STATISTICAL ANALYSIS PLAN

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**
Compound number (INN/Trademark):	**ALX0081** **Caplacizumab/Cablivi**
Study phase:	**Phase 3**
Short Title:	**Caplacizumab and immunosuppressive therapy without first-line therapeutic plasma exchange in adults with immune-mediated thrombotic thrombocytopenic purpura MAYARI**
Statistician:	[redacted] **(AIXIAL group)**
Statistical project leader:	[redacted]
Date of issue:	**07-Jun-2024**
Regulatory agency identifier number(s):	
IND:	107609
EudraCT/EU-trial number:	2022-001177-31
NCT:	NCT05468320
WHO:	U1111-1244-0426

Date: 07-Jun-2024 Total number of pages: 39

TABLE OF CONTENTS

LIST OF TABLES

VERSION HISTORY

This statistical analysis plan (SAP) for Study EFC16521 (MAYARI) is based on the amended protocol 01 dated 02 May 2023. There are no major changes to the statistical analysis features in this SAP.

The first participant was enrolled on 21 November 2022. This SAP is approved before the first interim analysis (IA) is conducted.

Major changes in the statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	07-Jun-2024	Included in the SAP, and not in the protocol are: definitions of the enrolled population, the FAS population, sensitivity analyses for efficacy endpoints and subgroup analyses for the primary endpoint	Original version

1 INTRODUCTION

1.1 STUDY DESIGN

This is an open-label, single-arm, Phase 3, multicenter study to evaluate the efficacy and safety of caplacizumab and immunosuppressive therapy (IST) without first-line therapeutic plasma exchange (TPE) in adults with immune-mediated thrombotic thrombocytopenic purpura (iTTP).

The anticipated study duration per participant, without a recurrence while on therapy, is a 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). All participants will receive open-label caplacizumab daily until sustained disintegrin and metalloproteinase with a thrombospondin type 1 motif13 (ADAMTS13) activity normalization (≥50%) is achieved at 2 consecutive visits, after platelet count normalization (defined as ≥150 × 10^9/L for 2 consecutive values) or 12 weeks of caplacizumab treatment, whichever occurs first.

For participants who experienced a first clinical recurrence (exacerbation or relapse) during the overall study period, the ongoing treatment plan may be adjusted including a start or re-start of TPE and adjustment of IST regimen and caplacizumab therapy. In case that caplacizumab treatment is maintained for a first clinical recurrence, the visit schedule will be the same as during the initial treatment period.

The primary analysis will be conducted after study completion of all participants, ie, when all the participants will have discontinued from the study.

In addition, an interim analysis (IA) will be conducted after the first 30 participants with baseline ADAMTS13 activity of <10% have completed the study (eg ended treatment period per protocol and completed the follow-up period of 12 weeks) (see Section 3.8 for further details). A Data Monitoring Committee (DMC), independent from the Sponsor, will be appointed to monitor the safety and the scientific integrity of this study on an on-going basis, and to provide in a timely fashion appropriate recommendations to the Sponsor.

1.2 OBJECTIVES AND ENDPOINTS

Table 1 - 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 thrombotic thrombocytopenic purpura (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%).
Other	[redacted]	

Objectives	Endpoints
[redacted]	

1.2.1 Estimands

Primary estimand defined for the primary endpoint is summarized in Table 2. More details are provided in Section 3.2.

Table 2 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Primary objective: 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)				
Primary endpoint (treatment policy estimand)	Remission	All enrolled participants who received at least 1 dose of IMP and with an ADAMTS13 activity <10% at baseline	Regardless of adherence to study intervention and/or study discontinuation	Proportion of participants achieving Remission without requiring TPE during the overall study period

2 ANALYSIS POPULATIONS

The following populations for analyses are defined.

Table 3 - Populations for analyses

Population	Description
Screened	All participants who sign the inform consent form (ICF).
Enrolled	All participants from the screened population who met the eligibility criteria (ie, who are not screen failures). Participants who received caplacizumab and did not meet inclusion or met exclusion criteria are not enrolled, such as a participant with a confirmed alternate diagnosis.
Full Analysis Set (FAS)	All enrolled participants, who received at least 1 dose of the investigational medicinal product (IMP, ie, *Caplacizumab)*. The FAS population will be used only for sensitivity analyses.
Modified ITT (mITT)	All enrolled participants who received at least 1 dose of IMP and with an evaluable primary endpoint. The mITT population will be the main efficacy analysis population. The primary endpoint is evaluable when the participant has an ADAMTS13 activity of <10% at baseline.
Safety	All enrolled participants who received 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 IMP will be considered as exposed and will be included in the safety population.

To note that amended protocol 01 permits participants who have already received a dose of marketed caplacizumab for the presenting episode of iTTP within 4 hours prior to enrollment/ICF signing to enroll in the study. Consequently, participants exposed to a single dose of marketed caplacizumab within 4 hours prior to enrollment will be included in any analysis population.

