AMENDED CLINICAL TRIAL PROTOCOL 02

Protocol title:	**An open-label, single-arm, multicenter study to evaluate the efficacy and safety of caplacizumab and immunosuppressive therapy without first-line therapeutic plasma exchange in adults with immune-mediated thrombotic thrombocytopenic purpura**
Protocol number:	**EFC16521**
Amendment number:	**02**
Compound number (INN/Trademark):	**ALX0081 caplacizumab/Cablivi**
Brief title:	**Caplacizumab and immunosuppressive therapy without first-line therapeutic plasma exchange in adults with immune-mediated thrombotic thrombocytopenic purpura**
Acronym:	**MAYARI**
Study phase:	**Phase 3**
Sponsor name:	**Sanofi-Aventis Recherche & Développement**
Legal registered address:	**82 Avenue Raspail** **94250 Gentilly** **France**
Monitoring team's representative name and contact information	

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02	All	05 September 2024, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	02 May 2023, version 1 (electronic 1.0)
Original Protocol		18 March 2022, version 1 (electronic 1.0)

Amended protocol 02 (05 August 2024)

This amended protocol (amendment 02) is considered to be non-substantial based on the criteria set forth in Article 2(2)(13) of the Regulation of the European Parliament and the Council of the European Union, because it does not significantly impact the safety or rights of the participants and/or the reliability and robustness of the data generated in the clinical trial.

OVERALL RATIONALE FOR THE AMENDMENT

The rationale for this protocol amendment is to update the Sponsor's legal registered address.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page	Updated the Sponsor's legal registered address.	Update.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

An open-label, single-arm, multicenter study to evaluate the efficacy and safety of caplacizumab and immunosuppressive therapy without first-line therapeutic plasma exchange in adults with immune-mediated thrombotic thrombocytopenic purpura

Brief title:

Caplacizumab and immunosuppressive therapy without first-line therapeutic plasma exchange in adults with immune-mediated thrombotic thrombocytopenic purpura

Rationale:

Caplacizumab is currently indicated for the treatment of patients with acquired thrombotic thrombocytopenic purpura (aTTP), also known as immune mediated thrombotic thrombocytopenic purpura (iTTP), in combination with therapeutic plasma exchange (TPE) and immunosuppressive therapy (IST). Although TPE has been considered a mainstay of iTTP treatment for several decades, it is a burdensome and invasive procedure for patients, and it is associated with significant complications, and a substantial number of patients remains at risk for morbidity and mortality when treated with TPE and IST alone. Based on pathophysiology of iTTP and mechanism of action of caplacizumab, it is hypothesized that caplacizumab and IST without initial TPE may be safe and effective as first-line therapy for iTTP. This concept is supported by pre-clinical data (1) as well as emerging real-world clinical evidence (2). Hence, the Sponsor is proposing an open-label, single-arm study to evaluate the hypothesis that caplacizumab and IST can be effectively and safely administered to treat an iTTP episode in adults without first-line TPE, which would be added only if clinically indicated.

A successful study will contribute to evidence of a new treatment paradigm and a new standard of care for treatment of iTTP with caplacizumab and IST without first-line TPE.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of caplacizumab in combination with immunosuppressive therapy (IST) without therapeutic plasma exchange (TPE) in adults with immune mediated thrombotic thrombocytopenic purpura (iTTP)	• Proportion of participants achieving Remission without requiring TPE during the overall study period **Remission** is defined as sustained Clinical Response (sustained platelet count ≥150 × 10^9/L and lactate dehydrogenase [LDH] <1.5 × upper limit of normal [ULN] and no clinical evidence of new or progressive ischemic organ injury for at least 2 consecutive visits) with either (a) no TPE and no anti- von Willebrand factor (anti-vWF) therapy for ≥30 days (Clinical Remission), or (b) with attainment of a disintegrin and metalloproteinase with a thrombospondin type 1 motif13 (ADAMTS13) ≥50% (Complete ADAMTS13 remission), whichever occurs first.

Objectives	Endpoints
Secondary	
• To evaluate the need for therapeutic plasma exchange in adult participants with an episode of iTTP treated with caplacizumab and IST.	• Proportion of participants achieving Remission during the overall study period • Proportion of participants who require TPE during the on-treatment period
• To evaluate the safety of caplacizumab in combination with IST without first-line TPE in adults with iTTP	• The occurrence of adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) during the treatment-emergent (TE) period
• To evaluate the effect of treatment with caplacizumab and IST without first-line TPE on clinical response	• Proportion of participants achieving Clinical Response during on-treatment period and during the overall study period **Clinical Response** is defined as sustained platelet count ≥150 × 10^9/L and LDH <1.5 × ULN and no clinical evidence of new or progressive ischemic organ injury for at least 2 consecutive visits.
• To evaluate the effect of treatment with caplacizumab and IST without first-line TPE on restoring platelet counts	• Time to platelet count response defined as time from start of treatment to initial platelet count ≥150 × 10^9/L that is sustained for ≥2 days
• To evaluate the effect of treatment with caplacizumab and IST without first-line TPE on refractory disease	• Proportion of participants refractory to therapy defined as lack of sustained platelet count increment (over 2 consecutive days) or platelet counts <50 × 10^9/L and persistently elevated LDH (>1.5 × ULN) despite 5 days of treatment during the on-treatment period
• To evaluate the effect of treatment with caplacizumab and IST without first-line TPE on clinically relevant iTTP-related events consisting of iTTP-related mortality	• Proportion of participants with TTP-related death during the on-treatment period and during the overall study period
• To evaluate the effect of treatment with caplacizumab and IST without first-line TPE on clinically relevant iTTP-related events consisting of exacerbation of iTTP	• Proportion of participants with a clinical exacerbation of iTTP during the on-treatment period and during the overall study period **Clinical Exacerbation** is defined as after a Clinical Response and before a Clinical Remission, platelet count decreases to <150 × 10^9/L (with other causes of thrombocytopenia excluded), with or without clinical evidence of new or progressive ischemic organ injury, within 30 days of stopping TPE or anti-vWF therapy.
• To evaluate the effect of treatment with caplacizumab and IST without first-line TPE on clinically relevant iTTP-related events consisting of relapse of iTTP	• Proportion of participants with a clinical relapse of iTTP during the on-treatment period and during the overall study period **Clinical Relapse** is defined as after a Clinical Remission, platelet count decreases to <150 × 10^9/L (with other causes of thrombocytopenia ruled out), with or without clinical evidence of new ischemic organ injury. A Clinical Relapse must be confirmed by documentation of severe ADAMTS13 deficiency (<10%).

Overall design:

This is a single-arm, open-label, Phase 3, multicenter study to evaluate the efficacy and safety of caplacizumab and IST without first-line TPE in adult patients with an acute episode of iTTP.

Adult participants with clinical diagnosis of initial or recurrent iTTP and a French TMA score of 1 or 2 will be enrolled from sites that are able to obtain baseline of a disintegrin and metalloproteinase with a thrombospondin type 1 motif13 (ADAMTS13) activity test results within 48 hours. Please see Section 4 and Section 5 for study enrollment criteria and eligibility assessments.

After confirmation of eligibility to study participation, participants will receive initial treatment consisting of caplacizumab and IST (corticosteroids ± anti-CD20 antibody [rituximab or biosimilar]) without first-line TPE. However, participants may start TPE later, if it is determined that there is lack of adequate response to treatment after the first 24 hours or if there is any clinical deterioration at any time during the study, including during the first 24 hours (please see Section 4.1 for additional details).

It is expected that the participant is hospitalized when the treatment is started, and the duration of initial hospitalization may vary based on clinical condition of the individual participant.
The maximum duration allowed for caplacizumab treatment will be 12 weeks for the presenting episode. The post-treatment follow-up period will be 12 weeks.

In case of clinical exacerbation and clinical relapse, please see Section 4 for additional details.

This study incorporates the revised consensus outcome definitions for iTTP published by the International Working Group for thrombotic thrombocytopenic purpura (TTP) that reflect current iTTP management (3). A Data Monitoring Committee (DMC) will be appointed to monitor the safety and scientific integrity of this study.

Brief summary:

This is a single group treatment, Phase 3, open-label, single-arm study to evaluate the efficacy and safety of caplacizumab and IST without first-line TPE with primary endpoint of remission in male and female participants aged 18 to 80 years with iTTP.

The anticipated study duration per participant without a recurrence while on therapy is maximum of approximately 24 weeks (ie, approximately 1 day for screening + maximum 12 weeks of treatment for the presenting episode + 12 weeks of follow-up). Participants will have daily assessments during hospitalization and weekly visits for assessments during ongoing treatment with caplacizumab and IST. There will be 3 outpatient visits for assessments during the follow-up period. There will be two additional follow-up visits for participants who do not have ADAMTS13 activity levels of ≥50% at the time of caplacizumab discontinuation.

Number of participants:

Approximately 61 participants will be enrolled in the study.

Intervention groups and duration:

All participants will receive open label caplacizumab daily until sustained ADAMTS13 activity normalization (≥50%) is achieved at 2 consecutive visits, after platelet count normalization (defined as ≥150 × 10^9/L × 2 consecutive values). The maximum duration allowed for caplacizumab treatment is 12 weeks for the presenting episode.

Study intervention(s)

This open-label single-arm study will be comprised of caplacizumab and IST without first-line TPE.

Investigational medicinal product (IMP): caplacizumab

- Formulation: lyophilized powder for solution for injection.
- Route(s) of administration: intravenous (IV) (for the first dose), subcutaneous (SC) (all subsequent doses).
- Dose regimen: Caplacizumab 10 mg (11 mg in US and Canada) IV for a single dose followed by caplacizumab 10 mg (11 mg in US and Canada) SC 4-6 hours after the IV dose (Day 1). An exception to this is detailed in Section 1.3.4 footnote[a]. This will be followed by caplacizumab 10 mg (11 mg in US and Canada) SC daily starting on Day 2 for a maximum treatment duration of 12 weeks for the presenting episode.

Note: Please see Section 4.1 for additional details related to IMP administration.

Noninvestigational medicinal products(s) (NIMP)

Immunosuppressive therapy:

- Corticosteroids:
  - Formulation: Prednisone or Prednisolone,
  - Route(s) of administration: IV or oral,
  - Dose regimen: Prednisone or Prednisolone 1.0-1.5 mg/kg/day for 1 week and taper over 3 to 4 weeks based on institutional guidelines. The dose and duration of therapy may be adjusted as clinically indicated.
- Anti-CD20 antibody therapy:
  - Formulation: anti-CD20 antibody therapy (rituximab or biosimilar),
  - Route(s) of administration: IV infusion (as per instructions on package insert),
  - Dose regimen: 375 mg/m^2 IV infusion × 3 - 4 doses, once a week or as per institutional guidelines.

  Note: Please see Section 4.1 for additional details regarding anti-CD20 antibody therapy.
- Therapeutic Plasma exchange (TPE), if needed:
  - Plasma (fresh frozen plasma, solvent detergent/viral-inactivated plasma and cryo-supernatant).
  - Route(s) of administration: IV,

- Dose regimen of TPE:
  - TPE with plasma at 1 to 1.5 × estimated plasma volume daily is recommended
  - TPE should be performed daily according to standard site practice and continued at least for 2 days after the platelet count normalization ($\geq 150 \times 10^9$/L). Tapering of TPE after platelet count normalization, defined as reducing its frequency to less than once per day, is strongly discouraged and if considered, should be discussed with the Medical Monitor.

Devices

The devices (ie, prefilled glass syringe containing solvent for reconstitution, vial adapter, needle for SC injections, and alcohol swabs) are included in the IMP kit.

Post-trial access to study medication

Not applicable.

Duration of study participation

Total duration of study participation for each participant with sequence and duration of study periods is as below:

- Screening: approximately 1 day
- Treatment period: variable with a maximum of 12 weeks for the presenting episode
- Follow-up period: 12 weeks.

Statistical considerations:

Sample Size Determination: The primary endpoint is the proportion of participants achieving Remission without requiring TPE during the overall study period. An adequate number of participants will be enrolled to ensure at least 55 participants with ADAMTS13 activity levels <10% at baseline are available for analysis of the primary endpoint. It is anticipated that approximately 61 participants will be enrolled in the study. With the sample size of 55, assuming the true responder rate of participants who achieve remission without requiring TPE during the overall study period is 70% (ie, overall, 85% remission rate and 18% of participants requiring TPE), the lower bound of 95% Wilson confidence interval (CI) would be 58%.

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, [Q1, Q3], minimum, and maximum, where appropriate. Categorical and ordinal data will be summarized using the count and percentage of participants.

No pre-specified success criterion and formal statistical hypothesis testing is planned.
No statistical adjustment on interim analyses.

The primary endpoint will be analyzed in modified intent-to-treat (mITT) population. Responders are participants who achieve remission without requiring TPE during the overall study period.

Each participant will be classified as a responder or non-responder per the response criteria, and the proportion of responders will be calculated together with a 95% Wilson CI.

All secondary efficacy endpoints will be analyzed using descriptive statistics, frequency, percentage, and CIs as appropriate. The time to events endpoints will be analyzed using a Kaplan-Meier analysis.

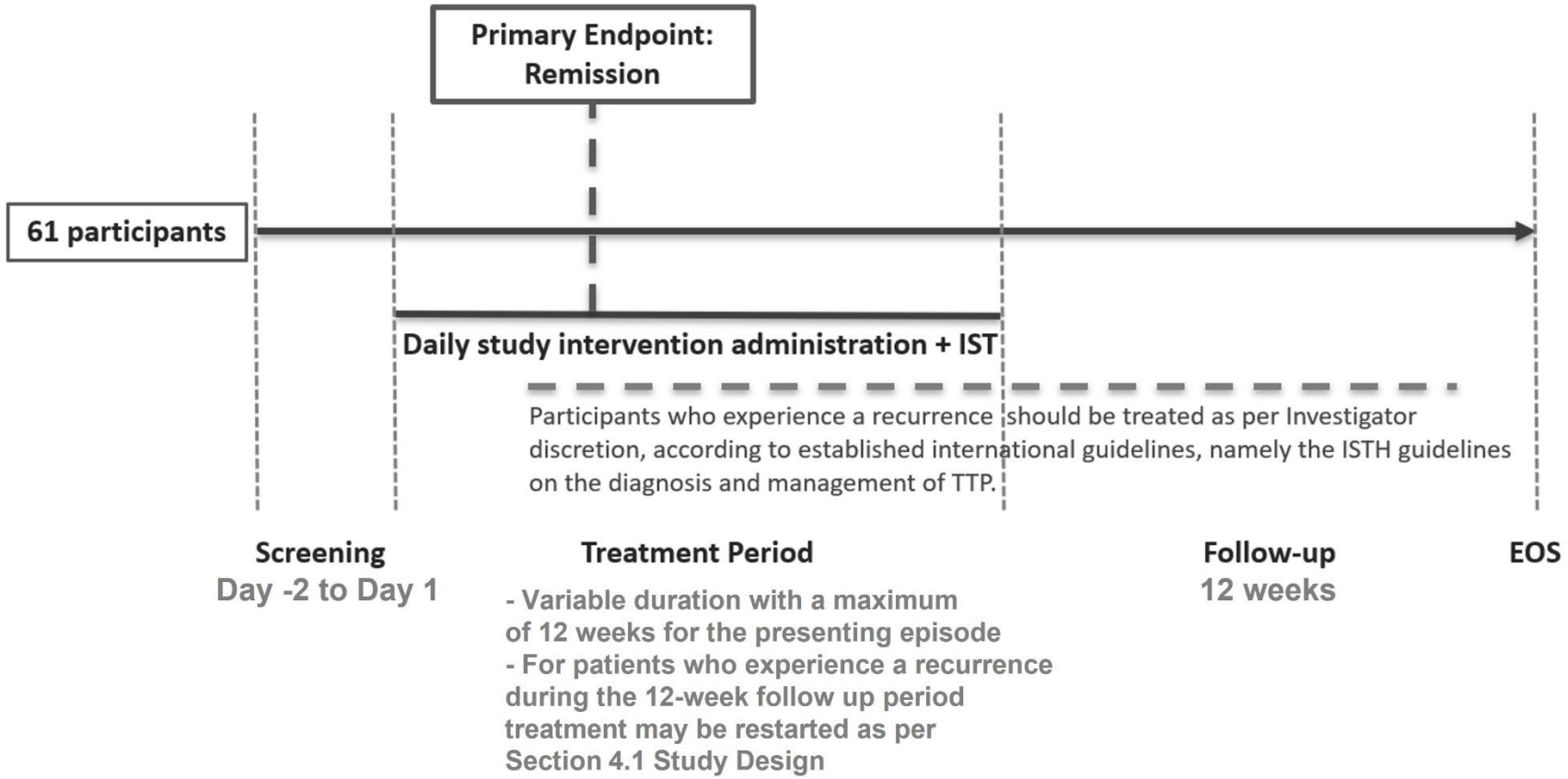
All efficacy endpoints will be summarized in mITT population, and selected efficacy endpoints may be summarized in intent-to-treat (ITT) population.

All safety analyses will be performed on the Safety population. Safety will be assessed through descriptive summaries of adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) during the treatment-emergent (TE) period. The incidence of AEs will be summarized by system organ class and preferred term.

Data Monitoring/Other committee: Yes

1.2 SCHEMA

Figure 1 - Graphical study design



Abbreviations: IST = immunosuppressive therapy; ISTH = International Society on Thrombosis and Haemostasis; iTTP = immune mediated thrombotic thrombocytopenic purpura.
The ISTH guidelines is available in the protocol references (4).

1.3 SCHEDULE OF ACTIVITIES (SOA)

1.3.1 Screening

Study Visit	Screening (Day -2 to Day 1)[a]
Procedures	
Informed consent	x
Demographics	x
Medical history[b]	x
COVID-19 test (SARS-CoV-2 RT-PCR or antigenic test)[c]	x
Hepatitis B and C and HIV serology tests[d]	x
Review of inclusion and exclusion criteria	x
Collection of data related to current hospitalization[e]	x
Physical examination	x
cTnI level[f]	x
12-lead ECG[g]	x
Neurologic assessment	x
Glasgow Coma Scale (GCS)[h]	x
Bleeding assessment[i]	x
Adverse events	x
Prior medication	x
Pregnancy test (urine or blood)[j]	x
Platelet count and blood smear[k]	x
Serum creatinine[k]	x

Study Visit	Screening (Day -2 to Day 1)[a]
IxRS registration	x

Abbreviations: ADAMTS13 = a disintegrin-like and metalloprotease with thrombospondin repeats 13; COVID-19 = coronavirus disease 2019; CRF = case report form; cTnI = cardiac troponin I;
ECG = electrocardiogram;
ICU = intensive care unit; IxRS = Interactive Voice/Web Response System; RT-PCR = reverse transcription polymerase chain reaction; TTP = thrombotic thrombocytopenic purpura.

a The Screening Period should not exceed more than 2 days. Screening may also take place on the same day as the baseline (Day 1) visit. COVID test and pregnancy test results should be available before any baseline procedure on Day 1.
b General medical history and TTP-specific medical history. The result of an ADAMTS13 activity test performed as per standard of care upon admission will be collected in the eCRF, if available.
c Results of COVID-19 tests performed within 72 hours prior to ICF signing are acceptable.
d Results of hepatitis B and C and HIV serology tests performed within 7 days of ICF signing are acceptable.
e Hospitalization information will include information on admission and discharge from hospital and ICU and dates of symptom onset and diagnosis.
f cTnI is the preferred assay. However, if this is not available, cTnT, high sensitivity cTnI or high sensitivity TnT are acceptable at Screening. Results of cTnI (or cTnT or high sensitivity cTnT or high sensitivity cTnT) tests performed within 24 hours prior to ICF signing are acceptable.
g 12-lead ECG performed within 4 hours prior to ICF signing is acceptable.
h To be assessed within 2 hours prior to enrollment.
i Bleeding assessment is a clinical assessment of signs and symptoms of bleeding (eg, petechiae, bruises, epistaxis, hematuria, menorrhagia, gastrointestinal bleeding) performed by the Investigator.
j Only for women of childbearing potential. Pregnancy test (urine or blood as required by local regulations) will be assessed locally. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required.
k Platelet count is included in the hematology laboratory test (Section 10.2). Samples for hematology test, blood smear and serum creatinine will be assessed by a local laboratory (values of samples taken as part of standard of care within 24 hours prior to ICF signing can be used, if available).

