5 cm Right: 2.5 cm
Font	Courier New 9pt
Headers (Centre)	Sponsor name and Protocol number(Left); Page X of Y (Right) TLF Number and Title
Footers (Left)	SAS program path and file name Date TLF generated

The font size may be reduced as necessary to allow additional columns to be presented, but not at the expense of clarity. Also the orientation may be changed to portrait if appropriate.

The date format for all presentations will be 'DDMMMYYYY'.

All TLF outputs will be generated using SAS® v9.2 or higher for Windows.

CRF data collected will be presented within data listings. The data listings will be sorted by treatment group, country, centre number, subject number and visit/week/day.

The treatment label for all Tables, Listings and Figures will be:

Treatment Group	**Treatment label for TLF**
ALX-0081 10mg	ALX-0081
Placebo	Placebo
All Subjects	Total (Tables only)

8. REFERENCES

1. Meinert, C. (1986). *Clinical Trials: Design, Conduct, and Analysis*. OxfordUniversity Press, New York.

2. Bandarenko N., Brecher M.E. and Members of the US TT Apheresis Study Group. United States Thrombotic Thrombocytopenic Purpura Apheresis Study group (US TTP ASG): Multicenter survey and retrospective analysis of current efficacy of therapeutics plasma exchange. Journal of Clinical Apheresis 1998; 13: 133-141.

3. Vesely S.K., George J.N., Lammle B. et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. Blood 2003; 102: 60-68.

4. George J.N., Vesely S.K. and Terrell D.R. The Oklahoma Thrombotic Thrombocytopenic Purpura-Hemolytic Uremic Syndrome (TTP-HUS) Registry: a community perspective of patients with clinically diagnosed TTP-HUS. Semin.Hematol. 2004; 41: 60-67.

9. APPENDICES

Appendix I – 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 3	1 day	see Table 3		±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														

	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)	(including tapering)- stop	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 3	1 day	see Table 3		±1d	±1d	±3d	±7d	±15d	±15d	±15d	as needed
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														
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

	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)	(including tapering)- stop	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 3	1 day	see Table 3		±1d	±1d	±3d	±7d	±15d	±15d	±15d	as needed
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

[a] Including RBC transfusion details
[b] Including concomitant medication related and simultaneous to PE.
[c] If abnormal at screening

Table 3 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
Subject 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

Assessment/ Activity	Daily PE treatment phase	Post daily PE (including PE tapering)
PK (central lab)	No	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	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 of the protocol.
[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).

Appendix II – Protocol ALX-0681-2.1/10: Definition of 'Major' Protocol Deviations (PDs) for Data Analysis

Major PD categories	Remarks	Source	How to assess?	DVTERM	DVDECOD
Inclusion criteria					
If one inclusion criterion or more are not met subject may not be randomised; 1. 18 years of age or older 2. Men or women willing to accept an acceptable contraceptive regimen 3. Subjects with clinical diagnosis of TTP 4. Necessitating PE 5. Subject accessible to follow-up 6. Obtained, signed and dated informed consent	For #6: IC has to be signed and dated by subject or legal representative before inclusion in the study	[redacted]	Review of listings or edit checks	Inclusion criterion 1-6 not met	Eligibility criteria not met
Exclusion criteria					
If one or more exclusion criteria are met subject may not be randomised; 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	Essential laboratory assessments to be done and recorded in the CRF: 1. Local lab platelet count at screening/baseline (missing platelet count is major PD) 2. – 3. – 4. At least 1 anti-PL ab test at screening/baseline (no anti-PL result (anticardiolipin test) is major PD) 5. – 6. Neg. pregnancy test (urine or serum) (major PD if positive; minor PD	[redacted]	Review of listings or edit checks	Exclusion criterion 1-18 not met	Eligibility criteria not met

Major PD categories	Remarks	Source	How to assess?	DVTERM	DVDECOD
10. Uncontrolled arterial hypertension 11. Known chronic treatment with anticoagulant treatment that cannot 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	if negative but result dated up to 72 hrs after randomisation) 7. – 8. – 9. – 10. – 11. – 12. – 13. – 14. – 15. – 16. – 17. Screening/baseline Lab tests minimally required (i.e. if any of bilirubin, ALT or AST are missing or above limits in exclusion criterium, this is a major PD): - bilirubin (direct) - ALT and AST (if AP and/or γGT are missing -> minor PD) 18. Serum creatinine (calculate GFR by	[redacted]			