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

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

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

When the notion of IMP is mentioned in the SAP, this refers to the study IMP.

The baseline value is defined as the last available value before the first dose of IMP, including participants who have received a dose of marketed caplacizumab for the presenting episode of iTTP within 4 hours prior to enrollment. For participants enrolled but not treated with IMP, the baseline value is defined as the last available value before enrollment.

Efficacy endpoints derived from laboratory data (platelet count, lactate dehydrogenase [LDH], cardiac troponin I [cTnI], creatinine, ADAMTS13 activity) will be analyzed using central measurements, unless they are missing for a visit but the local value available, in which case the local value will be used under certain conditions (see Section 5.4). A central measurement will be considered missing if the recorded status is “NOT DONE” and there is a reason for this status or if status is “NOT PERFORMED”.

The observation period will be divided into 4 segments:

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

The **overall study period** is defined as the time from the first caplacizumab administration (whatever marketed or study IMP) until the end of the study.

3.2 PRIMARY ENDPOINT ANALYSIS

3.2.1 Definition of endpoint

The primary endpoint is the proportion of participants (responders) 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.

More details regarding the endpoint derivation are provided in Section 5.4.

3.2.2 Main analytical approach

Primary estimand analysis will use handling of intercurrent events (treatment policy strategy: based on all assessments irrespective of the IMP discontinuation).

The primary endpoint will be analyzed on the mITT population.

The main analysis approach for the primary efficacy endpoint will be to analyze the endpoint on the mITT population, ie, all enrolled participants who received at least 1 dose of IMP and with an ADAMTS13 activity of <10% at baseline.

Each participant will be classified as a responder or non-responder (see derivation in Section 5.4) per the response criteria for the endpoint, and the proportion of responders will be calculated together with a 95% Wilson CI.

3.2.3 Sensitivity analyses

As a sensitivity analysis, the primary endpoint will be analyzed on the FAS population ie, all enrolled participants who received at least 1 dose of the IMP.

3.3 SECONDARY ENDPOINTS ANALYSIS

Secondary **efficacy** endpoints analyses are defined in this section.

Secondary **safety** endpoints analyses are defined in Section 3.6.2 (AE, serious AE [SAE], AE of special interest [AESI]) and Section 3.6.3 (clinical safety laboratory variables, vital signs, and electrocardiogram [ECG]).

The main analysis approach for the secondary efficacy endpoints will be to analyze the endpoints on the mITT population, ie, all enrolled participants who received at least 1 dose of IMP and with an ADAMTS13 activity of <10% at baseline.

Secondary endpoints listed below will be analyzed using the count and percentage of participants. Two-sided 95% 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 iTTP-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.

For the following time to event endpoint, median time to event (with 2-sided 95% CI) as well as Q1 and Q3 will be estimated using Kaplan-Meier estimates, and survival curve provided.

- Time to platelet count response, defined as time from start of treatment to initial platelet count $\geq 150 \times 10^9$/L that is sustained for ≥2 days.