1.3.2 Schedule of activities: during hospitalization

Study Visit[a]	Day 1 (Baseline)[a, b]	Day 2	Day 3	DAILY during hospitalization starting on Day 4
Procedures				
Height and weight	x			
Safety and laboratory assessments				
Physical examination[c]	x			
Neurologic assessments[d, c]	x	x	x	x
GCS[c]	x	x	x	x
Clinically significant TTP event	x	x	x	x
Bleeding assessment[e, c]	x	x	x	x
Vital signs[f]	x			
12-lead ECG[g, c]	x	x	x	x[h]
Adverse events	---------->			
Concomitant medications	---------->			
Clinical laboratory analyses[i]	x			
Platelet count[j]	x[k, j]	x	x	x
Blood smear[l]	x			
[redacted]				
Study treatment administration				
IMP administration[o]	x	x	x	x
Therapeutic plasma exchange (if needed)[p]		x	x	x
Corticosteroids	x	x	x	x
Anti-CD20 antibody therapy[q]	---------->			

Study Visit[a]	Day 1 (Baseline)[a, b]	Day 2	Day 3	DAILY
[redacted]				

Abbreviations: ADA = anti-drug antibody; ADAMTS13 = a disintegrin-like and metalloprotease with thrombospondin repeats 13; Ag = antigen; cTnI = cardiac troponin I; ECG = electrocardiogram; [redacted]; GCS = Glasgow Coma Scale; HCRU = Health care resource utilization; IV = intravenous; IMP = investigational medicinal product; LDH = lactate dehydrogenase; PD = pharmacodynamics; PK = pharmacokinetics; RICO = ristocetin cofactor activity; [redacted] SC = subcutaneous; TPE = therapeutic plasma exchange; TTP = thrombotic thrombocytopenic purpura; vWF = von Willebrand Factor

a The following guidance with regard to timing of assessments planned at a single visit should be followed: 1) ECG and vital signs have to be assessed prior to blood sampling, 2) assessments will be done prior to study intervention administration and prior to start of TPE if receiving TPE, and 3) IMP will be dosed subcutaneously after completion of TPE treatment, if receiving TPE. The eDiary will be dispensed on the day of discharge from the hospital.

b The baseline visit may occur on the same day as Screening.

c These assessments (physical exam, neurologic assessments, GCS, 12-lead ECG, bleeding assessment) do not need to be repeated at the Day 1 (baseline) visit if already performed at Screening and Screening is within 4 hours of Day 1 (baseline).

d Neurological assessments will include coma, stupor, seizures, disorientation/confusion, hemiparesis/hemiplegia, focal deficit, agitation, and dysarthria (primarily physical examination and as per standard of care and by Investigator's judgement: electroencephalogram [EEG], magnetic resonance imaging [MRI], etc).

e Bleeding assessment will be a clinical assessment of signs and symptoms of bleeding (eg, petechiae, bruises, epistaxis, hematuria, menorrhagia, gastrointestinal bleeding) performed by the Investigator.

f Vital signs (assessment after 5 min in supine position): temperature (oral or tympanic), respiratory rate, pulse and blood pressure.

g To be performed after 5 min in supine position. As of Day 4, ECG to be performed as needed (as judged by the Investigator). ECG reading will be performed locally by the Investigator.

h ECG will be performed daily during the Days 1, 2, 3, and 4 only. As of Day 4, ECG to be performed as needed (as judged by the Investigator). The interpretation of the ECG will be done locally by the Investigator.

i Clinical laboratory analyses will include hematology, coagulation parameters and clinical chemistry (Section 10.2). These must be sent to the central laboratory at Day 1 (Baseline) and all other timepoints indicated in subsequent tables.

j Samples for platelet count will be assessed by a local and/or central laboratory. If local platelet count was assessed at Screening within 3 hours of Baseline (D1) visit, the Baseline local platelet sample does not need to be sent (Baseline central platelet sample still needs to be sent). See sampling flow chart (Section 1.3.4) for details regarding timing of platelet counts. All platelet counts should be done locally during the hospitalization. In addition, baseline, 24-hour, 48-hour, 60-hour, and subsequent daily platelet count samples during the hospitalization will be sent to central laboratory.

k Baseline platelet count is included in the hematology test of Clinical laboratory analyses (Section 10.2).

l Blood smear will be assessed locally. If local blood smear was assessed at Screening within 3 hours of Baseline (Day 1) visit, the baseline local blood smear does not need to be sent.

[redacted]

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

o First dose of the study intervention will be administered IV. A second dose is to be administered SC 4 to 6 hours after the IV dose on Day 1 followed by daily SC dose administration. A time window of ± 1 hour is allowed for the daily SC study intervention administrations. Exception to this regimen: If a participant has received and tolerated a single dose of marketed caplacizumab intravenously (IV) for the presenting episode of iTTP within 4 hours prior to enrollment, the IV dose of study intervention at 0H will be skipped and the subcutaneous dose of caplacizumab due at 4-6H relative to the pre-study dose will be the first dose of study intervention. All subsequent doses will continue to follow the schedule as outlined in Section 1.3.4 below. Please see Section 1.3.4 below for details.

p For participants for whom TPE needs to be started only: TPE with plasma (eg, fresh frozen plasma, solvent detergent/viral-inactivated plasma, cryosupernatant) at 1 to 1.5 × estimated plasma volume daily as of enrollment. See details in Section 4.1.

q Recommend starting anti-CD20 antibody therapy (rituximab or biosimilar) once iTTP diagnosis is confirmed (ADAMTS13 level <10%) and is required if ADAMTS13 level remains <10%, 1 week after platelet count normalization or stop of TPE (if TPE was started).

[redacted]

s [redacted]

[redacted]

1.3.3 Schedule of activities: Treatment and follow-up period (may include in-hospital & out-patient visits)

Study Period Study Visit[a]	Treatment Period (maximum 12 weeks) Weekly visit[s] (± 3 days) Starting on Day 8	Early Treatment Discontinuation Visit (± 3 days after last dose intake)	Follow-up Period[u]				
			FU Visit 7 days after last dosing (± 1 day)	Additional[t] FU Visit 14 days after last dosing (± 1 day)	Additional[t] FU Visit 21 days after last dosing (± 1 day)	FU visit 28 days after last dosing (± 1 day)	FU visit (EOS) 12 weeks after last dosing (± 3 days)
Study treatment administration							
IMP administration (daily)[b]	x						
Therapeutic plasma exchange (if needed)[c]	x						
Corticosteroids	x						
Anti-CD20 antibody therapy[d]	x						
eDiary (IMP administration info)[e]	x	x					
Safety and laboratory assessments							
Neurologic assessments[f]	x	x				x	x
GCS	x	x					x
Clinically significant TTP event	x	x	x	x	x	x	x
Bleeding assessment[g]	x	x	x	x	x	x	x
Physical examination	x	x	x	x	x	x	x
Vital signs[h]	x	x	x	x	x	x	x
12-lead ECG[i]	x	x				x	x
Adverse events	---------->						
Concomitant medication	---------->						
Clinical laboratory analyses[j]	x	x				x	x
Platelet count[k]	x	x	x	x	x	x	x

Study Period Study Visit[a]	Treatment Period (maximum 12 weeks) Weekly visit[s] (± 3 days) Starting on Day 8	Early Treatment Discontinuation Visit (± 3 days after last dose intake)	Follow-up Period[u]				
			FU Visit 7 days after last dosing (± 1 day)	Additional[t] FU Visit 14 days after last dosing (± 1 day)	Additional[t] FU Visit 21 days after last dosing (± 1 day)	FU visit 28 days after last dosing (± 1 day)	FU visit (EOS) 12 weeks after last dosing (± 3 days)
[redacted]							

Abbreviations: ADA = anti-drug antibody; ADAMTS13 = a disintegrin-like and metalloprotease with thrombospondin repeats 13; CRF = case report form; cTnI = cardiac troponin I; ECG = electrocardiogram; EOS = end of study; EQ-5D-5L = 5-level EuroQol 5-dimensional questionnaire; FU = follow-up; FVIII = Coagulation factor VIII; FVIII:C = FVIII clotting activity; GCS = Glasgow Coma Scale; HCRU = Health care resource utilization; IMP = investigational medicinal product; IV = intravenous; LDH = lactate dehydrogenase; PD = pharmacodynamics; PK = pharmacokinetics; PRO = patient reported outcome; PQAT = Patient's Qualitative Assessment of Treatment;
RICO = ristocetin cofactor activity; SF-12 = short form 12-item survey ; SC = subcutaneous; TPE = therapeutic plasma exchange; TTP = thrombotic thrombocytopenic purpura; vWF = von Willebrand Factor.

a The following guidance with regard to timing of assessments planned at a single visit should be followed: 1) ECG and vital signs have to be assessed prior to blood sampling, and 2) assessments will be done prior to IMP administration and prior to start of TPE if receiving TPE, and 3) SC study intervention will be dosed after completion of TPE treatment, if receiving TPE.

b Study intervention will be administered daily SC. A time window of ± 1 hour is allowed for the daily SC IMP administrations.

c For participants for whom TPE needs to be started only: TPE with plasma (eg, fresh frozen plasma, solvent detergent/viral-inactivated plasma, cryosupernatant) at 1 to 1.5 × estimated plasma volume daily as of enrollment. See details in Section 4.1.

d Recommend starting anti-CD20 antibody therapy (rituximab or biosimilar) once iTTP diagnosis is confirmed (ADAMTS13 level <10%) and is required if ADAMTS13 level remains <10%, 1 week after platelet count normalization or stop of TPE (if TPE was started).

e The diary (IMP administration info) will need to be completed starting the day after hospital discharge. Paper diary can be used in place of eDiary in the event of an emergency when the eDiary is not available.
f Neurological assessments will include coma, stupor, seizures, disorientation/confusion, hemiparesis/hemiplegia, focal deficit, agitation, and dysarthria.
g Bleeding assessment will be a clinical assessment of signs and symptoms of bleeding (eg, petechiae, bruises, epistaxis, hematuria, menorrhagia, gastrointestinal bleeding) performed by the Investigator.
h Vital signs (assessment after 5 min in supine position): including temperature (oral or tympanic), respiratory rate, pulse and blood pressure.
i To be performed after 5 min in supine position.
j Clinical laboratory analyses will include hematology, coagulation parameters and clinical chemistry (Section 10.2).
k Samples for platelet count will be assessed by a central and local laboratory.
l Organ damage markers will include LDH, cTnI, creatinine, and will be assessed by a central and local laboratory. If cTnI is not available locally, cTnT high sensitivity cTnI or high sensitivity cTnT can be assessed locally. However, in these cases cTnI should still be sent centrally.
m In case of a severe and/or serious hypersensitivity reaction, an additional blood sample to characterize the reaction will be collected as soon as possible after the start of the event.
[redacted]
o To be performed on Week 2 (Day 8), Week 6 (Day 36), and Week 11 (Day 71) within the Treatment Period (when applicable).
p To be performed at the end of treatment only.
q [redacted]
s All assessments to be done on Weekly Visit include assessments done on daily basis plus extra weekly assessments.
t This visit will occur only for those participants who do not have ADAMTS13 levels of ≥50% at the time of caplacizumab discontinuation.
u If early discontinuation during FU Period, all assessments scheduled for EOS visit should be performed.
[redacted]

1.3.4 Sampling flow chart for Days 1 to 3

Day	Day 1					Day 2[b]			Day 3[b]	
Time (hour/minute)[a]	**0 H**	**3 H**	**4-6 H**	**12 H**	**18 H (±3 H)**	**24 H (±2 H)**	**30 H (±2 H)**	**36 H (±2 H)**	**48 H (±3 H)**	**60 H (± 3H)**
Study treatment administration										
Caplacizumab[d]	x[c]		x			x			x	
Therapeutic plasma exchange (if needed)[e]						x			x	
Safety and laboratory assessments										
Clinical laboratory analyses[f]	x[g]									
Platelet count[i]	x[g]	x	x[g]	x	(x)[i]	x[g]	x	x	x[g]	x
Blood smear[k]	x[g]									
LDH[l]	x[g]	x	x[g]	x	(x)[i]	x[g]	x	x	x[g]	x
[m]	[g]					[g]			[g]	x
[redacted]										

[redacted];GCS = Glasgow Coma Scale; IMP = investigational medicinal product; IV = intravenous; LDH = lactate dehydrogenase; PD = pharmacodynamics; PK = pharmacokinetics; RICO = ristocetin cofactor activity; SC = subcutaneous; TPE = therapeutic plasma exchange; TTP = thrombotic thrombocytopenic purpura; vWF = von Willebrand Factor.

a Time (hour/minute) is expressed in reference to the first administration of IMP (T0H). In cases in which the participant has received and tolerated a dose of marketed caplacizumab for the presenting episode of iTTP within 4 hours prior to ICF signing, see footnote [c] below for interpretation of the time.

b If TPE starts, blood draws during the TPE should be done only if possible.

c If a participant has received and tolerated a dose of marketed caplacizumab IV for the presenting episode of iTTP within 4 hours prior to enrollment, the specific time of this dose should be documented, the IV dose of study intervention at 0H will be skipped and the subcutaneous dose of caplacizumab due at 4-6H after the pre-study dose, will be the first dose of study intervention. In these cases, all subsequent administrations of study intervention will continue to follow this schedule. The laboratory sampling schedule should remain unchanged (the time [hour/minute] for lab sampling is then expressed in reference to the time of enrollment).

d First dose of the study intervention is to be administered IV. A second dose is to be administered SC 4 to 6 hours after the IV dose on Day 1 followed by daily SC dose administration. A time window of ± 1 hour is allowed for the daily SC study intervention administrations. An exception to this is detailed in footnote *a*.

e For participants for whom TPE needs to be started only: TPE with plasma (eg, fresh frozen plasma, solvent detergent/viral-inactivated plasma, cryosupernatant) at 1 to 1.5 × estimated plasma volume daily as of enrollment. See details in Section 4.1.

f Clinical laboratory analyses included hematology, coagulation parameters and clinical chemistry (Section 10.2).

g Pre-caplacizumab dose.

h Sample should be drawn before IMP administration and as close as possible to the IMP administration.

i Optional assessments.

j Baseline platelet count is included in the Clinical laboratory analyses (Section 10.2). Baseline samples for platelet count will be assessed by a local laboratory. All platelet counts should be done locally during the hospitalization. In addition, baseline, 24-hour, 48-hour, 60-hour, and subsequent daily platelet count samples during the hospitalization will be sent to central laboratory.

k Blood smear will be assessed locally.

l All LDH samples should be done locally during the hospitalization. In addition, baseline, 24-hour, 48-hour, 60-hour and subsequent daily LDH samples during the hospitalization will be sent to central laboratory.

m All cTnI and creatinine samples should be done locally during the hospitalization. If cTnI is not available, cTnT or high sensitivity cTnT can be assessed locally. In addition, baseline, 24-hour, 48-hour, 60-hour, and subsequent daily cTnI and creatinine samples during the hospitalization will be sent to a central laboratory.

2 INTRODUCTION

Caplacizumab is a Nanobody® compound (NANOBODY® is a registered trademark of Sanofi or an affiliate) developed for the treatment of immune-mediated thrombotic thrombocytopenic purpura (iTTP), also known as acquired thrombotic thrombocytopenic purpura (aTTP), a life-threatening thrombotic microangiopathy manifested by formation of microthrombi in the microvasculature and consequent organ ischemia, hemolytic anemia, and severe thrombocytopenia. It is caused by inhibitory autoantibodies to von Willebrand factor (vWF) cleaving enzyme ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif13, which results in a severe deficiency in the activity level of the enzyme.

Nanobodies are therapeutic proteins derived from the smallest functional fragments of heavy chain-only antibodies, which occur naturally in the Camelidae family (1). Caplacizumab consists of two identical humanized building blocks (PMP12A2hum1), linked by a 3-alanine linker and binds to the A1 domain of vWF and inhibits the interaction between vWF and platelets (5).

Caplacizumab is approved for the treatment of patients with aTTP (also known as iTTP), in conjunction with therapeutic plasma exchange (TPE) and immunosuppressive therapy (IST) at the following labeled dose(s) of 10 mg approved by the European Medicines Agency (EMA) and of 11 mg approved by the US FDA and Health Canada. Despite the difference in labelled doses, the formulations approved in both regions are identical and yield the same average dose of 10 mg.

2.1 STUDY RATIONALE

Caplacizumab is currently indicated for the treatment of patients with aTTP (also known as iTTP), in combination with TPE and IST. Although TPE has been considered a mainstay of iTTP treatment for several decades, it is a burdensome and invasive procedure for patients, and is associated with significant complications, and a substantial number of patients remains at risk for morbidity and mortality when treated with TPE and immunosuppression alone. Based on pathophysiology of iTTP and mechanism of action of caplacizumab, it is hypothesized that caplacizumab and immunosuppression without initial TPE may be safe and effective as first-line therapy for iTTP. This concept is supported by pre-clinical data (1) as well as emerging real-world clinical evidence (2). Hence, the Sponsor is proposing an open-label, single-arm study to support the hypothesis that caplacizumab and IST can be effectively and safely administered to treat either first or recurrent iTTP episode in adults without first-line TPE, which would be added only if clinically indicated. A successful study will establish a new treatment paradigm and a new standard of care for treatment of iTTP for the use of caplacizumab and immunosuppression without first-line TPE.

2.2 BACKGROUND

Immune-mediated thrombotic thrombocytopenic purpura (also known as aTTP) is a life-threatening, thrombotic microangiopathy characterized by severe thrombocytopenia, microangiopathic hemolytic anemia, and organ ischemia. It is an ultra-orphan disease with an annual incidence reported to be about 3 cases per million people in the US (6, 7).

It is caused by inhibitory autoantibodies to vWF-cleaving enzyme ADAMTS13 that result in a severe deficiency in the activity level of the enzyme. Severe deficiency (<10%) of ADAMTS13 enzyme activity has been recognized as a biomarker specific for iTTP and is used in the acute and long-term management of patients with iTTP (8).

Von Willebrand factor, a key protein in hemostasis, plays a pivotal role in the recruitment of platelets to sites of vascular injury. More than 90% of circulating vWF is expressed by endothelial cells and secreted into the systemic circulation as ultra-large vWF (ULvWF) multimers. Under high shear stress conditions such as in arterioles and capillaries, the platelet-binding A1 domain of the ULvWF multimers interact spontaneously with the glycoprotein Ib-IX-V receptor on platelets. In healthy individuals, ULvWF multimers are immediately cleaved into smaller, regular-sized multimers by the vWF-cleaving protease ADAMTS13. This prevents ULvWF interaction with platelets and limits microthrombus formation. When there is severe ADAMTS13 deficiency, ULvWF released from the endothelium are not cleaved appropriately, leading to vWF-dependent platelet aggregation eventually resulting in microvascular thrombosis (9). The consumption of platelets in these microthrombi results in thrombocytopenia, one of the clinical feature of iTTP, and may present with muco-cutaneous bleeding symptoms such as epistaxis, bruising, petechiae, hematuria, and gastrointestinal bleeding (10, 11).

Prior to the availability of caplacizumab, episodes of iTTP were associated with an acute mortality of 10–20% and thromboembolic morbidities such as myocardial infarction and cerebrovascular accident. In addition, tissue ischemia caused by microvascular thrombosis may result in multiorgan dysfunction including renal dysfunction. Most patients have very high levels of lactate dehydrogenase (LDH) as a result of the combination of hemolysis and tissue ischemia. Elevations of serum troponin I and troponin T are common (12, 13).

The current standard of care for iTTP consist of a combination of TPE, IST and anti-vWF therapy (caplacizumab) (4, 14). These treatments focus on the three major pathophysiological mechanisms in iTTP:

1. Therapeutic plasma exchange (TPE):

   TPE, a procedure in which blood of the patient is passed through a medical device which separates out plasma from other components of blood and the patient's plasma is removed and replaced with a replacement solution such as colloid solution (eg, albumin and/or plasma) or a combination of crystalloid/colloid solution (15). Therapeutic plasma exchange replenishes the ADAMTS13 enzyme and removes anti-ADAMTS13 antibodies, and ULvWF multimers gradually from the circulation.

   TPE is administered daily for the time needed to restore platelet counts to normal levels, which may take several days to weeks. Although the introduction of TPE treatment has substantially reduced mortality from around 90% to lower than 20%, in spite of greater

understanding of disease pathogenesis and the use of newer immunosuppressants, the mortality rate has not been further decreased until the availability of caplacizumab (12, 16, 17, 15, 18, 19, 20).

TPE is frequently associated with procedure and plasma-related complications. Reducing the duration of TPE, or eliminating TPE altogether, when possible, would therefore reduce the risk of patients experiencing these complications.

Complications of TPE

Although the introduction of TPE treatment has substantially reduced overall iTTP mortality from around 90% to lower than 20%, this therapeutic approach carries substantial morbidity and mortality risk in critically ill iTTP patients. Therapeutic plasma exchange related complications include procedural complications such as invasive catheter placement and associated AEs such as bleeding, thrombosis, infections, pneumothorax and plasma-related complications such as allergic reactions including anaphylaxis and serum sickness. Allergic reactions are more frequent due to large volumes of plasma required for the procedure. Fibrinogen levels may decrease after serial TPE procedures with cryoprecipitate depleted plasma as replacement (15).

Howard et al. reported 73 major complications related to TPE in 57 of 206 (28%) consecutive patients treated for clinically suspected TTP- hemolytic uremic syndrome (HUS) over 9 years. Five of 206 (2.4%) patients have died due to catheter-related complications (pulmonary hemorrhage, pneumothorax and systemic infection). Non-fatal catheter-related complications included systemic infections (documented bacteremia, suspected bacteremia, fungemia), thrombosis (catheter obstruction and venous obstruction requiring systemic anticoagulation therapy), pulmonary hemorrhage, retro peritoneal hemorrhage, pericardial tamponade and pneumothorax. Plasma related complications (all non-fatal) included hypotension requiring dopamine, anaphylaxis with cardiac arrest, hypoxia and vomiting (21).

Benhamou et al. reviewed data on all iTTP patients of the French reference Center for thrombotic microangiopathies registry prospectively enrolled through a 10-year period, between 2008 and 2018. They reported 48 venous thrombosis episodes in 314 patients with 378 iTTP episodes (12.7%) in those who received prolonged treatment with TPE. Venous thrombo-embolisms included catheter related thrombosis, deep venous thrombosis of extremities, pulmonary embolism, splanchnic vein thrombosis (22).

2. Immunosuppressive therapy:

Immunosuppressive therapy (corticosteroids and rituximab) addresses the formation of the neutralizing ADAMTS13 autoantibodies, ultimately resulting in a gradual restoration of ADAMTS13 activity over a period of days to weeks. Once ADAMTS13 activity levels have stably normalized, normal processing of ULvWF will occur and the underlying autoimmune component of the disease is considered resolved.

Importantly, neither TPE nor immunosuppression directly address the pathophysiological platelet aggregation that leads to the formation of the microthrombi, and, in cases of inadequate response and unresolved disease, patients may experience exacerbations after stopping TPE. Also, as neither TPE nor IST have an immediate onset, patients remain at

risk for microthrombotic damage and ensuing clinical consequences during the time needed for these treatments to take effect.

3. Anti-vWF Therapy (Caplacizumab)

   Caplacizumab (Cablivi®) is a bivalent Nanobody compound of approximately 28 kDa in size. Caplacizumab binds to the A1 domain of vWF and specifically inhibits the interaction between vWF and platelets, thereby immediately preventing the platelet adhesion and microthrombi formation leading to the clinical consequences of the disease. In this way it prevents the patient from further microthrombotic damage during the time needed for TPE and immunosuppression to take effect (5).

A detailed description of the chemistry, pharmacology, efficacy, and safety of caplacizumab is provided in the Investigator's Brochure.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of caplacizumab may be found in the Investigator's brochure, participant information leaflet, package insert or summary of product characteristics.

2.3.1 Risk assessment

Safety data for caplacizumab have been accrued in 3 distinct populations in the development program, which was comprised of healthy adult subjects, adult subjects experiencing an episode of iTTP, and adult subjects undergoing percutaneous coronary intervention (PCI).

The important identified and potential risks of treatment with caplacizumab are major bleeding and serious hypersensitivity reactions, respectively (Table 1).