Major PD categories	Remarks	Source	How to assess?	DVTERM	DVDECOD
	Cockcroft-Gault equation, if < 30 ml/min then major PD) [there is no box in the CRF to enter the calculated GFR value; GFR calculation according to Cockcroft-Gault formula requires serum creatinine, body weight, and age of subject as variables				
Clinically relevant bleeding (CRB)					
If study drug administration is not stopped when clinically relevant bleeding occurred	Monitoring check of CRF and Check in DB for start date CRB = stop date study drug (note that study drug is reported on daily basis, in fact the date should be missing in 'EX'). Also the bleeding is to be reported as AE with action taken regarding trial med = dose interrupted	[redacted]	Review of listings or edit checks	Bleeding occurred but drug not interrupted	Investigator mistake
If study drug is restarted when vWF:Ag < 50% and FVIII not normalised	Monitoring check of CRF and Check in DB for start date of study drug ≥ date of local lab vWF:Ag > 50% and FVIII value in normal range	[redacted]	Review of CTMS entries and listings Review of listings or edit checks	Drug restarted but vWF:Ag and FVIII levels not recovered yet	Investigator mistake
Study drug administration					
During daily PE treatment period					
Excursion of time window of sc administration after each daily PE to > 30 min post PE	Also dosing pre-PE is considered as major violation	[redacted]	Review of listings or edit	Excursion of dosing time	Treatment non compliance

Major PD categories	Remarks	Source	How to assess?	DVTERM	DVDECOD
			checks	window in daily PE period	
If ≥ 1 dose(s) are missed during daily PE treatment period		[redacted]	Review of listings or edit checks	Missing dose during x days in daily PE period	Treatment non compliance
During tapered PE (as applicable) and the 30 days post daily PE treatment period					
If study drug was administered on < 75% of treatment days	If ≥ 25% of doses (e.g. 0.25 x 30 days = 7.5 ⇨ 8 days) were not administered	[redacted]	Review of listings or checks	Subject not dosed on x days out of y days during post daily PE period	Treatment non compliance
If ≥ 2 consecutive doses were not administered	If PE is given (PE tapering): Drug should be given within 6 hours after PE: otherwise, consider as missing dose.	[redacted]	Review of listings or checks	Subject not dosed on x consecutive days during post daily PE period	Treatment non compliance
Applies to whole drug treatment period (during and after PE period)					
Randomised, no treatment administered		[redacted]	Review of listings or check	Randomised, no treatment	Investigator mistake
One or more incorrect (i.e. not as per randomised treatment assignment) treatment administrations		[redacted]	Review of CTMS entries Review of listings	Incorrect treatment administered (placebo/verum instead of verum/placebo)	Treatment non compliance
Administered more than protocol prescribed dose (overdose): if more than 1 dose and no or 1 PE on that day if more than 2 doses and not 2 PEs on that day		[redacted]	Review of CTMS entries	Subject overdosed (x doses instead of y)	Treatment non compliance
One PE prior to randomisation					

Major PD categories	Remarks	Source	How to assess?	DVTERM	DVDECOD
Prior to protocol amendment 12 any PE prior to randomisation is considered a major protocol deviation	Ablynx maintain a listing of which protocol version each subject is enrolled under. This will need to be used in collaboration with the PE and randomisation dates from the database in order to identify violating subjects.	[redacted]	Review of listings or check	X PE done before randomisation	Eligibility criteria not met
Starting from protocol amendment 12 first PE ended more than 24h prior to randomisation is considered a major protocol deviation.	As above	[redacted]	Review of listings or check	PE done x hours before randomisation	Eligibility criteria not met
Starting from protocol amendment 12 more than one PE prior to randomisation is a major protocol deviation	As above	[redacted]	Review of listings or check	X PE done before randomisation	Eligibility criteria not met
Other					
Disallowed concomitant therapy taken: only one disallowed = desmopressin	Any concomitant medication with HTC code "H01BA" (coded term "VASOPRESSIN AND ANALOGUES").	[redacted]	Review of listings	Disallowed medication taken (name of drug, start date – stop date)	Excluded concomitant medication
Subject becomes pregnant but is not withdrawn from the trial		[redacted]	Review of listings	Subject pregnant but not withdrawn	Subject not withdrawn as per protocol
Subject is lost to follow up but is not withdrawn from the trial	If a subject is lost to follow up, they should be in the database as discontinued otherwise a query should fire, so at the end of the study there should be no subjects lost to follow-up who were not withdrawn.			Subject lost to follow up but not withdrawn	Subject not withdrawn as per protocol
Subject withdraws consent but is not withdrawn from the trial	If a subject withdraws consent, they should be in the database as discontinued otherwise a			Subject withdraws consent but not	Subject not withdrawn as per protocol