The overall safety profile observed in healthy subjects treated with caplacizumab was characterized mainly by mucocutaneous bleeding treatment emergent adverse events (TEAEs). There were no study drug-related SAEs and no subject discontinued study drug due to TEAEs. In subjects undergoing PCI, the most frequently reported SAEs were cardiovascular in nature and this indication was not subsequently pursued.

Similar to the findings in healthy subjects, the principal risk of treatment of iTTP with caplacizumab is bleeding. This is consistent with the mechanism of action of caplacizumab given its inhibitory effect on vWF-mediated platelet aggregation and mucocutaneous bleeding events are similar to those observed in Von Willebrand disease.

The safety of caplacizumab in adults experiencing an episode of iTTP was established in 2 placebo-controlled, double-blind clinical trials (Phase 2 TITAN and Phase 3 HERCULES studies). A total of 106 subjects received at least 1 dose of study drug in pooled analysis of the blinded study periods. The most common bleeding TEAEs in iTTP subjects treated with caplacizumab were gingival bleeding (n=17, 16%) and epistaxis (n=31, 29%). Most of these events were mild in intensity and resolved spontaneously.

Serious bleeding events were reported in both the caplacizumab and the placebo groups, reflecting the life-threatening nature of an episode of iTTP. Among 106 patients treated with caplacizumab during the TITAN and HERCULES studies, serious bleeding adverse reactions were reported in ≥2% patients and included epistaxis (4%) and subarachnoid hemorrhage (2%).

All studies revealed no safety issues that would preclude the use of caplacizumab as treatment for iTTP. There has been no association between the presence of anti-drug antibodies (ADAs) and safety findings and the data from the post-HERCULES open-label study support the long-term safety of caplacizumab treatment, as well as the safety of its repeat use in patients with iTTP.

Cases of major bleeding, including life-threatening and fatal bleeding, have been reported in patients receiving caplacizumab in the post-marketing setting, mainly in those using concomitant anti-platelet agents or anticoagulants. Bleeding was previously considered an "important identified risk" due to its frequency, nature and relation with the mechanism of action of caplacizumab. As a result of post-marketing experience, the important identified risk of "Bleeding" was updated to "Major bleeding" in the Core RMP V2.0 dated 22 July 2021. Caplacizumab should be used with caution in patients with underlying conditions that may predispose them to a higher risk of bleeding.

Serious hypersensitivity reaction remains a potential risk as with other biological products and known class effects of monoclonal antibodies. No anaphylactic reactions were reported in the TITAN and HERCULES studies.

Risks associated with the COVID-19 pandemic and use of caplacizumab are currently unknown.

Table 1 - Risk assessments

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Study intervention(s) - Caplacizumab		
Major Bleeding (Important Identified Risk)	Bleeding events were the most commonly reported AEs in clinical trials in both treatment groups and were reported with a higher frequency in caplacizumab-treated patients compared to placebo-treated patients (Phase 2 study ALX0681-2.1/10 [TITAN] and Phase 3 study ALX0681-C301 [HERCULES]). These were generally events of mucocutaneous bleeding (eg, epistaxis, gingival bleeding), in the respiratory, gastrointestinal, and urogenital tracts. None of these events were fatal or life-threatening. The time to onset of these events from the administration of caplacizumab does not seem to follow a clear pattern. Events of major bleeding, including life-threatening and fatal bleeding, have been reported in the post-marketing setting (PBRER n°4, DLP 30-Aug-2021) and further support that the risk of bleeding is increased with concomitant use of drugs affecting hemostasis and coagulation. Product labeling has been updated accordingly.	Participants will receive a Patient Alert Card. Primary objectives of the Patient Alert Card are to inform/alert treating physicians (especially in an emergency situation) about: • Their patient having iTTP and being treated with caplacizumab; • The associated risk of bleeding; • The need to take into consideration the above for the medical treatment and monitoring of the patient; • What to do in case of emergency Participants will be given the card on study enrollment. Participants at high risk for bleeding events, including those with inherited or acquired coagulation disorders or those receiving chronic anticoagulation therapy that cannot be suspended will be excluded from the study (Section 5.2, Exclusion Criteria).

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Serious hypersensitivity reactions (Important Potential Risk)	No anaphylactic or other clinically important immune reactions were reported as related to caplacizumab in the clinical trials used to support the MAA (Phase 2 study ALX-0681-2.1/10 [TITAN] and Phase 3 study ALX0681-C301 [HERCULES]). However, as with other biological medicinal products, severe immune mediated reactions including clinically important hypersensitivity reactions remain a potential risk.	First bolus injection and initial SC injections will occur in a controlled hospital environment where any hypersensitivity reaction can be appropriately and quickly managed. Participants will be educated as to the risks of hypersensitivity reactions to caplacizumab. Participants will be educated to the risks of hypersensitivity reactions for their concomitant therapies (eg, rituximab, and plasma exchange, if required), thus mitigating the risk of negative clinical outcomes of hypersensitivity reactions during the period of out-of-hospital administration. In addition, caplacizumab is contraindicated in participants with hypersensitivity to the active substance or any of the excipients.
Other		
COVID-19 pandemic	Ongoing global pandemic of SARS-CoV-2.	The trial will be conducted in compliance with COVID-19 safety restrictions by local authorities.

Risks are determined as important and included in core RMP.

Adapted from core RMP version 2.0 (DLP 22 Jul 2021) and PBRER version 4.0 (DLP 30 Aug 2021) with exception of COVID risk and pre-existing bleeding risk.

2.3.2 Benefit assessment

Significant progress has been made in the areas of diagnosis and treatment of iTTP over the last decade. The current standard of care for those with an iTTP episode includes caplacizumab, TPE and IST. Although TPE has been considered a mainstay of iTTP treatment for several decades, this therapeutic approach carries substantial morbidity and mortality risk in these critically ill patients as described earlier (Section 2.2). This study will evaluate the efficacy and safety of caplacizumab and immunosuppression without first-line TPE. A successful study may lead to drastic changes in the way iTTP patients are managed and establish a new treatment paradigm and a new standard of care for treatment of iTTP. Furthermore, this study will provide additional evidence on the effectiveness of first-line use of caplacizumab for all iTTP patients (1st episode and relapse) and establish a data driven treatment duration for caplacizumab therapy using the iTTP specific biomarker ADAMTS13 activity level.

The data from the Phase 3 HERCULES study showed that treatment with caplacizumab resulted in significant reduction in morbidity and mortality associated with iTTP. Caplacizumab therapy was associated with clinically meaningful and statistically significant reductions in the proportion of subjects with TTP-related death, a recurrence of TTP, or at least one TE major thromboembolic event; the proportion of subjects who died from TTP during the study drug treatment period and the proportion of subjects with a recurrence of TTP during treatment and overall were also reduced (23).

Recently, real-world evidence data was published from a prospective study in France in which 90 patients treated with a triplet regimen (TPE, IST with corticosteroids and rituximab, and caplacizumab) were compared to a historical cohort of 180 iTTP patients managed with the standard regimen (TPE and corticosteroids, with rituximab as salvage therapy) (24). The primary outcome was a composite of refractoriness and death within 30 days since diagnosis. The composite primary outcome was met for 12.2% of historical patients versus only 2.2% of patients in the triplet regimen met the composite primary outcome of refractoriness and death within 30 days since diagnosis (p=0.01%). The study also confirmed the effect of caplacizumab on the prevention of exacerbation: a significant decrease in exacerbations was noted in the triplet regimen cohort compared to the historical cohort (3.4% vs. 44%, p<0.01). Patients in the triplet cohort showed durable platelet recovery 1.8 times faster than historical patients (95% confidence interval [CI], 1.41-2.36, p <0.01), and required fewer TPE sessions (5 days vs. 10 days, p <0.01). After a median follow-up of 127 days (range: 47-200 days), only one clinical relapse (1.1%) occurred in the triplet regimen cohort (patient with ADAMTS13 <10% at time of stopping caplacizumab) suggesting that it is possible to decrease disease recurrence when caplacizumab is given until the underlying disease is controlled.

In addition to the benefits provided by caplacizumab with immunosuppression and TPE regimen as above, the proposed caplacizumab regimen is expected to provide additional direct benefits to iTTP patients. As the regimen does not include first-line TPE, there will be decreased treatment-related burden with reduction in TPE-related complications including procedural complications (invasive catheter placement and associated AEs such as bleeding, thrombosis, infections, pneumothorax) and plasma related complications such as allergic reactions including anaphylaxis, serum sickness, hypotension requiring dopamine). In addition, this caplacizumab treatment regimen will decrease the health care related financial impact on the patient and improve quality-of-life due to decreased burden of care (relative to caplacizumab with first-line TPE) and increase patient satisfaction with treatment.

This regimen will also result in a reduction in iTTP-associated healthcare resource utilization (HCRU).

There is limited availability of data on efficacy of caplacizumab without TPE as first-line therapy. There are published case reports for 11 acute episodes in 10 patients (2, 25, 26, 27, 28), treated with caplacizumab and immunosuppression without requiring TPE. All had platelet count recovery within 5 days. In the published case series by Volker et al, the platelet counts normalized (>150 × 10^9/L) after median 84 hours (3.5 days) with a range of 48 hours to 96 hours (2- 4 days) (2). In the Phase 3 HERCULES study, the median time to normalization of the platelet count was shorter with caplacizumab than with placebo (2.69 days [95% CI,1.89 to 2.83] vs. 2.88 days [95% CI, 2.68 to 3.56], P = 0.01). However, it is important to note that all HERCULES study patients had a TPE prior to study entry, and this may have shortened the time to platelet response. In the Phase 2 TITAN study, the median time to confirmed platelet response was 2.97 days (95% CI: 2.74, 3.65) in the caplacizumab group and 4.79 days (95% CI: 3.51, 5.94) in the placebo group. Majority of the patients in the TITAN study did not receive a prior TPE.

In summary, treatment with caplacizumab and immunosuppression without first-line TPE may reduce the morbidity and mortality associated with TPE-related complications. It will improve

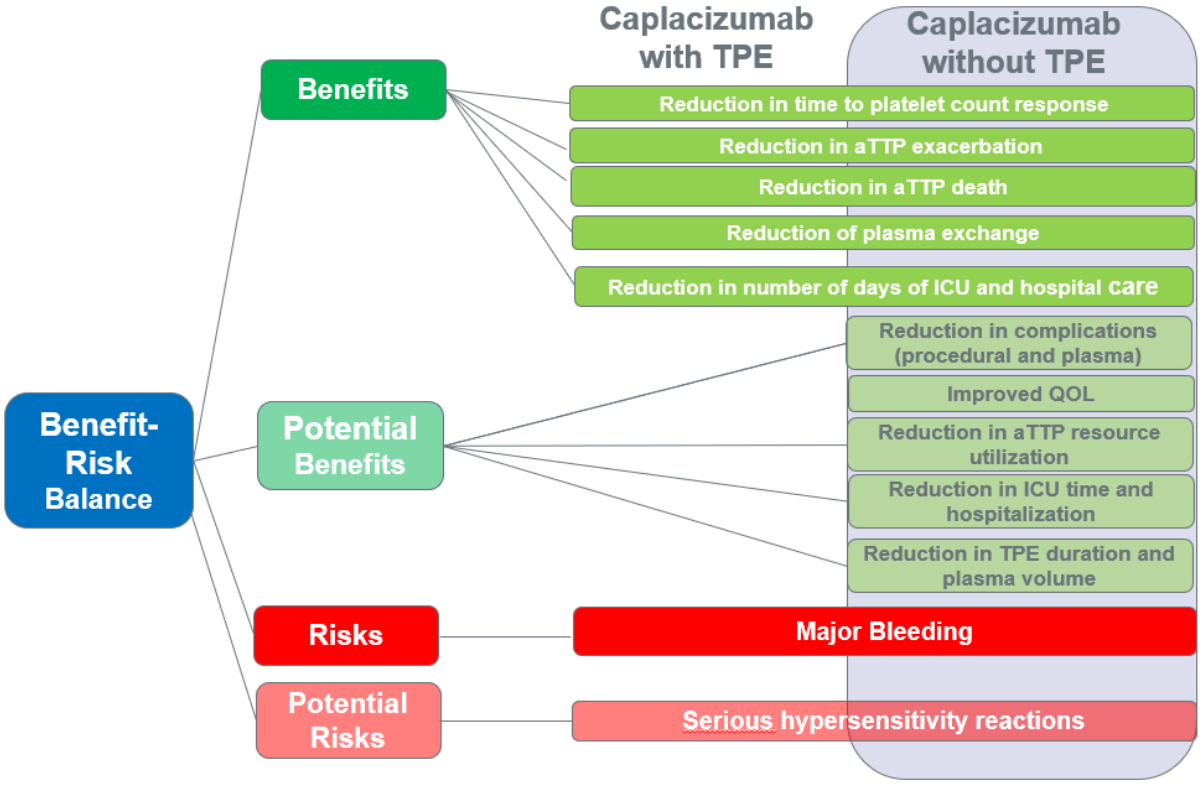
patients' quality of life while reducing the overall iTTP related health care resource utilization and costs (ie, the number of days in intensive care unit (ICU), length of hospitalization and number of days and volume of plasma needed if requires TPE). Although, there is limited availability of data on efficacy of caplacizumab/Cablivi® without TPE as first-line therapy, there are published case reports for 11 acute episodes in 10 patients, treated with caplacizumab and IST without TPE. All patients showed platelet count recovery within 5 days and no new safety findings were reported.

2.3.3 Overall benefit/risk conclusion

The clinical development program for caplacizumab is supported by the available nonclinical and clinical data with benefits in patients with iTTP. The benefit-risk profile of caplacizumab and IST without first-line TPE is positive for investigational use in adults with iTTP under the current recommended conditions of use including risk minimization measures.

A value tree providing a concise, visual representation of the key benefits and key risks considered in the overall benefit-risk assessment of caplacizumab both with and without TPE is presented below in Figure 2.

Figure 2 - Value tree for Benefit-Risk Assessment of caplacizumab with/without first-line TPE



Abbreviations: TPE: therapeutic plasma exchange; QOL: quality of life; TTP: thrombotic thrombocytopenic purpura; ICU: intensive care unit.
Risks are determined as important and included in core RMP (Version 2.0, DLP 22-Jul-2021).

Based on all available data, the Sponsor considers that benefit-risk assessment for caplacizumab without first-line TPE is favorable for further investigation of this new study treatment regimen.

3 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of caplacizumab in combination with immunosuppressive therapy (IST) without therapeutic plasma exchange (TPE) in adults with immune mediated thrombotic thrombocytopenic purpura (iTTP)	• Proportion of participants achieving Remission without requiring TPE during the overall study period **Remission** is defined as sustained Clinical Response (sustained platelet count ≥150 × 10^9/L and lactate dehydrogenase [LDH] <1.5 × upper limit of normal [ULN] and no clinical evidence of new or progressive ischemic organ injury for at least 2 consecutive visits) with either (a) no TPE and no anti- von Willebrand factor (anti-vWF) therapy for ≥30 days (Clinical Remission), or (b) with attainment of a disintegrin and metalloproteinase with a thrombospondin type 1 motif13 (ADAMTS13) ≥50% (Complete ADAMTS13 remission), whichever occurs first.
Secondary	
• To evaluate the need for therapeutic plasma exchange in adult participants with an episode of iTTP treated with caplacizumab and IST.	• Proportion of participants achieving Remission during the overall study period • Proportion of participants who require TPE during the on-treatment period
• To evaluate the safety of caplacizumab in combination with IST without first-line TPE in adults with iTTP	• The occurrence of adverse events (AEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) during the treatment-emergent (TE) period
• To evaluate the effect of treatment with caplacizumab and IST without first-line TPE on clinical response	• Proportion of participants achieving Clinical Response during on-treatment period and during the overall study period **Clinical Response** is defined as sustained platelet count ≥150 × 10^9/L and LDH <1.5 × ULN and no clinical evidence of new or progressive ischemic organ injury for at least 2 consecutive visits.
• To evaluate the effect of treatment with caplacizumab and IST without first-line TPE on restoring platelet counts	• Time to platelet count response defined as time from start of treatment to initial platelet count ≥150 × 10^9/L that is sustained for ≥2 days
• To evaluate the effect of treatment with caplacizumab and IST without first-line TPE on refractory disease	• Proportion of participants refractory to therapy defined as lack of sustained platelet count increment (over 2 consecutive days) or platelet counts <50 × 10^9/L and persistently elevated LDH (>1.5 × ULN) despite 5 days of treatment during the on-treatment period
• To evaluate the effect of treatment with caplacizumab and IST without first-line TPE on clinically relevant iTTP-related events consisting of iTTP-related mortality	• Proportion of participants with TTP-related death during the on-treatment period and during the overall study period

Objectives	Endpoints
• To evaluate the effect of treatment with caplacizumab and IST without first-line TPE on clinically relevant iTTP-related events consisting of exacerbation of iTTP	• Proportion of participants with a clinical exacerbation of iTTP during the on-treatment period and during the overall study period **Clinical Exacerbation** is defined as after a Clinical Response and before a Clinical Remission, platelet count decreases to <150 × 10^9/L (with other causes of thrombocytopenia excluded), with or without clinical evidence of new or progressive ischemic organ injury, within 30 days of stopping TPE or anti-vWF therapy.
• To evaluate the effect of treatment with caplacizumab and IST without first-line TPE on clinically relevant iTTP-related events consisting of relapse of iTTP	• Proportion of participants with a clinical relapse of iTTP during the on-treatment period and during the overall study period **Clinical Relapse** is defined as after a Clinical Remission, platelet count decreases to <150 × 10^9/L (with other causes of thrombocytopenia ruled out), with or without clinical evidence of new ischemic organ injury. A Clinical Relapse must be confirmed by documentation of severe ADAMTS13 deficiency (<10%).
Other	
[redacted]	

Objectives	Endpoints
[redacted]	

3.1 APPROPRIATENESS OF MEASUREMENTS

Each of the safety and efficacy assessments chosen for use in this study are considered well established and relevant in iTTP. In addition, suitable steps have been built into each of these assessments to ensure their reliability and accuracy to minimize risks to participant safety.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a single-arm, open-label, Phase 3, multicenter study to evaluate the efficacy and safety of caplacizumab and IST without first-line TPE in adult patients with an acute episode of iTTP.

This study incorporates the revised consensus outcome definitions for iTTP published by the International Working Group for TTP that reflect current iTTP management (3). A Data Monitoring Committee will be appointed to monitor the safety and scientific integrity of this study.

Participants will be recruited from sites that are able to obtain baseline ADAMTS13 activity test results within 2 days (48 hours) and provide TPE services, overnight and during weekends if needed.

Adult participants will be enrolled based on a clinical diagnosis of iTTP (initial or recurrent). Those with thrombocytopenia (defined as platelet count $<100 \times 10^9$/L) and who have evidence of microangiopathic hemolytic anemia (eg, presence of schistocytes in peripheral blood smear) and relatively preserved renal function are considered to have a clinical diagnosis of iTTP. In addition, we will use the French TMA Score, a clinical scoring system that predicts severe ADAMTS13 deficiency (29) to further establish the clinical diagnosis. A French TMA score of 2 (platelet count $\leq 30 \times 10^9$/L and serum creatinine $\leq$2.27 mg/dL) is considered highly suggestive of iTTP. Those with a French score of 1 (either platelet count $\leq 30 \times 10^9$/L or serum creatinine $\leq$2.27 mg/dL) will be considered having probable iTTP.

After confirmation of eligibility to participate in the study, the enrolled participants will undergo baseline laboratory studies including ADAMTS13 activity level.

The initial treatment regimen consists of caplacizumab and IST (corticosteroids ± anti-CD20 antibody [rituximab or biosimilar]) without first-line TPE. Those participants with a clinical diagnosis of iTTP and a French score of 1 or 2, will be started on treatment with Caplacizumab and corticosteroids immediately pending the availability of baseline ADAMTS13 activity level from the local laboratory. It is important to note that the baseline ADAMTS13 activity results will be available within 48 hours. It is recommended that participants start anti-CD20 antibody therapy after confirmation of diagnosis of iTTP (<10% ADAMTS13 activity).

Study participants will not receive TPE as first-line therapy. However, participants may receive TPE if it is determined that there is lack of adequate response to treatment after first 24 hours or if there is any clinical deterioration at any time during the study, including during the first 24 hours (please see below for additional details). It is expected that the participant is hospitalized when the treatment is started, and the duration of initial hospitalization may vary based on clinical condition of the individual participant.

Caplacizumab treatment will be continued until sustained ADAMTS13 activity level of ≥50% at 2 consecutive visits after platelet count normalization (defined as $\geq 150 \times 10^9$/L × 2 consecutive values) or 12 weeks, whichever occurs first. Thus, the maximum treatment duration of caplacizumab will be 12 weeks for the presenting episode.

The post-treatment follow-up period will be 12 weeks. The anticipated study duration per participant without a recurrence while on therapy is maximum of approximately 24 weeks (ie, approximately 1 day for screening + maximum 12 weeks of treatment for the presenting episode + 12 weeks of follow-up).

Initial treatment regimen during hospitalization:

1. anti-vWF therapy: Caplacizumab

   Recommended dose: Caplacizumab 10 mg (11 mg in US and Canada; see Section 2) intravenous (IV) for a single dose followed by caplacizumab 10 mg (11 mg in US and Canada) subcutaneous (SC) 4-6 hours after the IV dose (Day 1) (exceptions to this are detailed in Section 1.3.4). This will be followed by caplacizumab 10 mg (11 mg in US and Canada) SC daily starting on Day 2 for a maximum treatment duration of 12 weeks.

   Note: The baseline ADAMTS13 activity level results from the local laboratory, available within 48 hours will be used to confirm the diagnosis of iTTP. It is expected that there will be minimal discrepancy between local and central laboratory ADAMTS13 activity levels. The central laboratory test results will be available only after 3-4 days.

   - If the baseline central laboratory ADAMTS13 activity is <10% of normal → continue caplacizumab and IST.
   - If the baseline central laboratory ADAMTS13 activity is between 10% - 20% of normal → use clinical judgment in deciding to continue or stop caplacizumab treatment after evaluation of the totality of signs and symptoms plus other laboratory data.
   - If the baseline central laboratory ADAMTS13 activity is >20% of normal → **Caplacizumab therapy should be discontinued,** and other diagnoses should be considered. Please see Section 7 of the protocol for additional details.

2. Immunosuppressive therapy:
   - Corticosteroid therapy: It is expected that all participants will receive corticosteroids. Recommended dose: Prednisone or Prednisolone 1.0-1.5 mg/kg/day, IV or oral, for 1 week and taper over 3 to 4 weeks based on institutional guidelines. The dose and duration of therapy may be adjusted as clinically indicated.
   - Anti-CD20 antibody therapy (rituximab or biosimilar): Recommend starting anti-CD20 antibody therapy at the beginning of the study, once iTTP diagnosis is confirmed (ADAMTS13 activity level <10%) and is required if ADAMTS13 activity level remains <10%, 1 week after platelet count normalization or stop of TPE (if TPE was started)

     Recommended dose:
     375 mg/m^2 IV infusion (as per instructions on package insert) × 3-4 doses once a week or as per institutional guidelines.

Note:

If there is inadequate response to the initial IST regimen (corticosteroids with or without anti-CD20 antibody therapy) and ADAMTS13 activity level remains <10% after 4 weeks of therapy, the Investigator may consider optimizing IST further (including adding anti-CD20 antibody if not done before) or consider alternative immunosuppressive therapies as per local standard of care.

Therapeutic Plasma Exchange (TPE):

After the first 24 hours of treatment (caplacizumab + IST) (or during the first 24 hours per the judgement of the investigator if there is any evidence of clinical deterioration, as explained below), TPE may be started under the conditions listed below. Initial response to therapy will be evaluated based on laboratory data obtained during the first 24-hours including those performed at the 24-hour timepoint. However, please note that the platelet response is expected within the first 6 to 12 hours based on previously published data (2).

Caplacizumab and IST will be continued after starting TPE.

TPE may be started:

- If there is no initial response to therapy defined as absence of increase from baseline in platelet counts (over at least 2 consecutive values) and absence of decrease from baseline in LDH (at least 2 consecutive values) after 24 hours of treatment.
- If there is persistent thrombocytopenia, defined as lack of a sustained platelet count increment or platelet counts of $<50 \times 10^9$/L and a persistently raised LDH level (>1.5 × upper limit of normal [ULN]) despite five days of treatment.
- If there is clinical evidence of new or progressive ischemic organ injury (worsening of presenting signs and symptoms or appearance of new signs and symptoms such as but not limited to neurologic manifestations [seizures, sudden onset numbness or weakness of the face, arm, or leg especially on one side of the body, mental status changes including confusion, trouble speaking, or understanding speech, sudden visual impairment, sudden difficulty walking, loss of balance or coordination, sudden severe headache with no known cause], cardiac manifestations such as chest pain with or without electrocardiogram (ECG) changes suggestive of myocardial ischemia, increasing troponin, renal manifestations such as worsening serum creatinine at any time after starting therapy, TPE may be started at Investigator discretion at any point during the study, including the first 24 hours and caplacizumab and IST continued.

If participant needs TPE:

Recommend TPE with plasma (eg, fresh frozen plasma, solvent detergent/viral-inactivated plasma, cryosupernatant) at 1 to 1.5 × estimated plasma volume. TPE should be performed daily according to standard site practice and continued at least for 2 days after the platelet count normalization ($\geq 150 \times 10^9$/L). Of note, TPE with 1 to 1.5 × estimated plasma volume may be spread over multiple sessions within 24 hours. Tapering of TPE after platelet count normalization, defined as reducing its frequency to less than once per day, is strongly discouraged and if considered, should be discussed with the Medical Monitor.

Treatment plan for continued therapy with caplacizumab and IST regardless of hospitalization status:

If there is response to initial therapy:

- The participant will continue caplacizumab 10 mg (11 mg in US and Canada) SC daily until sustained ADAMTS13 normalization (≥50%) at 2 consecutive visits after platelet count normalization defined as $\geq 150 \times 10^9$/L, or for 12 weeks, whichever occurs first. The maximum treatment duration of caplacizumab is 12 weeks for the presenting episode.

- Immunosuppressive therapy will be continued as described earlier. If there is inadequate response to the initial immunosuppressive regimen (corticosteroids with or without anti-CD20 antibody therapy) and the ADAMTS13 activity level is <10% after 4 weeks of therapy, the Investigator may consider optimizing immunosuppression further (including adding anti-CD20 antibody if not done before) or consider alternative immunosuppressive therapies as per local standard of care.
- Laboratory monitoring of platelets and LDH will be performed weekly during the out-patient treatment phase and at the 3 follow-up visits*.

  *Note: there will be two additional follow-up visits for participants who do not have ADAMTS13 activity levels of ≥50% at the time of caplacizumab discontinuation.
- ADAMTS13 activity levels will be obtained once a week starting on Day 8 of caplacizumab treatment. If the ADAMTS13 activity level is <10% after 4 weeks of therapy, consider optimizing immunosuppression further.

If participant requires TPE:

- The participant will continue caplacizumab 10 mg (11 mg in US and Canada) SC daily until sustained ADAMTS13 normalization (≥50%) at 2 consecutive visits after stop of daily TPE. During the time, the participant is receiving TPE, caplacizumab will be given after the TPE. The maximum treatment duration of caplacizumab is 12 weeks for the presenting episode.
- Immunosuppressive therapy will be continued as described earlier. If there is inadequate response to the initial immunosuppressive regimen (corticosteroids with or without anti-CD20 antibody therapy) and the ADAMTS13 activity level is <10% after 4 weeks of therapy, the Investigator may consider optimizing immunosuppression further (including adding anti-CD20 antibody if not done before) or consider alternative immunosuppressive therapies as per local standard of care.
- Laboratory monitoring of platelets and LDH will be performed weekly during the out-patient treatment phase and at the 3 follow-up visits*.

  *Note: there will be two additional follow-up visits for participants who do not have ADAMTS13 activity levels of ≥50% at the time of caplacizumab discontinuation.
- ADAMTS13 activity levels will be obtained once a week starting on Day 8 of caplacizumab treatment. If the ADAMTS13 activity level is <10% after 4 weeks of therapy, consider optimizing IST further.

Follow-up after treatment completion:

Participants will be followed up for a period of 12 weeks after completion of study treatment. During the follow-up period they will be evaluated in the out-patient setting at 7±1 days, 28±1 days and 12 weeks (±3 days) after the last dose of the IMP.

There will be two additional follow-up visits (14±1 days and 21±1 days after last caplacizumab dosing) for participants who do not have ADAMTS13 activity levels of ≥50% at the time of caplacizumab discontinuation.

A physical exam will be performed, and laboratory tests including platelet count and organ damage markers will be obtained during the visits.

Treatment of a first clinical recurrence (exacerbation or relapse):

Clinical Exacerbation is defined as after a Clinical Response and before a Clinical Remission, platelet count decreases to <150 × 10^9/L (with other causes of thrombocytopenia excluded), with or without clinical evidence of new or progressive ischemic organ injury, within 30 days of stopping TPE or anti-vWF therapy.

Clinical Relapse is defined as after a Clinical Remission, platelet count decreases to <150 × 10^9/L (with other causes of thrombocytopenia ruled out), with or without clinical evidence of new ischemic organ injury. A Clinical Relapse must be confirmed by documentation of severe ADAMTS13 deficiency (<10%).

In case of a first clinical recurrence (exacerbation or relapse) of the presenting TTP episode during the overall study period, it is up to the Investigators to adjust the ongoing treatment plan, which may include start or restart of TPE and adjustment of IST regimen and caplacizumab therapy. In case that caplacizumab treatment is maintained for a first clinical recurrence (exacerbation or relapse), the visit schedule will be the same as during the initial treatment period.

If a participant develops a second clinical recurrence (exacerbation or relapse) the participant will discontinue from the study (Section 7.1.1). At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Caplacizumab is a Nanobody compound developed for the treatment of iTTP, a life-threatening thrombotic microangiopathy. It binds to the A1 domain of vWF and specifically inhibits the interaction between vWF and platelets, thereby immediately preventing the platelet adhesion and microthrombi formation responsible for the clinical consequences of the disease. The mechanism of action and safety profile of caplacizumab are both well documented at this time. Results of the HERCULES study, a double-blind, placebo-controlled Phase 3 study demonstrated that those treated with caplacizumab had better clinical outcomes, including faster normalization of the platelet count, and a lower incidence of a composite of TTP-related death, recurrence of TTP, or a major thromboembolic event during the treatment period as well as a lower rate of recurrence of TTP during the trial than with placebo (23). In addition, published real-world evidence also demonstrate that caplacizumab with TPE and immunosuppression with corticosteroids and rituximab prevents unfavorable outcomes of the disease and substantially alleviates the burden of care in these patients (24). Current standard of care of iTTP includes caplacizumab, IST and TPE, but TPE is associated with many complications and increased morbidity (15, 21, 22). This open-label single-arm study is intended to establish efficacy of caplacizumab without first line TPE, while conferring a better safety profile by definition.

Based on the pathophysiology of iTTP and mechanism of action of caplacizumab, it is hypothesized that caplacizumab and IST without initial TPE, may be safe and effective as first line therapy for iTTP. This concept is supported by pre-clinical data as well as emerging real-world evidence (2, 25, 26). Another important consideration is the low incidence of iTTP, which has been reported to range from 3.1 to 6.0 cases per million (6, 7, 30). A fully powered 2-arm

study against a comparator, requiring a large sample size, would be challenging due to likely recruitment difficulties in this rare disease context. Therefore, a single-arm, open-label Phase 3, multicenter study to evaluate the efficacy and safety of caplacizumab and immunosuppression without first-line TPE in adults with an acute episode of iTTP will be conducted.

Adult participants with a clinical diagnosis of iTTP and a French TMA score of 1 or 2 will be enrolled. After confirmation of eligibility, participants will receive initial treatment consisting of caplacizumab and IST (corticosteroids ± anti-CD20 antibody [rituximab or biosimilar]) without first-line TPE. However, participants may receive TPE if it is determined that there is lack of adequate response to treatment after first 24 hours or if there is any clinical deterioration at any time during the study including during the first 24 hours (see Section 4.1 for details). All participants will receive open label caplacizumab daily until sustained ADAMTS13 activity normalization (≥50%) is achieved at 2 consecutive visits, after platelet count normalization. The maximum duration allowed for caplacizumab treatment is 12 weeks and the post-treatment follow-up period will be 12 weeks for the presenting episode.

This study incorporates the revised consensus outcome definitions for iTTP published by the International Working Group for TTP that reflect current iTTP management (3) The primary endpoint, and many of the secondary endpoints of this study, are aligned with the consensus report. The primary endpoint is the proportion of participants achieving remission without requiring TPE during the overall study period. Remission is defined as sustained Clinical Response with either (a) no TPE and no anti-VWF therapy for ≥30 days (Clinical Remission) or (b) with attainment of ADAMTS13 activity level ≥50% (Complete ADAMTS13 Remission), whichever occurs first. Remission is assessed starting from the clinical response (for participants not requiring TPE) or the end of TPE (for participants requiring TPE), until the end of study.

4.2.1 Participant input into design

Not applicable.

4.3 JUSTIFICATION FOR DOSE

The dose of 10 mg (11 mg per US/Canada label) was chosen based on a PK/PD model characterizing the relationship between drug exposure and pharmacodynamic effect. The adequacy of the dosing regimen was validated in aTTP patients in the Phase 2 ALX-0681-2.1/10 (TITAN) study and the Phase 3 ALX0681-C301 (HERCULES) study. The initial 10 mg IV bolus aimed to achieve immediate neutralization of vWF, subsequently maintained by the daily 10 mg SC dosing regimen, for a fast normalization of platelet counts.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all periods of the study including the last scheduled procedure shown in the Schedule of Activities (Section 1.3).

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the Schedule of Activities for the last participant in the trial.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be enrolled in the study only if all of the following criteria apply:

Age

I 01. Participant must be 18 to 80 years of age, inclusive, at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Participants with a clinical diagnosis of iTTP (initial or recurrent), which includes thrombocytopenia, microangiopathic hemolytic anemia (eg, presence of schistocytes in peripheral blood smear) and relatively preserved renal function. The iTTP diagnosis should be confirmed by ADAMTS13 testing within 48 hours (2 days).

I 03. Participants with a clinical diagnosis of iTTP and a French TMA score of 1 or 2.

Note: French Score is a clinical scoring system that predicts severe ADAMTS13 deficiency in those with features of thrombotic microangiopathy (TMA). A French Score of 2 (platelet count $\leq 30 \times 10^9$/L and serum creatinine ≤ 2.27 mg/dL) is considered highly suggestive of iTTP. Those with a French Score of 1 (either platelet count $\leq 30 \times 10^9$/L or serum creatinine ≤ 2.27 mg/dL) will be considered having probable iTTP (29).

Weight

Not applicable.

Sex, contraceptive/barrier method and pregnancy testing requirements/breastfeeding

I 04. All

Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a) Male participants

Male participants with female partners of childbearing potential must agree to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the overall treatment period and for at least 2 months after last study drug administration.

b) Female participants

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
  - Is a woman of nonchildbearing potential (WONCBP) as defined in Appendix 4 Contraceptive and barrier guidance (Section 10.4),

  OR

  - Is a woman of childbearing potential (WOCBP) and agrees to use an acceptable contraceptive method (as described in Section 10.4) during the study intervention period and for at least 2 months after the last administration of study intervention. The Investigator should evaluate the potential for contraceptive method failure (eg, noncompliance, recently initiated) in relationship to the first administration of study intervention.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) during Screening before the first administration of study intervention, see Section 8.2.5 Pregnancy testing. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Informed Consent

I 01. Capable of giving signed informed consent as described in Appendix 1 of the protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Platelet count ≥100 × 10^9/L.

E 02. Serum creatinine level >2.26 mg/dL (200 µmol/L) in case platelet count is >30 × 10^9/L (to exclude possible cases of atypical HUS).

E 03. Known other causes of thrombocytopenia including but not limited to:

- Clinical evidence of enteric infection with E. coli 0157 or related organism.
- Atypical HUS.
- Hematopoietic stem cell, bone marrow or solid organ transplantation-associated thrombotic microangiopathy.
- Known or suspected sepsis.
- Diagnosis of disseminated intravascular coagulation.

E 04. Congenital TTP (known at the time of study entry).

E 05. Clinically significant active bleeding or known co-morbidities associated with high risk of bleeding (excluding thrombocytopenia).

E 06. Inherited or acquired coagulation disorders.

E 07. Malignant arterial hypertension.

E 08. Participants requiring or expected to require invasive procedures immediately (eg, stroke requiring thrombolytic therapy, those who need mechanical ventilation, etc.).

E 09. Those presenting with severe neurological (ie, coma, seizures, GCS ≤8, stroke) or severe cardiac disease (per Investigator's discretion or cTnl > 5 × ULN, or cTnT > 5 x ULN, high sensitivity cTnT > 5 x ULN, or high sensitivity cTnI > 5 x ULN). The preferred assessment is cTnI, but cTnT, high sensitivity cTnT, or high sensitivity cTnI may be used if cTnI is unavailable.

E 10. Clinical condition other than that associated with TTP, with life expectancy <6 months, such as end-stage malignancy.

Prior/concomitant therapy

E 11. Known chronic treatment with anticoagulants and anti-platelet drugs that cannot be stopped (interrupted) safely, including but not limited to:
- vitamin K antagonists.
- direct-acting oral anticoagulants.
- heparin or low molecular weight heparin (LMWH).
- non-steroidal anti-inflammatory molecules other than acetyl salicylic acid.

Prior/concurrent clinical study experience

E 12. Participants who were previously enrolled in this clinical study (study EFC16521).

E 13. Participants who received an investigational drug, or device, other than caplacizumab, within 30 days of anticipated IMP administration or 5 half-lives of the previous investigational drug, whichever is longer. However, participants who have received any dose(s) of caplacizumab for the presenting episode of iTTP more than 4 hours before enrollment in Study EFC16521 are also excluded.

Diagnostic assessments

E 14. Positive result on the Screening SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test or on SARS-CoV-2 antigen test.

Other exclusions

E 15. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates participation in the study.

E 16. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 17. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 18. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with section 1.61 of the ICH-GCP Ordinance E6).

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Activity

Participants will abstain from strenuous exercise while on caplacizumab treatment and for 4 weeks after the last dose. Participants may participate in light recreational activities during studies (eg, watching television, reading).

5.4 SCREEN FAILURES

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened during the same episode of iTTP. However, if the participant subsequently develops a relapse, he/she may be rescreened during this relapsed episode. Rescreened participants should be assigned a new participant number for every screening/rescreening event. Participants who are rescreened are required to sign a new ICF.

5.5 CRITERIA FOR TEMPORARILY DELAYING ENROLLMENT OR ADMINISTRATION OF STUDY INTERVENTION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency should be considered for enrollment or administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

After confirmation of eligibility to participate in the study, participants will receive caplacizumab in addition to IST.

Specific details pertaining to the IMP can be found in the pharmacy manual.

Table 3 - Study intervention(s) administered

Intervention label	Caplacizumab
Intervention name	Caplacizumab
Intervention description	Please see details below
Type	Biological/Vaccine
Dose formulation	Lyophilized powder for solution for injection.
Unit dose strength(s)	10 mg (or 11mg for US and Canada) - One vial contains 12.5 mg of caplacizumab and comprises an overfill to compensate for losses during reconstitution and liquid transfer
Dosage level(s)	Caplacizumab 10 mg (11 mg in US and Canada) IV for a single dose followed by caplacizumab 10 mg (11 mg in US and Canada) SC 4-6 hours after the IV dose (Day 1) (exceptions to this are detailed in Section 1.3.4 footnote [a]). This will be followed by caplacizumab 10 mg (11 mg in US and Canada) SC daily starting on Day 2 for a maximum treatment duration of 12 weeks for the presenting episode.
Route of administration	IV (first dose), SC (all subsequent doses)
Use	Experimental
IMP and NIMP	IMP
Packaging and labeling	The study medication is provided by the Sponsor in a kit containing 1 vial with caplacizumab lyophilized powder for solution, 1 pre-filled syringe with water for injection, 1 vial adapter, 1 SC safety needle and 2 alcohol swabs. The study medication will be labeled per country requirements
[Current/former name(s) or alias(es)]	ALX-0081/Cablivi

Table 4 - Study arm(s)

Arm title	Caplacizumab and immunosuppressive therapy without first-line therapeutic plasma exchange
Arm type	Experimental
Arm description	All participants will receive open label caplacizumab daily and immunosuppressive therapy (corticosteroid +/-anti-CD20 antibody therapy antibody [rituximab or biosimilar]) without first line TPE
Associated intervention labels	Caplacizumab, corticosteroid, anti-CD20 antibody therapy

Noninvestigational medicinal products (NIMPs)

For details of administration guidance please refer to Section 4.1.

Immunosuppressive therapy: Corticosteroids:

- Formulation: Prednisone or Prednisolone
- Route(s) of administration: IV or oral
- Dose regimen: Prednisone or Prednisolone 1.0-1.5 mg/kg/day for 1 week and taper over 3 to 4 weeks based on institutional guidelines. The dose and duration of therapy may be adjusted as clinically indicated.

Anti-CD20 antibody therapy:

- Formulation: anti-CD20 antibody therapy (rituximab or biosimilar)
- Route(s) of administration: IV infusion (as per instructions on package insert)
- Dose regimen: 375 mg/m^2 IV infusion × 3 - 4 doses, once a week or as per institutional guidelines.

  Note: Please see Section 4.1 for additional details regarding anti-CD20 antibody therapy.

Therapeutic Plasma exchange (TPE), if needed:

- Plasma (fresh frozen plasma, solvent detergent/viral-inactivated plasma and cryosupernatant)
- Route(s) of administration: IV
- Dose regimen of TPE:
  - TPE with plasma at 1 to 1.5 × estimated plasma volume daily is recommended
  - TPE should be performed daily according to standard site practice and continued at least for 2 days after the platelet count normalization (≥150 × 10^9/L).
  - Tapering of TPE after platelet count normalization, defined as reducing its frequency to less than once per day, is strongly discouraged and if considered, should be discussed with the Medical Monitor.

The IMP and NIMP may be supplied at the site or from the PI/site/Sponsor to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the participant.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

6.1.1 Devices

- The Sponsor manufactured medical devices (or devices manufactured for Sponsor by a third party) provided for use in this study are:
  - One prefilled glass syringe containing solvent for reconstitution (containing water for injection).
  - One "vial adapter" device to facilitate transfer of the solvent for reconstitution and subsequent recovery of the reconstituted drug.
  - One safety needle for SC use (please note that a needle for the first IV bolus injection is not included in the kit).
  - Two alcohol swabs.

  These devices will be placed in the IMP kit provided by the Sponsor, jointly with the glass vial containing lyophilized powder for reconstitution (containing caplacizumab).
- Instructions for medical device use are provided in the Pharmacy Manual.
- All device deficiencies (including malfunction, use error and inadequate labelling) shall be detected, documented, and reported by the Investigator throughout the clinical investigation (see Section 8.3.7) and appropriately managed by the Sponsor.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of IMP/NIMP/device (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.7).

A potential defect in the quality of caplacizumab or any anti-CD20 antibody therapy supplied globally may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the caplacizumab or any anti-CD20 antibody therapy supplied globally and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP/NIMP/device to a third party (except for DTP shipment, for which a courier company has been approved by the Sponsor), allow

the IMP/NIMP/device to be used other than as directed by this clinical trial protocol, or dispose of IMP/NIMP/device in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Not applicable in this single-arm, open-label trial.

6.4 STUDY INTERVENTION COMPLIANCE

The following describes methods used by the Investigator or his/her delegate to ensure that the IMP was administered

- IMP compliance:
  - Intervention units are returned by the participant at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract)
  - The Investigator counts the number of vials, etc, remaining in the returned packs, and fills in the Intervention Log Form
  - The Investigator confirms the dosing information on the appropriate page(s) of the electronic case report form (eCRF)
  - The monitor in charge of the study then checks the eCRF data by comparing them with the IMP which he/she has retrieved and the Inventory form and accountability form

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

When participants self-administer (or the caregiver administers) study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned vials, etc, during the site visits and documented in the source documents and relevant form. Deviation(s) from the prescribed dosage regimen should be recorded.

A record of the quantity of caplacizumab dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays will also be recorded.

6.5 DOSE MODIFICATION

Not applicable.

6.6 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Not applicable.

6.7 TREATMENT OF OVERDOSE

Please see Section 8.3.6 for the definition of overdose.

Sponsor does not recommend specific treatment for an overdose.

In case of an overdose, there is a potential for increased risk of bleeding based on the pharmacological action of study drug.

Participants should be monitored closely for signs and symptoms of clinically relevant bleeding in case of actual or suspected overdose. In case of clinically relevant bleeding associated with (suspected) overdose, appropriate treatment for bleeding according to standard practice should be initiated and treatment with caplacizumab must be interrupted. The use of rescue medications is allowed whenever correction of hemostasis is needed. For details of rescue medication guidance please refer to Section 6.8.1. Treatment with study intervention should only be restarted when the bleeding has stopped. If caplacizumab is restarted, monitor closely for signs of bleeding.

In case of (suspected) overdose with no clinically relevant bleeding observed, caplacizumab administration may continue with the next daily dose or after the next TPE (if started on TPE) as applicable.

Note that permanent discontinuation of caplacizumab should be considered for participants who develop a severe bleeding requiring urgent medical and/or surgical intervention which is accompanied by significantly low vWF:Ag and/or FVIII:C levels which are slow to respond to study drug interruption and replacement therapy (also see Section 7.1.1).

In the event of an overdose, the Investigator should:

- Contact the Sponsor as soon as possible.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Evaluate the participant to determine whether study intervention should be interrupted.
- [redacted]
- Document appropriately in the eCRF.

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Sponsor based on the clinical evaluation of the participant.

6.8 CONCOMITANT THERAPY

Any medication or vaccine (including over the counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use.
- Dates of administration including start and end dates.
- Dosage information including dose and frequency.

Prohibited medication: desmopressin (DDAVP®) promotes the release of vWF. Therefore, it is not authorized in patients with iTTP as it may worsen the condition.

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

Note that existing use of anticoagulant treatment (such as vitamin K antagonists, direct-acting oral anticoagulants, heparin or LMWH), or anti-platelet drugs, non-steroidal anti-inflammatory molecules except acetyl salicylic acid needs to be stopped prior to the participant's inclusion in the study but if needed may be re-started at the discretion of the Investigator and should be used with caution (due to an increased bleeding risk). Prophylactic LMWH may be instituted for thromboprophylaxis in the inpatient setting per Investigator discretion, if the participant's platelets count exceeds 50×10^9/L and no active bleeding.

COVID-19 vaccination is permitted on study in eligible participants as per the discretion of the Investigator.

The Sponsor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants must abstain from taking prescription or nonprescription drugs (including vitamins, recreational drugs, and dietary or herbal supplements) from start of study intervention until completion of the follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

6.8.1 Rescue medicine

In case of active, clinically significant bleeding, treatment with caplacizumab should be interrupted. The use of rescue medications is allowed whenever correction of hemostasis is needed. If a participant develops severe bleeding due to clinically low levels of vWF and coagulation factor VIII (FVIII) related to caplacizumab treatment, consider administering a von Willebrand Factor/coagulation FVIII complex (vWF/FVIII) immediately to antagonize the activity of caplacizumab and help restore adequate hemostasis.

The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded. Caplacizumab should only be restarted upon the advice of a physician experienced in the management of thrombotic microangiopathies. If caplacizumab is restarted, monitor closely for signs of bleeding.

Please note that the Sponsor will not supply vWF/FVIII concentrates as rescue medication, and it should be obtained locally.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1).

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for the early treatment discontinuation visit and the follow-up visit 28 days after the last study intervention administration. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

- If after initiation of caplacizumab on Day 1, the baseline central laboratory ADAMTS13 activity result is between 10%-20% of normal, the Investigator should use clinical judgement in deciding to continue or stop caplacizumab treatment after evaluation of the totality of signs and symptoms and other laboratory data.
- If the baseline central laboratory ADAMTS13 activity is >20% of normal, caplacizumab therapy should be discontinued and other diagnoses should be considered.
- Permanent discontinuation of study intervention should be considered in case the participant develops severe (including life-threatening) bleeding requiring urgent medical and/or surgical intervention which is accompanied by significantly low vWF and/or FVIII levels which are slow to respond to study drug interruption and replacement therapy.
- Discontinuation of study intervention for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in the algorithm (Section 10.6) or if the Investigator believes that it is in best interest of the participant.
- Any abnormal laboratory value will be immediately rechecked for confirmation (after 24 hours) before making a decision of definitive discontinuation of the IMP for the concerned participant.
- Any female participant who becomes pregnant while participating in the study will discontinue study drug administration.
- If a participant develops a second clinical recurrence (exacerbation or relapse) the participant will discontinue from the study (Section 4.1).

Handling of participants after permanent intervention discontinuation

After the definitive discontinuation of study intervention, and if the participants are not withdrawing consent for post-treatment follow-up, they will be invited to attend early termination visit and follow-up visits, or followed-up up to recovery or stabilization of any AE, whichever comes last.

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP including a pharmacokinetics sample, if appropriate.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator when a participant meets one of the conditions outlined in the algorithm (Section 10.6) or in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

7.1.3 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Appendix 9 [Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency]). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

Temporary discontinuation of study drug should be considered in case the subject develops a severe or serious bleeding. All study participants experiencing any bleeding should be treated for the bleeding by the standard medical and/or surgical intervention (also see Section 6.7). Treatment with study drug should only be restarted when the bleeding has stopped. If study drug is restarted, monitor closely for signs of bleeding.

The temporary intervention discontinuation decided by the Investigator corresponds to more than 1 dose not administered to the participant.

7.1.4 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned adverse event was unlikely. If IMP is restarted, the participants will be monitored closely for evidence of re-bleeding.

7.1.4.1 Study intervention restart or rechallenge after liver stopping criteria are met

Study intervention restart/rechallenge after liver chemistry stopping criteria are met is allowed in this study only if derangements are deemed not related to the study intervention. If the participant meets liver chemistry stopping criteria, do not restart/rechallenge participant with study intervention unless:

- Sponsor board approval **is granted**
- Ethics and/or Institutional Review Boards (IRB) approval is obtained, if required, and
- Separate consent for intervention restart/rechallenge is signed by the participant

NOTE: If study intervention was interrupted for suspected intervention-induced liver injury, the participant should be informed of the risk of death, liver transplantation, hospitalization, and jaundice and re-consented before resumption of dosing.

If Sponsor board approval to restart/rechallenge the participant with study intervention is **not granted**, then the participant must permanently discontinue study intervention and may continue in the study for protocol-specified follow-up assessments.

7.1.4.2 Restart Following Transient Resolving Liver Chemistry Events Not Related to Study Intervention

- Restart refers to resuming study intervention following liver chemistry events for which there are clear underlying causes (other than Drug Induced Liver Injury [DILI]) (eg, biliary obstruction, pancreatic events, hypotension, acute viral hepatitis). Furthermore, there should be no evidence of alcoholic hepatitis or hypersensitivity.
- Approval by the Sponsor for study intervention restart can be considered when:
  - The Investigator requests consideration for study intervention restart if liver chemistry events have a clear underlying cause (eg, biliary obstruction, pancreatic events, hypotension, acute viral hepatitis) and ALT recovers to <3 × ULN and total bilirubin recovers to baseline or <1.5 × baseline. All criteria must be met prior to requesting consideration for study drug restart.
  - Possible DILI has been excluded by the Investigator and the study team. This includes the absence of markers of hypersensitivity (otherwise unexplained fever, rash, eosinophilia).
  - There is no evidence of alcoholic hepatitis.
  - IRB/IEC approval of study intervention restart has been obtained.

If restart of study intervention is approved by the Sponsor in writing:

- The participant must be provided with a clear description of the possible benefits and risks of study intervention administration including the possibility of recurrent, more severe liver injury or death.
- The participant must provide signed informed consent specifically for the restart of study intervention. Documentation of informed consent must be recorded in the study file.
- Study intervention must be administered at the dose specified by the Sponsor.

- Participants approved by the Sponsor for restart of study intervention must return to the clinic twice a week for liver chemistry tests until stable liver chemistry tests have been demonstrated and then standard laboratory monitoring may resume as per protocol.
- If the participant meets protocol-defined liver chemistry stopping criteria after study intervention restart, study intervention should be permanently discontinued.
- The Sponsor, and the IRB/IEC, must be informed of the outcome for the participant following study intervention restart.
- The Sponsor must be notified of any AEs.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants screened, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
  - In case of a first clinical recurrence (exacerbation or relapse) of the presenting TTP episode during the overall study period, it is up to the Investigators to adjust the ongoing treatment plan, which may include start or restart of TPE and adjustment of IST regimen and caplacizumab therapy. In case that caplacizumab treatment is maintained for a first exacerbation or relapse, the visit schedule will be the same as during the initial treatment period.
- During the treatment period, the baseline samples for PK, [redacted] and safety will be obtained before caplacizumab administration on Day 1 (exceptions to this are detailed in Section 1.3.4 footnote [a]). Other laboratory tests will be performed as indicated in SoA (Section 1.3). Please see Section 4.1 for additional details. If PE is indicated, samples will be obtained prior to TPE.

  Following guidance with regard to timing of assessments planned at a single visit should be followed:
  - ECG and vital signs should be assessed prior to blood sampling, and
  - Assessments will be done prior to study intervention administration (including IV dose administration on Day 1, exceptions to this are detailed in Section 1.3.4 footnote [a]), and
  - After Day 1, for those in whom TPE is needed, assessments should be done prior to start of TPE, and
  - SC study drug should be dosed after all other assessments have been performed (and if TPE is needed, during the daily TPE period, SC study drug should be dosed after end of the day's TPE).
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count, urine tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3).
- The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will be within a safe limit for human clinical trials as recommended by the local IRBs and IECs.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.
- Samples that remain, after protocol-specific assessments have been performed, may be used by the Sponsor for further exploratory work in the context of the development of caplacizumab or evaluation of iTTP (only for participants who consent to future research

of their biological samples and data [Section 8.9] and if permitted per local regulations). These samples may be kept for at least 5 years after the end of the study. No human deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) analysis will be performed.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

8.1 EFFICACY ASSESSMENTS

Planned timepoints for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1 Platelet count, peripheral blood smear, LDH, ADAMTS13 activity, and antibodies

Blood samples for assessments of platelets, blood smear, LDH, ADAMTS13 activity and antibodies will be collected at the time points indicated in the SoA (Section 1.3).

In general, blood samples will be collected via an indwelling IV catheter or by direct venipuncture. Details on method, sampling and processing procedures will be provided in a separate Lab Manual. Samples for blood smear will be assessed by the local laboratory. Samples for platelet counts, LDH, cTnI, and creatinine will be assessed by the central lab and/or local laboratory as indicated in the SoA (Section 1.3).

8.1.2 Clinically significant TTP events

Clinically significant TTP events will be assessed at the time points indicated in the SoA (Section 1.3).

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

- Neurological
- Cardiovascular
  - Elevated cardiac troponins I (cTnI) (value and local upper limit of reference range)
  - Acute myocardial infarction (ECG finding)
  - Conduction abnormality (ECG finding)
  - Repolarization abnormality (ECG finding)
  - Heart failure (severity)
  - Other (to be specified)
- Renal
- Exacerbation of TTP
- Relapse of TTP
- Death due to TTP
- Other (to be specified)

8.1.3 Neurological assessment and Glasgow Coma Scale

At screening, the neurologic status of the adult subjects will be assessed using the Glasgow Coma Scale (GCS), a neurological scale that measures the conscious state of the subject. The GCS is to be assessed within 2 hours prior to enrollment. The best eye, verbal and motor responses will be scored according to the scale, and the separate scores added up to obtain the final score, ranging from 3 to 15. An example of the GCS is provided in Section 8.1.3.1.

At all other time points defined in the SoA (Section 1.3), the neurological status of the subjects will also be assessed by examination of the neurological system and presence (including severity) or not of the following: coma, stupor, seizures, disorientation/confusion, hemiparesis/-plegia, focal deficit, agitation, and dysarthria (primarily physical examination and as per standard of care and by Investigator's judgement: electroencephalogram [EEG], magnetic resonance imaging [MRI], etc).

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

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

8.1.3.1 Glasgow coma scale score

The GCS (31) is scored between 3 and 15, 3 being the worst, and 15 the best. It is composed of three parameters: Best Eye Response, Best Verbal Response, Best Motor Response, as given below:

Best Eye Response. (4)

1. No eye opening
2. Eye opening to pressure
3. Eye opening to sound
4. Eyes open spontaneously

Best Verbal Response. (5)

1. No verbal response
2. Sounds
3. Words
4. Confused
5. Orientated

Best Motor Response. (6)

1. No motor response
2. Extension
3. Abnormal flexion
4. Normal flexion
5. Localising
6. Obeys commands

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

8.1.4 Cardiac assessment including cTnI level

Cardiac ischemia/ infarction (cardiac troponin I [cTnI] (preferred) or cardiac troponin T or high sensitivity cardiac troponin T or high sensitivity cardiac troponin I, depending on the availability at the site, and ECG) and arrhythmia/conduction abnormality on ECG will be assessed.
The Investigator will determine whether the observed abnormality is to be considered as a clinically significant TTP event.

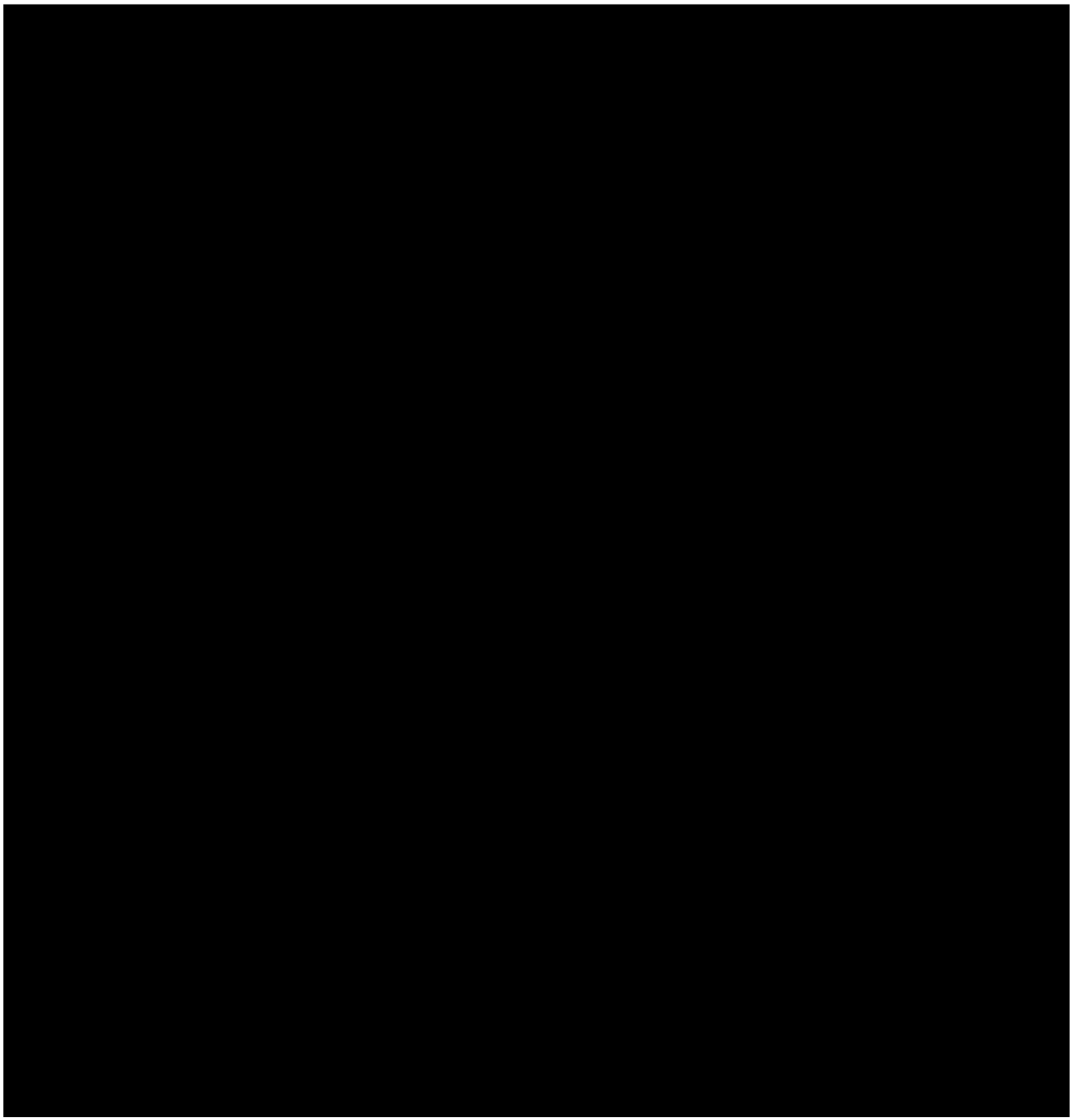
For information on ECG, please refer to Section 8.2.3.

8.1.5 Patient reported outcomes

The Table 5 shows the concepts of [redacted] along with their related questionnaires to be used in the study. The Sponsor or designee will provide the translations for all patient-reported [redacted] instruments, where translations are available. Where available, the COAs will be distributed to patients (Caregiver or Provider) as specified in the SoA (Section 1.3). If an instrument is not available in the participant's language, the instrument will not be completed. All Patient Reported Clinical Outcome assessment are collected via an electronic tablet and transmitted to a third-party vendor data server over public networks using encrypted data.

Participants should attempt to complete the assessment. If a participant is unable to complete the assessment, the caregiver should complete the assessment with the participant.

[redacted]



8.2 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events which are presented in Section 8.3.

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

A complete physical examination will be performed at the time points indicated in the SoA (Section 1.3). Of note, additional physical examinations may be performed upon the discretion of the Investigator (eg, in case of AEs).

A complete physical examination will include, at a minimum, assessments of the following:

- General appearance
- Head, eyes, ears, nose, throat
- Central and peripheral nervous system
- Respiratory
- Cardiovascular
- Gastrointestinal
- Musculoskeletal
- Skin
- Lymph node palpation
- Urogenital
- Height and weight will be assessed on Day 1 of hospitalization only
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

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

8.2.2 Vital signs

Vital signs parameters will be measured at the time points indicated in the SoA (see Section 1.3). All parameters will be recorded in the eCRF.

The following vital signs parameters will be assessed: oral or tympanic temperature, systolic and diastolic blood pressure, pulse and respiratory rate.

- Blood pressure and pulse measurements will be assessed after 5 minutes in the supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- For the safety of the participant, additional vital sign assessments may be added as per the discretion of the Investigator.

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. ECG may be repeated as needed per Investigator discretion if clinically indicated.

8.2.4 Clinical safety laboratory tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- Laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the Investigator
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - All clinically significant laboratory findings will be recorded as AEs in the eCRF (also see Section 8.3).
  - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.
  - In the event of unexplained or unexpected clinical laboratory test values, the test(s) will be repeated and followed up until the results have returned to the normal range and/or an adequate explanation for the abnormality is noted.

8.2.5 Pregnancy testing

A woman of childbearing potential (WOCBP) must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) during Screening before the first administration of the study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

8.3 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.3.6

The definitions of unsolicited and solicited adverse events can be found in Appendix 3 (Section 10.3).

The definitions of device-related safety events, adverse device effects (ADEs) and serious adverse device effects (SADEs), can be found in Appendix 7 (Section 10.7). Device deficiencies are covered in Section 8.3.7.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) that meet the definition of an AE or SAE and remain responsible for following up all AEs (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs, including SAEs and AESIs, will be collected from the signing of the ICF until the end of study visit at the timepoints specified in the SoA (Section 1.3). In addition, any AEs, including SAE and AESI, that occurred from the first dose of caplacizumab until the ICF is signed, will also be collected.

All SAEs and AESIs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available (Refer to Section 10.8.1 for country-specific requirements for Germany).

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs and nonserious AESIs as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information in the product label.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the package insert and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 2 months after last dose of study intervention.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed for up to 6 to 8 weeks after the end of pregnancy to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former participant/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

8.3.6 Adverse events of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see Section 8.3.5).
- Symptomatic overdose (serious or nonserious) with IMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the intended dose within the intended therapeutic interval.
- Increase in alanine transaminase (ALT) >3 times the ULN
- Other project specific AESI(s):
  - All major bleeding events, including bleeding into a critical organ, life threatening or fatal bleeding

8.3.7 Guidelines for reporting product complaints

Any defect in the IMP/NIMP/device must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.3.7.1 Medical device deficiencies

Medical devices are being provided for use in this study as the study intervention. To fulfill regulatory reporting obligations worldwide, the Investigator is responsible for the detection and documentation of events meeting the definitions of device deficiencies that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 7 (Section 10.7).

NOTE: Deficiencies fulfilling the definition of an AE/SAE will follow the processes outlined in Appendix 7 (Section 10.7) of the protocol.

8.3.7.1.1 Time period for detecting medical device deficiencies

- Medical device deficiencies of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the Investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such deficiency is considered reasonably related to a medical device provided for the study, the Investigator will promptly notify the Sponsor.

The method of documenting medical device deficiency is provided in Appendix 7 (Section 10.7).

8.3.7.1.2 Follow-up of medical device deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention.
- The Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the Investigator.

8.3.7.1.3 Prompt reporting of device deficiencies to the Sponsor

- Device deficiencies will be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the protocol definition of a medical device deficiency.
- The medical device deficiency report form will be sent to the Sponsor by email. If email is unavailable, then facsimile should be utilized.
- The Sponsor will be the contact for the receipt of device deficiency reports.
- The Investigator will assess whether or not a medical device deficiency has to be reported together with an AE or SAE.
- Device deficiencies reports should be sent to: MP-Quality-Complaints@sanofi.com

8.3.7.1.4 Regulatory reporting requirements for device deficiencies

- The Investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the Sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The Investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

8.4 PHARMACOKINETICS

- Sparse blood samples will be collected for measurement of plasma concentrations of total caplacizumab levels as specified in the SoA (Section 1.3).
- Additional samples may be collected at other timepoints during the study if warranted and agreed upon between the Investigator and the Sponsor.

- Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate document. The actual date and time of each sample will be recorded. Pharmacokinetic samples will be tested by the Sponsor or Sponsor's designee.
- Samples collected for analyses of total caplacizumab plasma concentration (free + complexed caplacizumab) may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

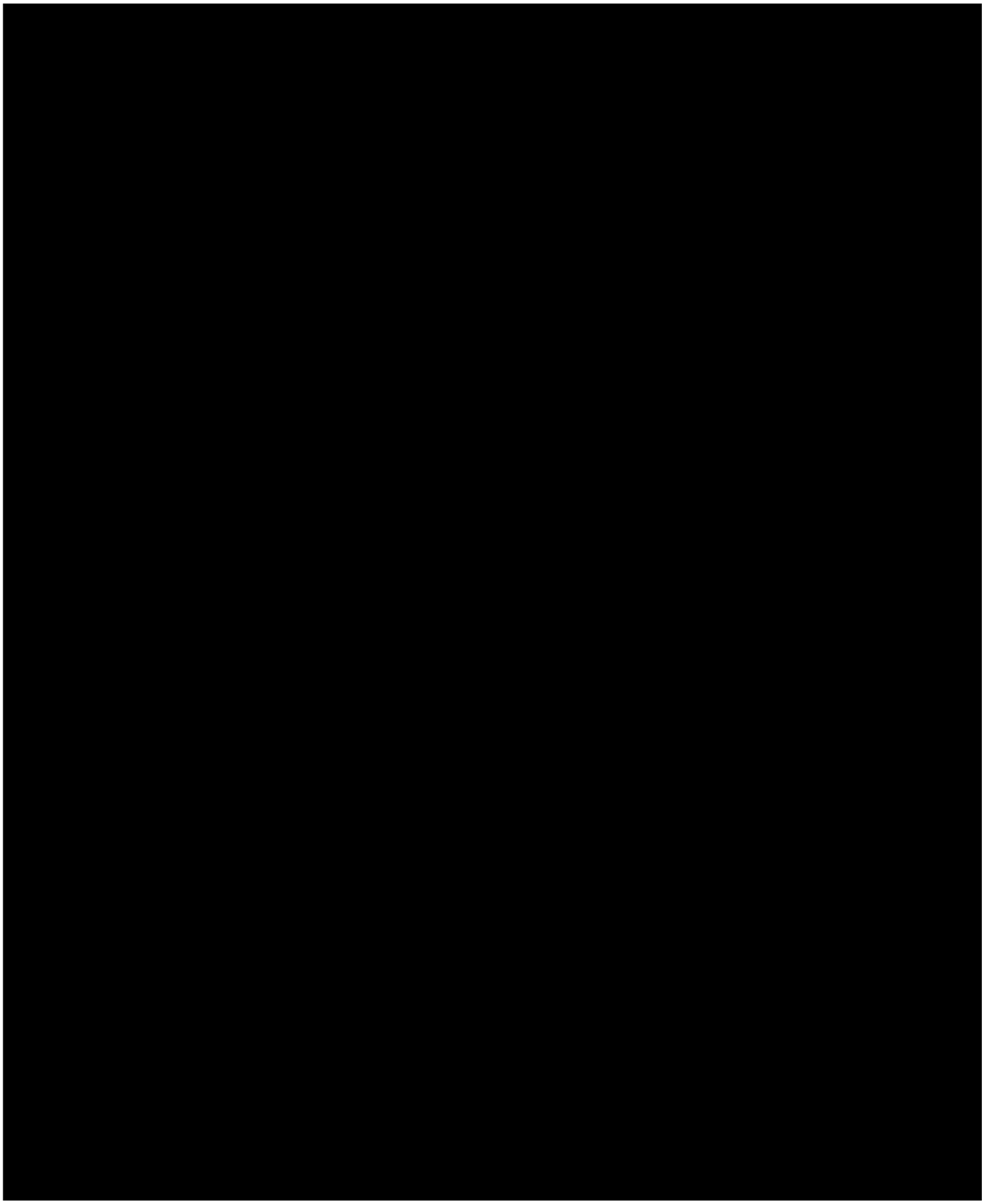
Individual total caplacizumab plasma concentrations (free + complexed caplacizumab) will be tabulated and summarized by descriptive statistics.

An exploratory pharmacokinetic analysis will be done after pooling the results of this study with other available data. The results of this exploratory analysis will not be included in the study report but will be kept on file.

Left over samples after the PK analysis may be used for exploratory research as described in Section 8.9.

[redacted]

[redacted]



9 STATISTICAL CONSIDERATIONS

Details on statistical methods will be provided in the statistical analysis plan (SAP).

9.1 POPULATIONS FOR ANALYSES

The following populations for analyses are defined:

Table 6 - Populations for analyses

Population	Description
Intent-to-treat (ITT)	All enrolled participants, regardless of whether the investigational medicinal product (IMP) was received or not.
Modified ITT (mITT)	All participants from ITT population who received at least 1 dose of IMP and with an evaluable primary endpoint. The primary endpoint is evaluable when the following condition is met: The participant has an ADAMTS13 activity <10% at baseline.
Safety	All enrolled participants who take at least 1 dose of IMP.
Pharmacokinetic (PK)	All enrolled and treated participants (safety population) with at least one post-baseline PK sample with adequate documentation of dosing and sampling dates and times.

Enrolled participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population.

9.2 STATISTICAL ANALYSES

The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.2.1 General considerations

In general, continuous data will be summarized using the number of observations available, mean, SD, median, [Q1, Q3], minimum, and maximum, where appropriate. Categorical and ordinal data will be summarized using the count and percentage of participants.

No pre-specified success criterion and formal statistical hypothesis testing is planned.
No statistical adjustment on interim analyses.

The baseline value is defined as the last available value before the first dose of open-label IMP. For participants enrolled but not treated, the baseline value is defined as the last available value before enrollment.

The observation period will be divided into 4 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration.
- The **treatment-emergent (TE) period** is defined as the period from the first IMP administration to the last IMP administration + 28 days. The treatment-emergent period includes the following 2 periods:
  - The **on-treatment period** is defined as the period from the first IMP administration to the last administration of the IMP,
  - The **residual treatment period** is defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.
- The **post treatment-emergent (TE) period** is defined as the period from the end of the treatment emergent period.

The **overall study period** for analysis is defined as the time from first IMP administration until the end of the study.

9.2.2 Primary endpoint(s) analyses

The primary endpoint will be analyzed in mITT population.

The primary endpoint is the proportion of participants achieving remission without requiring TPE during the overall study period. Remission is defined as sustained Clinical Response with either (a) no TPE and no anti-VWF therapy for ≥30 days (Clinical Remission) or (b) with attainment of ADAMTS13 activity level ≥50% (Complete ADAMTS13 Remission), whichever occurs first. Remission is assessed starting from the clinical response (for participants not requiring TPE) or the end of TPE (for participants requiring TPE), until the end of study.

Clinical response is defined as sustained platelet count ≥150 × 10^9/L and LDH <1.5 × ULN and no clinical evidence of new or progressive ischemic organ injury for at least 2 consecutive visits.

Clinical remission is defined as sustained Clinical Response with no TPE and no anti-vWF therapy for ≥30 days.

Complete ADAMTS13 Remission is defined as sustained Clinical Response with attainment of ADAMTS13 activity level ≥50% for at least 2 consecutive visits during the overall study period.

Responders are participants who achieve remission without requiring TPE during the overall study period. Each participant will be classified as a responder or non-responder per the response criteria, and the proportion of responders will be calculated together with a 95% Wilson CI.

9.2.3 Secondary endpoint(s) analyses

Secondary endpoints are listed in Table 2.

Secondary efficacy endpoints analyses are defined in this section. Secondary safety endpoints analyses are defined in Section 9.2.6.1 (AE, SAE, AESI), and Section 9.2.6.2 (clinical safety laboratory variables, vital signs, and ECG).

All secondary endpoints will be analyzed using descriptive statistics, frequency, percentage, and CIs as appropriate. The time to event endpoints will be analyzed using a Kaplan-Meier analysis.

The following secondary efficacy endpoints will be analyzed in mITT population and summarized using the count and percentage of participants. Two-sided 95% confidence intervals (CIs) will be provided.

- Proportion of participants achieving Remission during the overall study period
- Proportion of participants who require TPE during the on-treatment period
- Proportion of participants achieving Clinical Response during on-treatment period and during the overall study period
- Proportion of participants refractory to therapy during the on-treatment period
- Proportion of participants with TTP-related death during the on-treatment period and during the overall study period
- Proportion of participants with a clinical exacerbation of iTTP during the on-treatment period and during the overall study period
- Proportion of participants with a clinical relapse of iTTP during the on-treatment period and during the overall study period

Time to platelet count response will be analyzed in mITT population and analyzed using a Kaplan-Meier analysis. Median time to event (with two-sided 95% CIs) will be reported.

Selected efficacy endpoints may be summarized in ITT population.

[redacted]

9.2.5 Multiplicity adjustment

All analyses will be descriptive in nature and therefore adjustments for multiplicity will not be applied.

9.2.6 Safety analyses

All safety analyses will be performed on the Safety population.

9.2.6.1 Adverse events

All adverse events will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- TEAEs: AEs that developed, worsened or became serious during the treatment-emergent period
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

The primary focus of adverse event reporting will be on TEAEs. Pre-treatment and post-treatment adverse events will be described separately.

Safety will be assessed through descriptive summaries of AEs, SAEs, and AESIs during the TE period. The incidence of AEs will be summarized by system organ class and preferred term. The AE summaries will be generated with number (%) of participants experiencing at least one event.

9.2.6.2 Clinical safety laboratory variables, vital signs and electrocardiograms (ECGs)

Clinical safety laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed in the Safety population.

For clinical safety laboratory variables and vital signs, descriptive statistics for results and changes from baseline will be provided by time point during the on-treatment period. Clinical safety laboratory variables and vital signs will be converted into standard international units.

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal

9.2.6.3 Product complaints

Product complaints will be summarized in the Safety population. Product complaint summaries during the on-treatment period will be summarized using the count and percentage of participants experiencing at least one event.

[redacted]

9.3 INTERIM ANALYSES

An interim analysis will be performed after the first 30 participants with baseline ADAMTS13 activity <10% have completed treatment period and 12 weeks of follow-up.

The SAP will describe the planned interim analyses in greater detail.

9.4 SAMPLE SIZE DETERMINATION

The primary endpoint is the proportion of participants achieving Remission without requiring TPE during the overall study period. The responder rate will be estimated, and no pre-specified success criterion and formal statistical hypothesis testing is planned.

An adequate number of participants will be enrolled to ensure at least 55 participants with ADAMTS13 activity levels <10% at baseline are available for analysis of the primary endpoint. It is anticipated that approximately 61 participants will be enrolled in the study.

With the sample size of 55, assuming the true responder rate of participants who achieve remission without requiring TPE during the overall study period is 70% (ie, overall, 85% remission rate and 18% of participants requiring TPE), the lower bound of 95% Wilson CI would be 58% (Table 7).

Table 7 - Lower bound of 95% Confidence Interval given various assumed rates of participants achieving Remission without requiring TPE during the overall study period

Assumed responder rate	Lower bound of 95% CI of responder rate[a]
65% or below	At most 52%
70%	58%
75%	64%
80%	68%
85% or greater	At least 74%

a In post-hoc analysis of HERCULES, the upper confidence limit of remission rate for the placebo arm (placebo + IST + TPE) was 54%.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - Applicable laws and regulations (eg, data protection law as General Data Protection Regulation - GDPR)
- The protocol, protocol amendments, ICF, Investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:
    - The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
    - The finding reveals a substantial risk of a serious health condition or has reproductive importance, AND has analytical validity, AND has clinical validity.

- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

As applicable, according to Directive 2001/20/EC, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as "substantial" (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participants or their legally authorized representative (refer to Section 10.8.1 for country specific requirements for Germany), and answer all questions regarding the study, including what happens to the participant when his/her participation ends (post-trial access strategy for the study).
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative (refer to Section 10.8.1 for country specific requirements for Germany) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the Global Data Protection Regulation (GDPR) and of the French law, and Health Insurance Portability and Accountability Act (HIPAA) where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s). Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc.).
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative (refer to Section 10.8.1 for country specific requirements for Germany), where applicable.

Participants who are rescreened are required to sign a new ICF.

The ICF contains 2 separate sections that addresses the use for research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking a checkbox in CSICF Part 3. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including trial participants, Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant personal data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

Participant race and ethnicity will be collected in this study because they are expected to modify the drug response/because they are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan). They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers, when applicable, will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of personal data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study,
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.
- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.

- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry/). Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

10.1.5.1 Data monitoring committee

- A Data Monitoring Committee (DMC) will be appointed to monitor the safety and scientific integrity of this study. The DMC, independent from the Sponsor and the Investigators, is responsible for monitoring the safety of the study participants enrolled in the clinical trial on an on-going basis in order to provide, in a timely fashion, appropriate recommendations to the Sponsor.
- An early aggregated safety data review will be performed by the DMC, the goal of which is to allow for a cautious, approach to study intervention administration. The DMC has the possibility to request an ad-hoc meetings (teleconferences), clearly identifying the safety-related reason for such an additional meeting and taking account of the then current recruitment status and recruitment rate. At each DMC meeting during the conduct of the trial, the DMC makes a recommendation to the Sponsor/Steering Committee to continue the trial as planned, or with an amendment, or to terminate the trial. Details regarding the DMC are included in the DMC charter.
- Participant safety will be continuously monitored by the Sponsor's internal safety review team, which includes safety signal detection at any time during the study.
- All safety data collected will be reviewed by the Sponsor's internal safety team for agreement of next steps.
- In particular, data will be reviewed by the Sponsor for identification of the following events that would potentially contribute to a requirement to pause/stop the study.
  - Any deaths, regardless of causality
  - Any major bleeding events, including bleeding into a critical organ, life threatening or fatal bleeding
  - Other

10.1.6 Dissemination of clinical study data and results

Study participants

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use "coded" data of all the study participants to independently verify the study's results.

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include ClinicalTrials.gov, euclinicaltrials.eu, and sanofi.com, as well as some national registries. For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).

In addition, results from clinical trials in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org.

Individual anonymized participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org.

Professionals involved in the study or in the drug development program

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in CRF Completion Instructions.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and

mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.

- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in the CRF Completion Guideline/ Instruction.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first site open and will be the study start date.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
  - Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- Screening tests will be performed by the local laboratory.
- For tests to be performed by the central laboratory: local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 8 - Protocol-required laboratory tests

Laboratory tests	Parameters
Blood smear	Blood smear[a]
Hematology	
	Platelet count[f]
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices:
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	Mean corpuscular hemoglobin concentration (MCHC)
	%Reticulocytes
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Coagulation parameters	
	Prothrombin time (PT)
	Activated partial thromboplastin time (aPTT)
Clinical chemistry[b]	
	Blood urea nitrogen (BUN)
	Creatinine
	Glucose
	Chloride
	Potassium
	Sodium
	Calcium

Laboratory tests	Parameters
	Aspartate aminotransferase (AST)
	Alanine aminotransferase (ALT)
	Alkaline phosphatase[c]
	Total and direct bilirubin
	Total protein
Other screening tests	COVID test (SARS-CoV-2 RT-PCR or antigen test)
	Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody)
	Pregnancy test: Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential). If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required.
Organ damage markers	Cardiac troponin I (cTnI)[f]
	Creatinine[d, f]
	Lactate dehydrogenase (LDH)[f]
ADAMTS13	
	ADAMTS13 activity
	Anti-ADAMTS13 antibody
[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

NOTES:

a Blood smear that will be assessed by a local laboratory.

b Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 7.1.2 Liver Chemistry Stopping Criteria and Appendix 6 (Section 10.6) Liver safety: Suggested actions and follow-up assessments. All events which may indicate severe liver injury (possible Hy's Law) must be reported to Sponsor in an expedited manner (excluding studies of hepatic impairment or cirrhosis).

c If alkaline phosphatase is elevated, consider fractionating.

d Serum creatinine will be tested as part of the clinical chemistry tests.

e Baseline ADAMTS13 activity test will be done locally, and also a sample will be sent to central laboratory for ADAMTS13 activity and antibody tests. Subsequent ADAMTS13 activity and antibodies samples will be tested by central laboratory.

f Platelet count, LDH, cTnI, and creatinine should be assessed locally throughout the entire hospitalization but baseline, 24-hour, 48-hour, 60-hour, and subsequent daily samples during the hospitalization must be assessed centrally as well.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of unsolicited and solicited AE

- An unsolicited adverse event is an adverse event that was not solicited and that is communicated by a participant/legally authorized representative (LAR) who has signed the informed consent. Unsolicited AEs include serious and nonserious AEs.
- Potential unsolicited AEs may be medically attended (ie, symptoms or illnesses requiring a hospitalization, emergency room visit, or visit to/by a health care provider). The participant/legally authorized representative (LAR) will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of participant/legally authorized representative (LAR) concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the participant's records.
- Unsolicited AEs that are not medically attended nor perceived as a concern by the participant/legally authorized representative (LAR) will be collected during an interview with the participant/legally authorized representative (LAR) and by review of available medical records at the next visit.
- Solicited AEs are predefined local and systemic events for which the participant is specifically questioned.

Events <u>meeting</u> the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a) Results in death

b) Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
    - Intensive treatment in an emergency room or at home for:
      - Allergic bronchospasm,
      - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
      - Convulsions (seizures, epilepsy, epileptic fit, absence, etc),
    - Development of drug dependence or drug abuse.

10.3.3 Recording and follow-up of AE and/or SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. An event that is easily tolerated by the participant, causing no to minimal discomfort, and not interfering with daily activities.
- Moderate: An event that results in sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgement to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study drug:

Relationship of Event to Study Treatment	
Not related	An adverse event will be considered "not related" to the use of the investigational drug if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include, but are not limited to: the lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the adverse event (eg, the event occurred before administration of drug), or the presence of a more likely alternative explanation for the adverse event.
Related	An adverse event will be considered "related" to the use of the investigational drug if there is a possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include, but are not limited to: a positive rechallenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the adverse event, or a lack of an alternative explanation for the adverse event.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information (refer to Section 10.8.1 for country specific requirements for Germany).

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by fax or email.
- Contacts for SAE reporting can be found in Investigator file.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes.
- Contacts for SAE reporting can be found in Investigator file.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below).

- A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.
- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy
- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

10.4.2 Contraception guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:

Highly effective methods[b] that have low user dependency *Failure rate of <1% per year when used consistently and correctly.*

- Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)[c]
- Bilateral tubal occlusion
- Azoospermic partner (vasectomized or due to a medical cause)
  Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
  Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

Highly effective methods[b] that are user dependent *Failure rate of <1% per year when used consistently and correctly.*

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c]
  - oral
  - intravaginal
  - transdermal
  - injectable
- Progestogen-only hormone contraception associated with inhibition of ovulation[c]
  - oral
  - injectable
- Sexual abstinence
  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

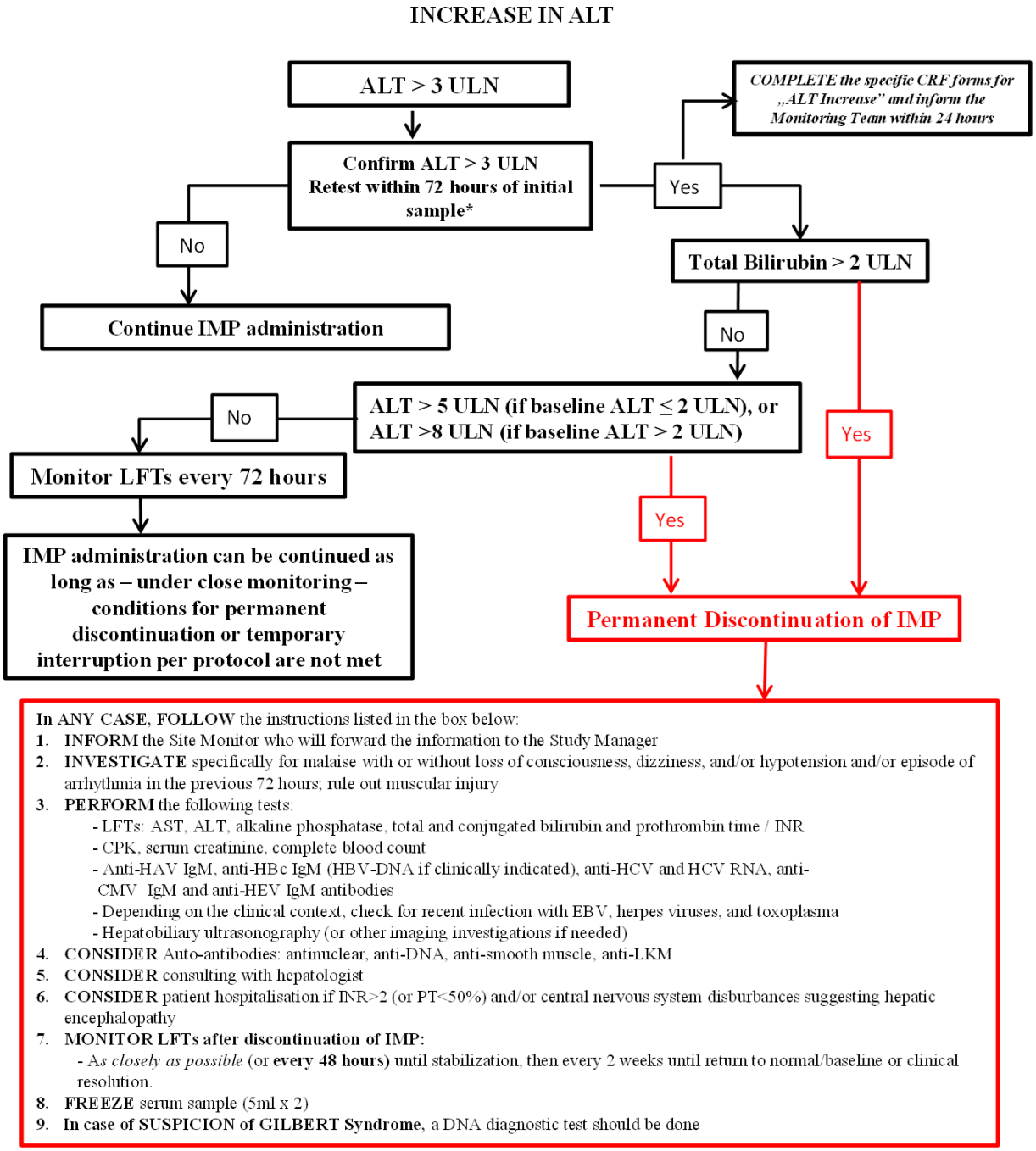
a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.
b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.
c Male condoms must be used in addition to hormonal contraception
Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

10.5 APPENDIX 5: GENETICS

Not applicable.

10.6 APPENDIX 6: LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

The following figure provides suggested actions and follow-up assessments for liver function test derangements and discontinuation criteria. Refer to Section 7.1.4.1 for additional details.



*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.
Note:
"Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
See Section 10.3 for guidance on safety reporting.
Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

10.7 APPENDIX 7: AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).

Both the Investigator and the Sponsor will comply with all local medical device reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all Sponsor medical devices provided for use in the study (see Section 6.1.1) for the list of Sponsor medical devices).

10.7.1 Definition of medical device AE and ADE

Medical device AE and ADE definition

- A medical device AE is any untoward medical occurrence in a clinical study participant, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.
- An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.7.2 Definition of medical device SAE, SADE and USADE

A medical device SAE is an any serious adverse event that:

a) Led to death

b) Led to serious deterioration in the health of the participant, that either resulted in:

- A life-threatening illness or injury. The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- A permanent impairment of a body structure or a body function.

- Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Chronic disease (MDR 2017/745).

c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect

SADE definition

- A SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE.
- Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

Unanticipated SADE (USADE) definition

- An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is defined as a SADE that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.7.3 Definition of device deficiency

Device deficiency definition

- A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequacy of the information supplied by the manufacturer.

10.7.4 Recording and follow-up of AE and/or SAE and device deficiencies

AE, SAE and device deficiency recording

- When an AE/SAE/device deficiency occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the Investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

- For device deficiencies, it is very important that the Investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
  - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one of the following categories:

- Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Moderate: Minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL). Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc
- Severe: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self care ADL. Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency. The Investigator will use clinical judgment to determine the relationship.
- A *reasonable possibility* of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the product information, for marketed products, in his/her assessment.
- For each AE/SAE/device deficiency, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE/SAE/device deficiency

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE/SAE/device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.7.5 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next table) or to the Sponsor via fax or email.
- Contacts for SAE reporting can be found in Investigator file.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in Investigator file.

10.7.6 Reporting of SADEs

SADE reporting to the Sponsor

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the Sponsor within 24 hours after the Investigator determines that the event meets the definition of a device deficiency.
- The Sponsor will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in Investigator file.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

10.8.1 Germany-specific requirements

For Section 8.3.1 Time period and frequency for collecting AE and SAE information and Section 10.3.3 Recording and follow-up of AE and/or SAE

This study will comply with the German GCP ordinance (§ 12 (4) GCP-V) regarding the reporting of SAEs as described below.

- The Investigator will submit any SAE data to the Sponsor immediately after obtaining knowledge.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool to immediately report the event, after obtaining knowledge.

For Section 10.1.3 Informed consent process

“Legally authorized representative” is not applicable for adult participants in Germany.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Contingency procedures are suggested for an emergency that prevents access to the study site, to ensure the safety of the patients, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, screening and enrollment may be temporarily delayed/halted. Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of patients and those important to preserving the main scientific value of the study.

For European countries contingency measures are currently only applicable for the COVID-19 pandemic.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely. Possibility of visit extension must be discussed on a case by case basis with the Sponsor considering first of all subject's safety and best interests.
- If onsite visits or alternative location (out of patient's home) are not possible, visits will have be performed at home by a trained healthcare professional and if allowed by local competent authorities for the following but not limited to:
  - Monitoring of injection site reactions, AEs and SAEs
  - Collect study samples for safety, and pregnancy test (if applicable)
  - Perform study examinations (eg, Measuring vital signs)
- IMP Injection Training: In case of emergency (eg, natural disaster, pandemic) different training ways (eg, training remotely with instruction provided by phone) can be performed (and will be documented in the patient's study file).
- After Sponsor agreement is obtained, the IMP may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and agreed upon by the patients.

Use of local clinic or laboratory locations may be allowed for safety follow up in case the central lab cannot be used.

If onsite visit and home visit are not possible, the Investigator or delegate will perform a phone-call visit at each onsite planned visit to collect safety data and concomitant treatment. All data collected remotely will be properly documented in the patient's medical record and the study CRF.

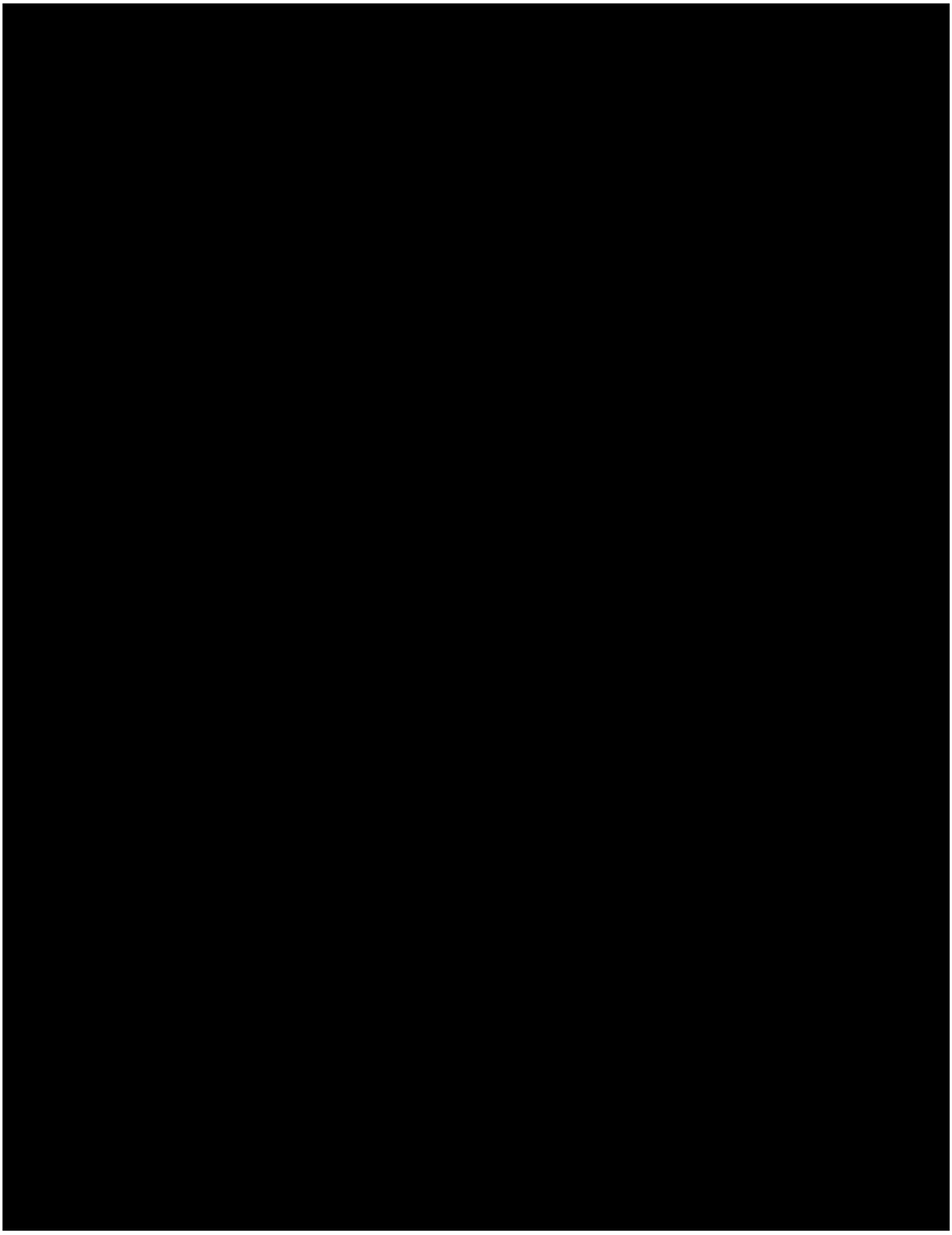
If onsite visits are possible and there is a need to reduce the time spent on site to a minimum, the focus should be on IMP administration, collection of safety information (vital signs, adverse events) and safety blood collection (mainly biochemistry, hematology and ADA, if planned for the visit).

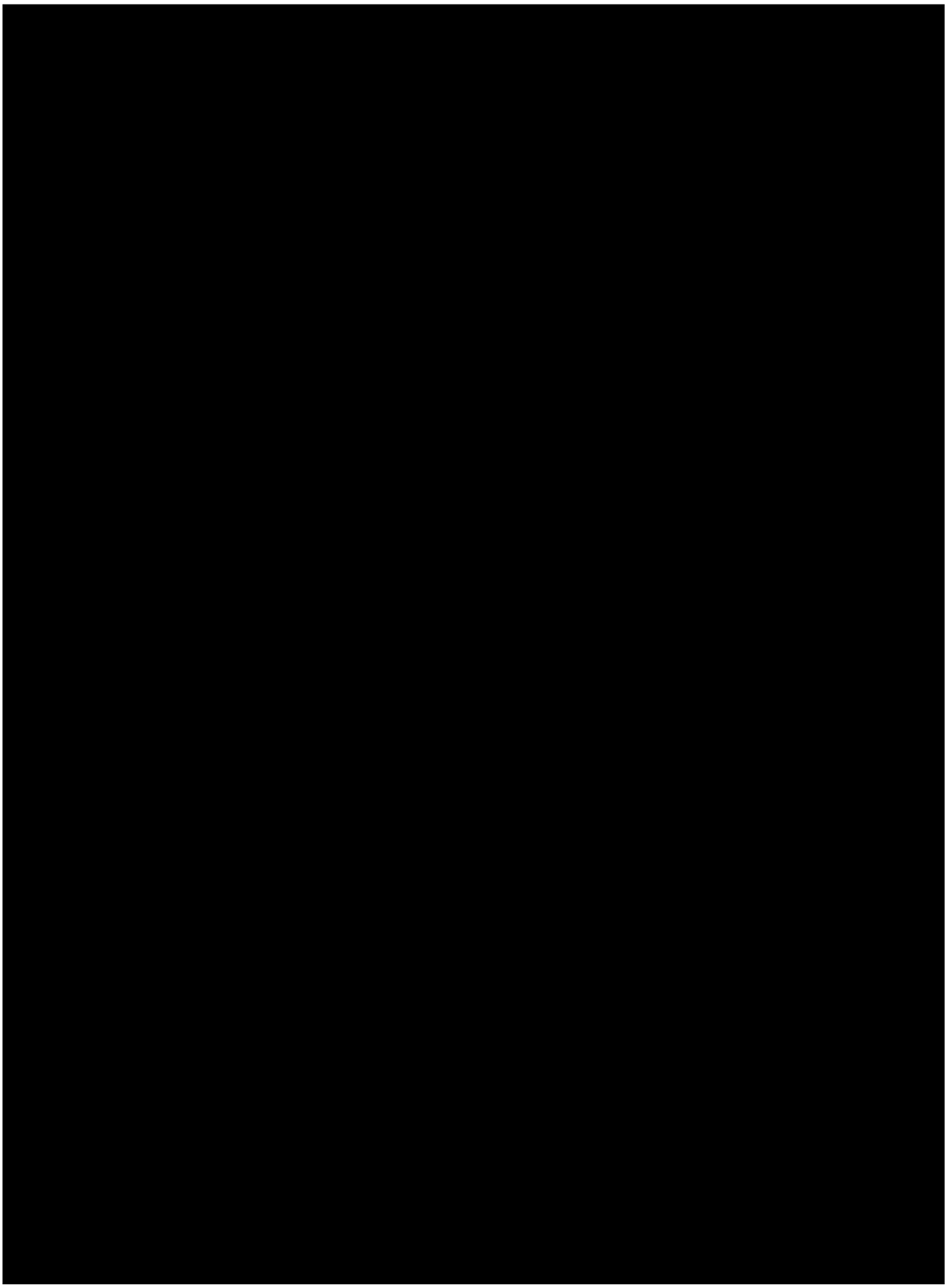
Contingencies implemented due to emergency will be documented.

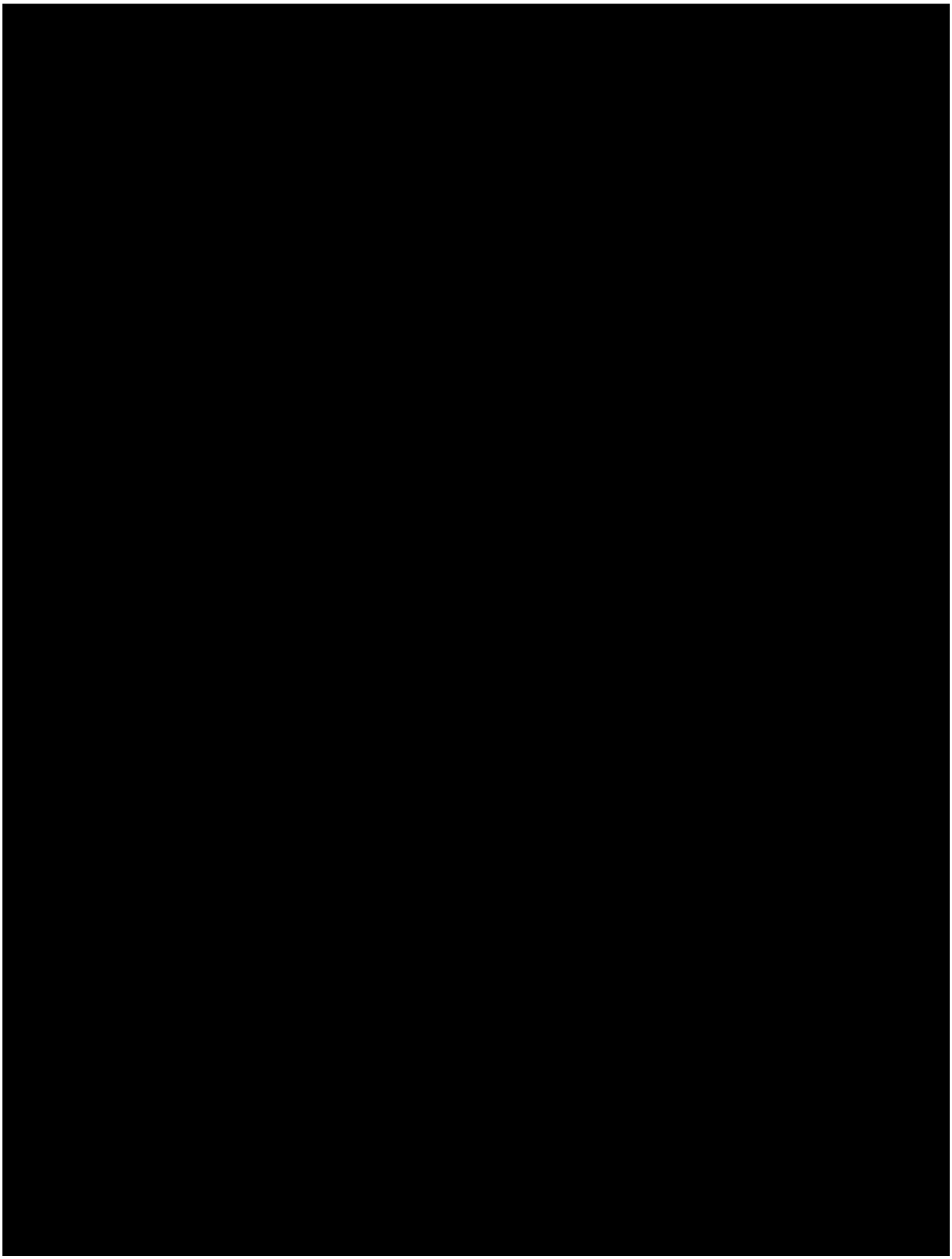
For a regional or national emergency declared by a governmental agency, contingency procedures may be implemented for the duration of the emergency. The participants or their legally authorized representative should be verbally informed prior to initiating any changes that are to be implemented for the duration of the emergency (eg. study visit delays/treatment extension, use of local labs).

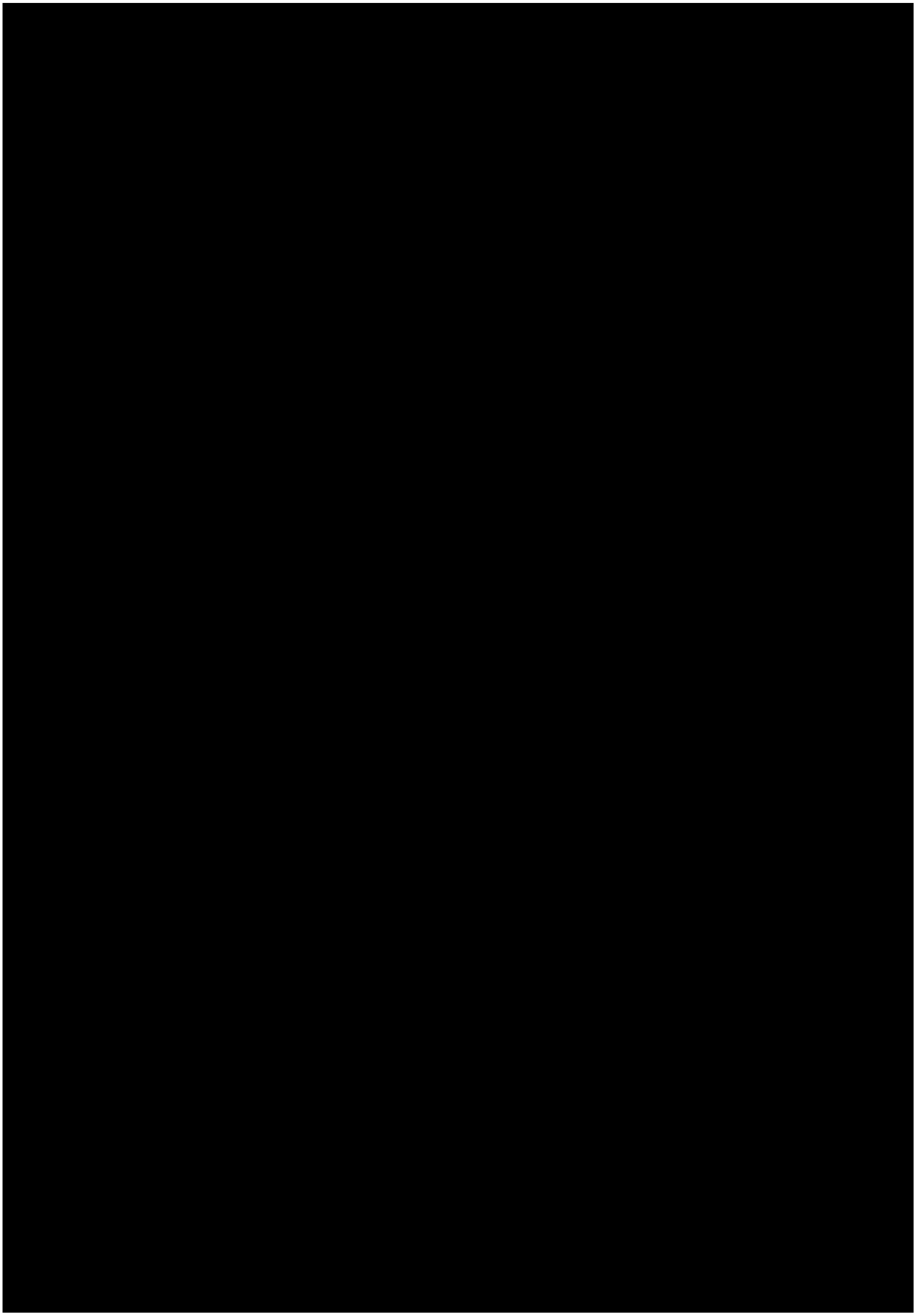
10.10 APPENDIX 10: ADDITIONAL APPENDICES

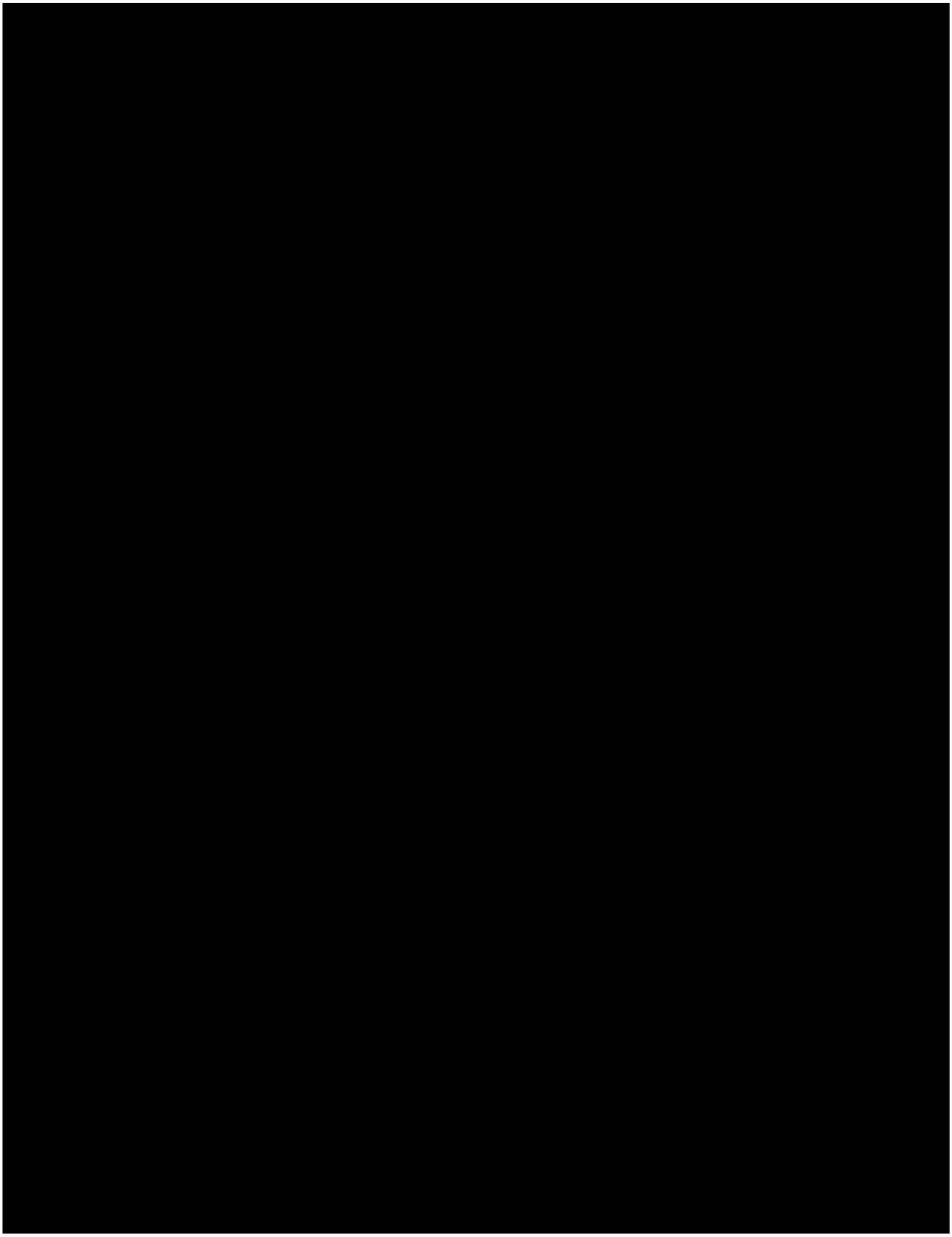
[redacted]

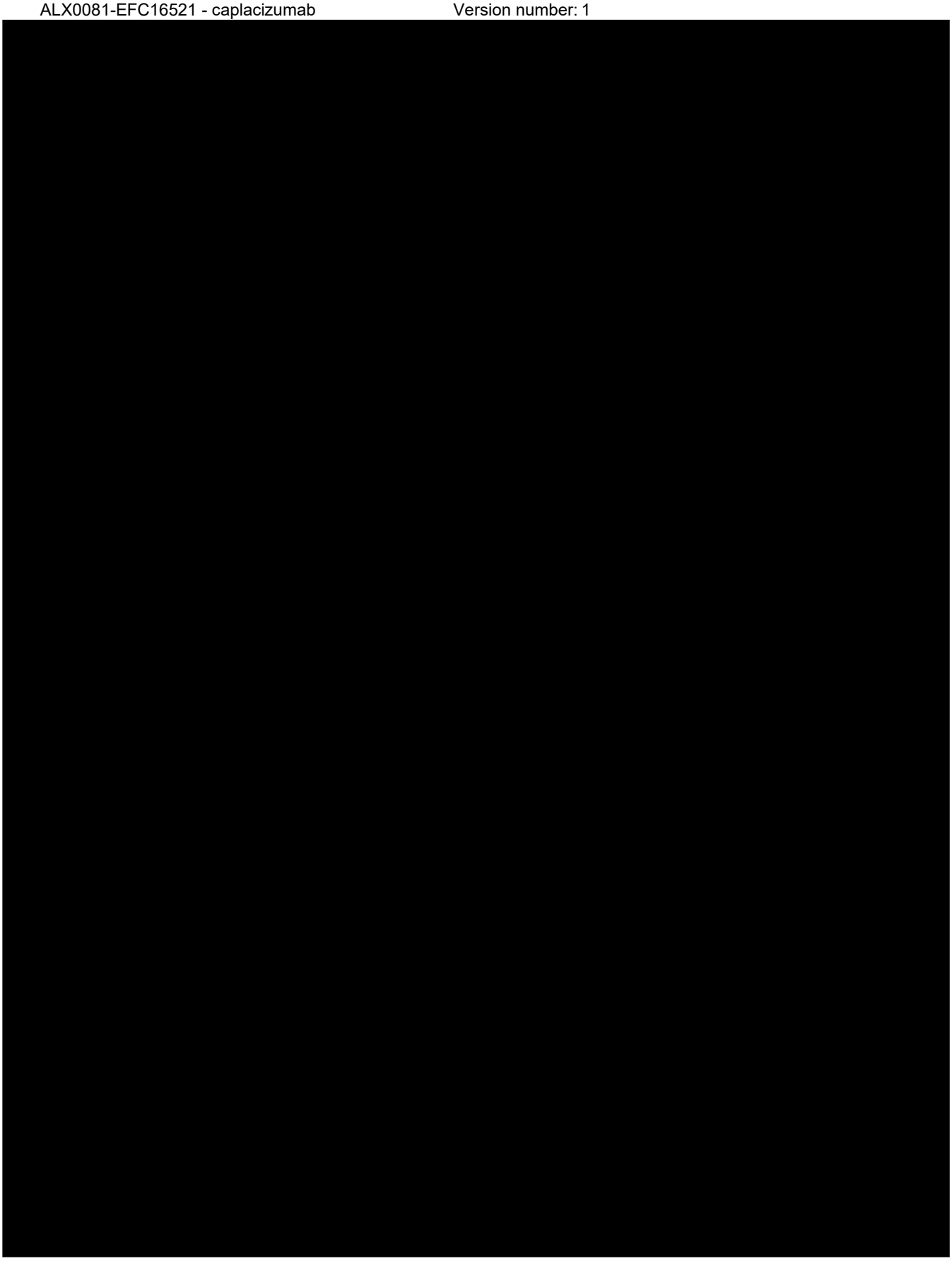


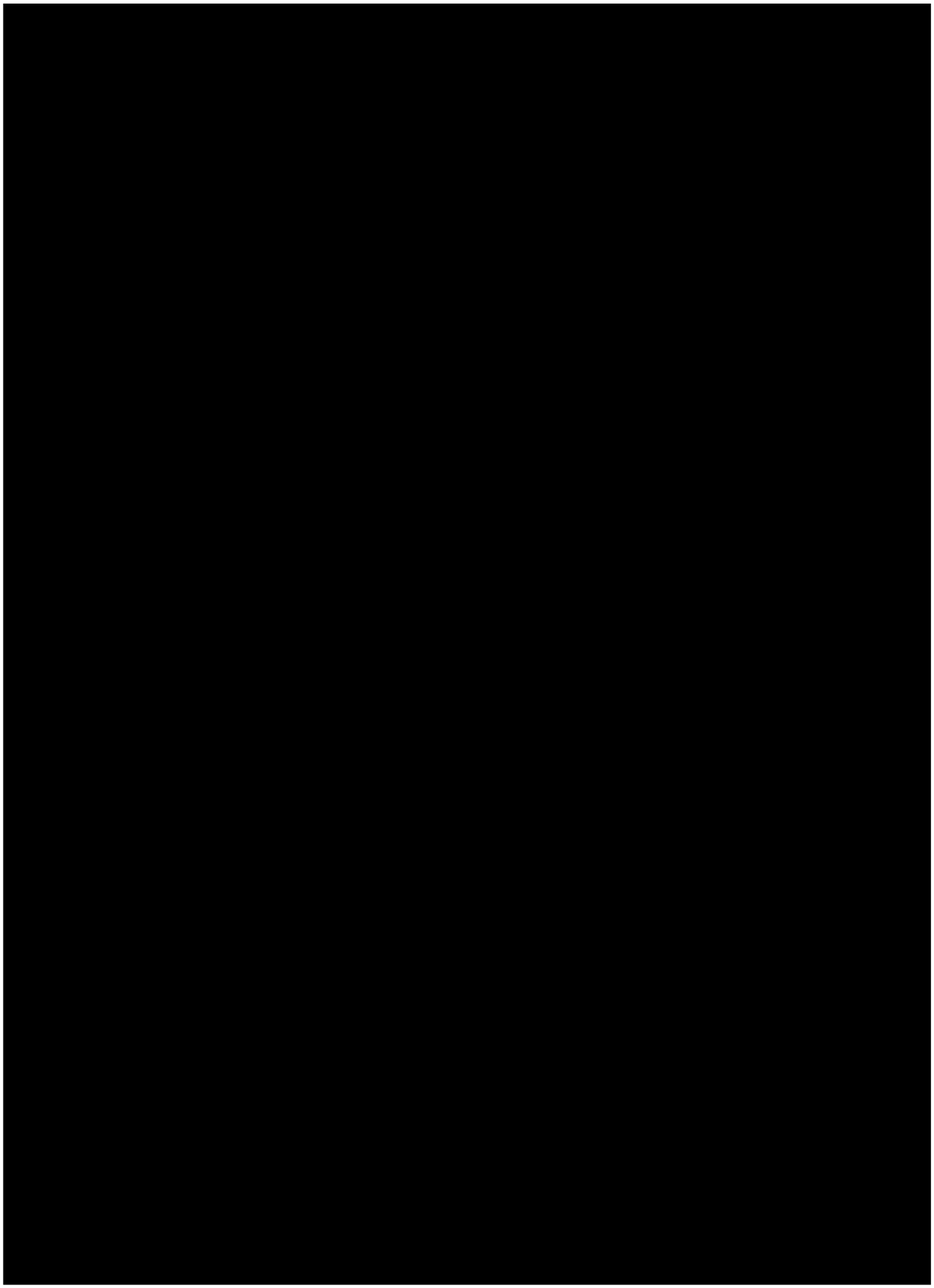


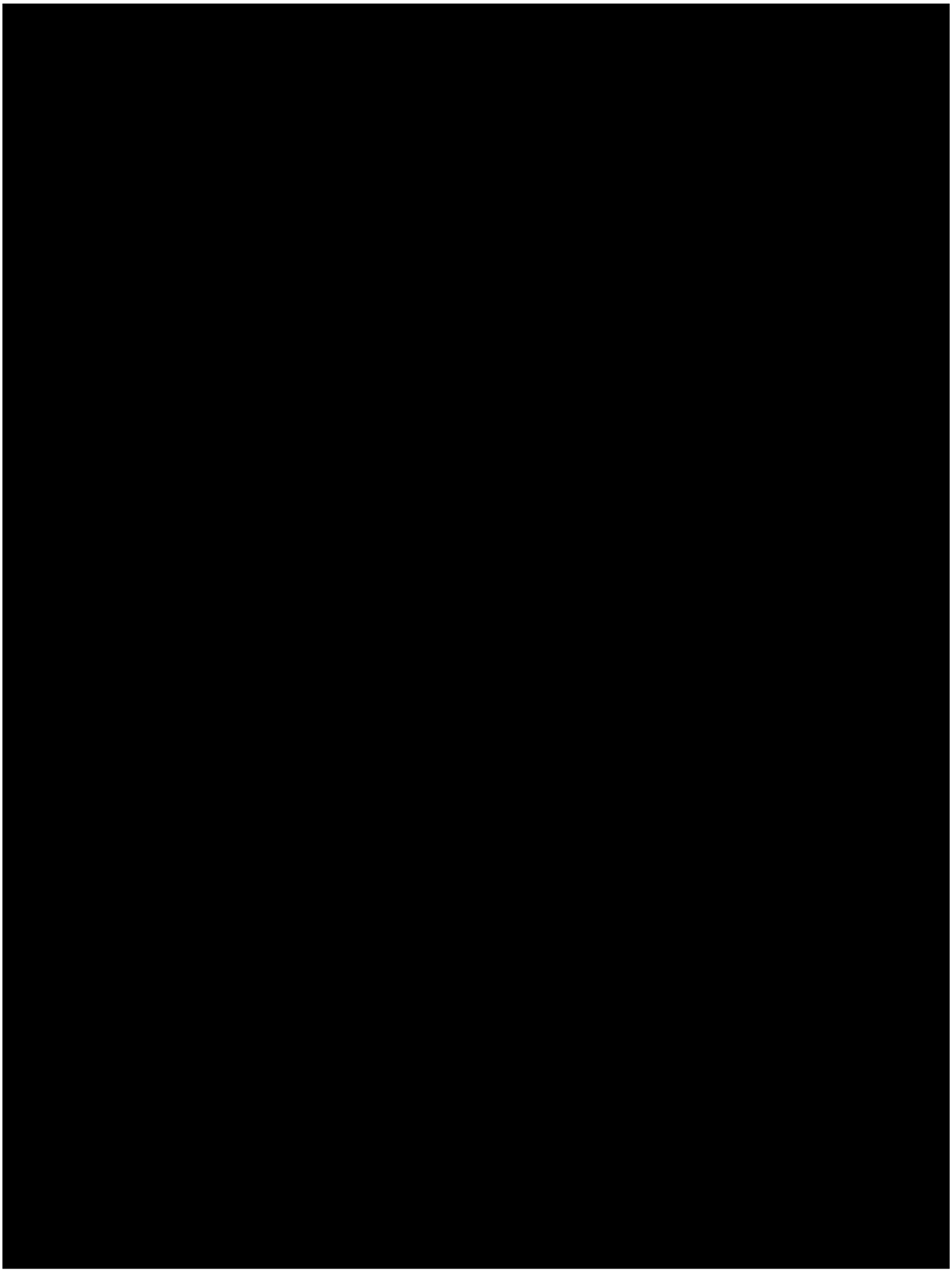


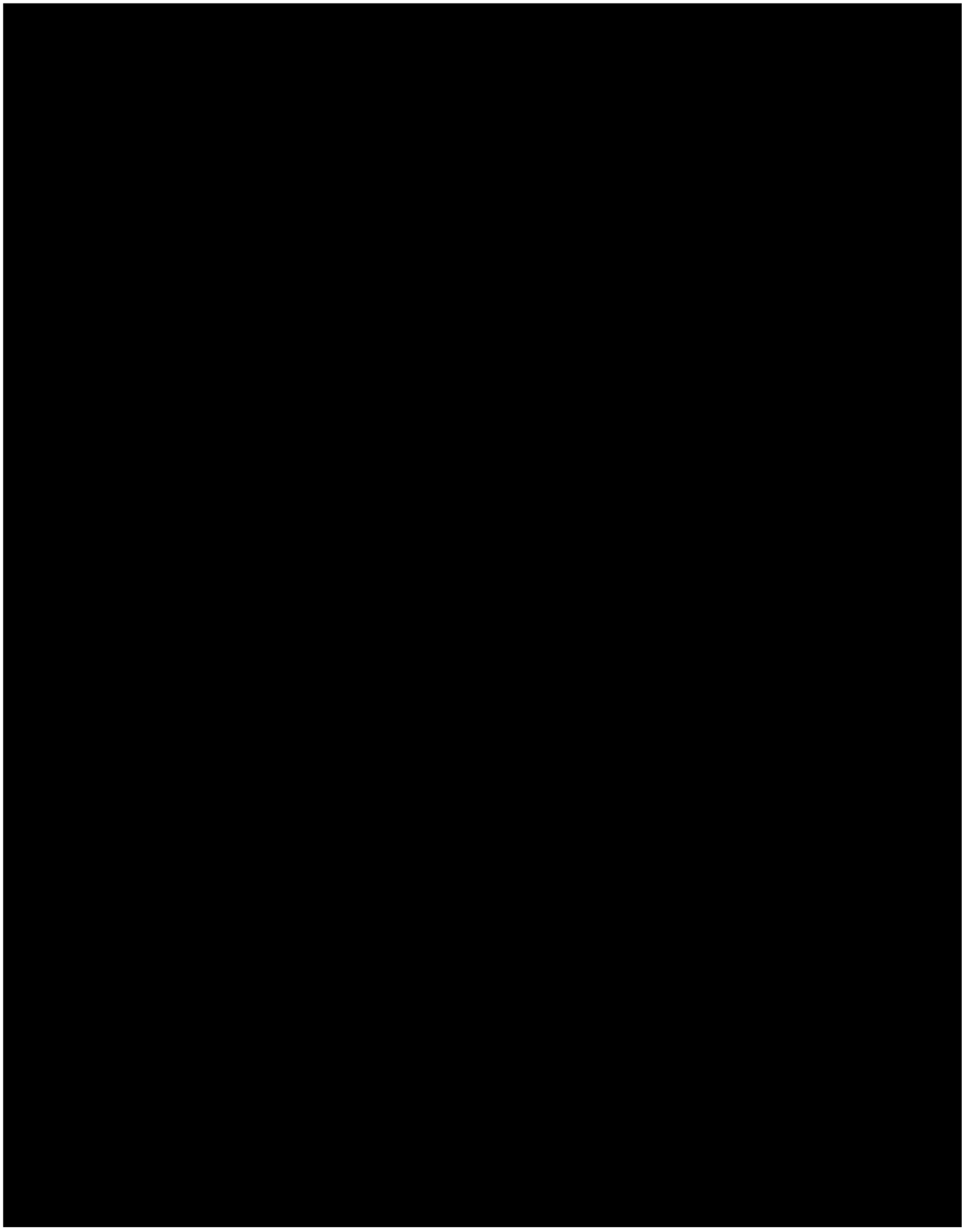












10.11 APPENDIX 11: ABBREVIATIONS

ADA: anti-drug antibody
ADAMTS13: a disintegrin and metalloproteinase with a thrombospondin type 1 motif13
ADE: adverse device effect
ADL: Activities of Daily Living
AE: adverse event
AESI: adverse event of special interest
aTTP: acquired thrombotic thrombocytopenic purpura
CI: confidence interval
[redacted]
COVID-19: coronavirus disease 2019
cTnI: cardiac troponin I
DMC: Data Monitoring Committee
ECG: electrocardiogram
eCRF: electronic case report form
EQ-5D-5L: 5-level EuroQol 5-dimensional questionnaire
GCS: Glasgow Coma Scale
HCRU: healthcare resource utilization
HUS: hemolytic uremic syndrome
ICF: Informed consent form
ICU: intensive care unit
IEC: Independent Ethics Committee
IMP: investigational medicinal product
IRB: Institutional Review Boards
IST: immunosuppressive therapy
ITT: intent-to-treat
iTTP: immune mediated thrombotic thrombocytopenic purpura
IV: intravenous
LDH: lactate dehydrogenase
LMWH: low molecular weight heparin
mITT: modified intent-to-treat
NIMP: noninvestigational medicinal product
PD: pharmacodynamics
PK: pharmacokinetics
PQAT: Patient's Qualitative Assessment of Treatment
SADE: serious adverse device effect
SAE: serious adverse event
SAP: statistical analysis plan
SC: subcutaneous
SD: standard deviation
SF-12: short form 12-item survey
SUSAR: suspected unexpected serious adverse reaction
TE: treatment-emergent
TMA: thrombotic microangiopathy

TPE: therapeutic plasma exchange
TTP: thrombotic thrombocytopenic purpura
ULN: upper limit of normal
ULvWF: ultra-large von Willebrand factor
USADE: unanticipated serious adverse device effect
vWF: von Willebrand factor
WOCBP: woman of childbearing potential

10.12 APPENDIX 12: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the table of contents (TOC).

10.12.1 Amended protocol 01 (02 May 2023)

This amended protocol (amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The rationale for this protocol amendment is to allow sites to select which troponin and COVID-19 tests to use during Screening, and permit participants who have already received a dose of marketed caplacizumab prior to ICF signing to enroll in the study.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
1.2 Schema	Schema updated	Update
1.3 Schedule of Activities (SoA)	Footnotes added or modified for COVID-19 tests, HBV, HCV and HIV serology tests, serum creatinine, 12-lead ECG, platelet count, blood smear, and troponin test.	Decrease participant's burden and permit some screening tests performed within a period of time prior to ICF signing to be used for Screening
	Screening header corrected: "Screening (Day -2 to Day 1)" and footnote added to explain that baseline may occur on the same day as screening.	Correction of error
	Footnote added or modified to not perform some assessments locally at D1 if done at Screening, within 3 to 4 hours of Day 1 but all must still be performed centrally.	Decrease participant's burden
	Footnote and specifics added for IMP administration to participants who received and tolerated a single dose of marketed caplacizumab IV for the presenting episode of iTTP within 4 hours prior to enrollment.	In many sites the standard of care is to administer the first dose of caplacziumab intravenously when iTTP is diagnosed clinically. This may occur before study enrollment. This SoC should not be withheld. These participants should still be permitted to enroll as long as the first dose for the presenting episode was given within 4 hours of ICF signing and is clearly documented in the eCRF.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	Footnote modified for [redacted]: they should be completed within 3 days of the baseline visit.	Update
	Footnote added for IMP diary: completion should begin after discharge, and paper diary can be used if eDiary is not available.	Clarification
	IMP/TPE administration deleted at 60H.	Correction of error
	"(+/- 3 days after last dose intake)" added to early treatment discontinuation visit column header.	Clarification
	"+/-2H" to "24H, 30H, 36H" and "+/-3H" to "48H, 60H" added to column headers.	Clarification
2. Introduction	Updated "European Commission" to "European Medicines Agency (EMA)"	Update
5.2 Exclusion criteria and throughout the document	Text updated to allow the use of cTnT, high sensitivity cTnT, or high sensitivity cTnI tests.	Update
	Defining severe cardiac disease as "per Investigator discretion" or troponin level ">5x ULN".	Troponin elevation is common in iTTP and minor elevations are not necessarily indicative of severe cardiac disease. The exclusion criterion has been modified to permit physician discretion and include a sample population more representative of the entire iTTP population.
6.4 Study intervention compliance	Updated	Update
8.1.5 Patient Reported Outcomes; 1.3 Schedule of activity (SoA)	Updated to reflect that caregiver is not allowed to complete the assessments alone.	Update
8.3.1 Time period and frequency for collecting AE and SAE information	Added collection of AEs from first caplacizumab administration to ICF signing.	Update
8.4 Pharmacokinetics	Added statement to use the left over samples for further research as described in Section 8.9	Update
8.7 Immunogenicity assessments	Added option of a functional neutralizing antibody assessment	Update
8.9 Use of biological samples and data for future research	Updated	Update
9.4 Sample size determination	Footnote added to Table 7	Update
10.1.4 Data protection	Wording updated	Update
10.1.6 Dissemination of clinical data and results	Replacement of "ClinicalTrialsRegister.eu" by "euclinicaltrials.eu". New standard texts added for results publication. Clarification of the wording.	Updated as per current template

Section # and Name	Description of Change	Brief Rationale
10.9 Appendix 9: Contingency measures for a regional or national emergency that is declared by a governmental agency	Updated	Contingency measures for COVID-19
10.12 Appendix 12: protocol amendment history	Section added	Update
Throughout the document	Added the following text for TPE initiation: “including during the first 24 hours”.	Clarification
	Added the following text for caplacizumab discontinuation rules: “or 12 weeks, whichever occurs first”.	Consistency throughout document
	Addition of SARS-CoV-2 antigen test for screening	Contingency measures for COVID-19
	Reformatting of existing content when necessary. Minor, editorial, stylistic changes as necessary. Updated table of contents, section numbers, references, abbreviations as necessary.	Update in accordance with Sponsor’s standards

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