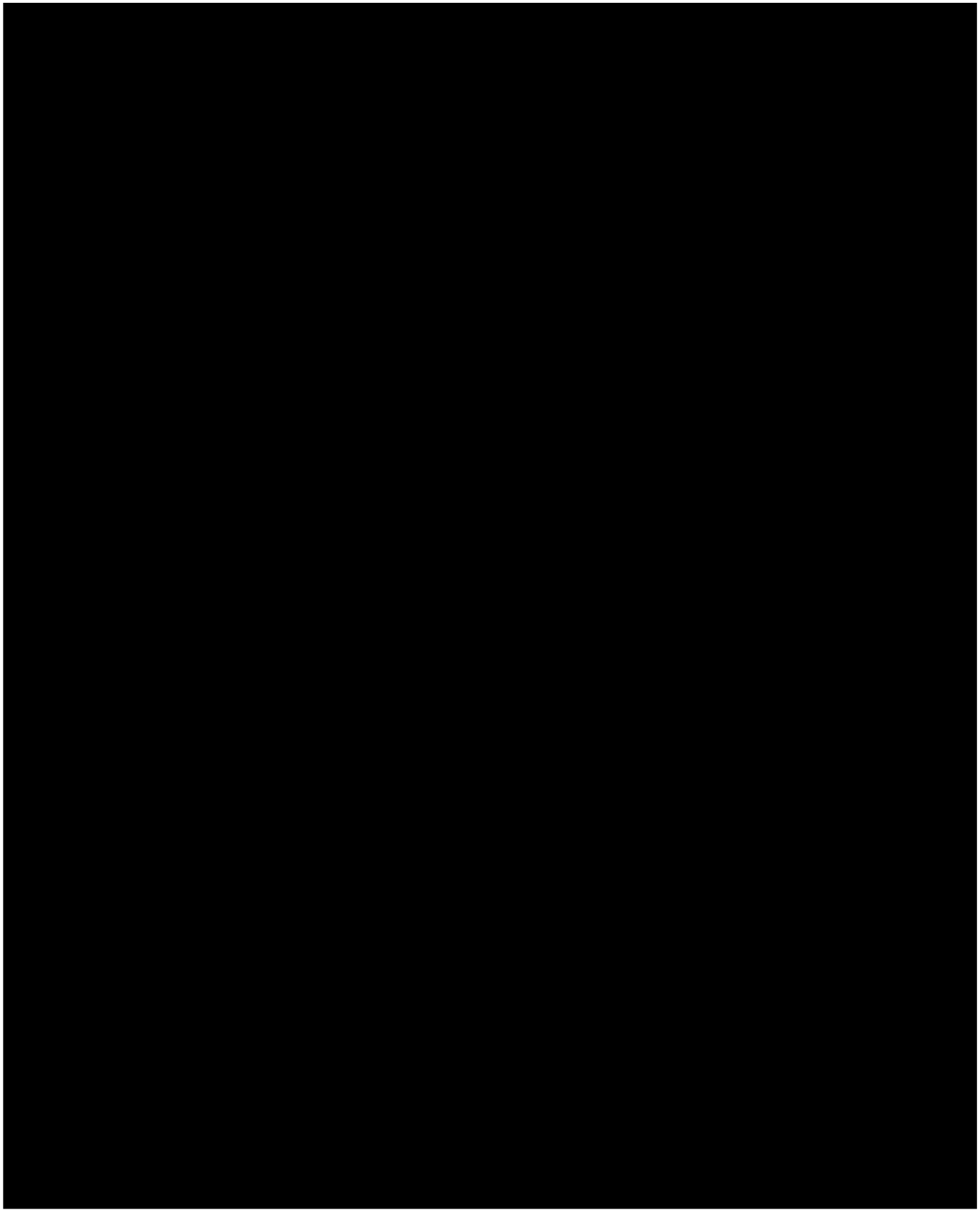
The percentage of event at the following timepoints during the on-treatment period, will be also provided: Day 1, Day 2, Day 3, Day 4, Day 5, Week 1, Week 2, Week 3, Week 4, Week 8, and Week 12.

More details regarding the definition and derivation of these endpoints are provided in Section 5.4.

3.3.1 Sensitivity analysis for secondary endpoints

As a sensitivity analysis, the secondary efficacy endpoints will be analyzed on the FAS population ie, all enrolled participants who received at least 1 dose of the IMP.

3.4 OTHER ENDPOINTS ANALYSIS



[redacted]

3.5 MULTIPLICITY ISSUES

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

3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety population as defined in Section 2, unless otherwise specified.

3.6.1 Extent of exposure and compliance

The extent of study IMP exposure will be assessed by the duration of IMP exposure, and the overall exposure for caplacizumab treatment will be presented as described below. All information will be summarized within the safety population.

Duration of IMP exposure

Duration of IMP exposure (in days) is defined by date of the last administration of caplacizumab – date of first administration of caplacizumab (whether marketed or study caplacizumab) + 1 day, regardless of unplanned intermittent discontinuations.

The duration of IMP exposure will be calculated from the maximum date reported among ***Treatment Status*** form, ***IMP administration on Site*** form, ***Exposure (eDiary)*** form, and ***Exposure (paper IMP diary)*** form.

For DMC review specifically, the duration of IMP exposure will be the minimal duration of IMP exposure.

Duration of IMP exposure will be summarized quantitatively.

3.6.1.1 Overall exposure

The number of treated participants and actual and cumulative dose for caplacizumab will be presented. Caplacizumab exposure data will be presented on-site and off-site separately.

The dose information administered on-site will be assessed using the following variables:

- intended daily dose (mg)
- actual total daily dose (mg)
- cumulative dose (mg)

- route
- reason in case of partial volume injected
- reason for not taken

The dose information administered off-site will be assessed using e-diary information with the help of the following variables:

- part of abdomen injected
- person in charge of the administration
- reason for the non-administration if any
- if there were partial administration and the reason if any

In addition, the number of participants who started with marketed caplacizumab will be presented, as well as the number of participants who re-initiated the treatment.

3.6.1.2 Compliance

The compliance to IMP administration is calculated as (the number of IMP administrations received divided by the number of IMP administrations planned) *100, and will be summarized within the safety population.

3.6.2 Adverse events

General common rules for adverse events

All AEs will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently 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.
- Treatment-emergent adverse events (TEAEs): AEs that developed, worsened, or became serious during the TE period.
- Post-treatment AEs: AEs that developed, worsened, or became serious during the post-treatment period.

Similarly, the deaths will be analyzed in the pre-treatment, TE, and post-treatment periods.

The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP, ie, to caplacizumab.

If the severity is missing for 1 of the TE occurrences of an AE, the severity will be imputed with the maximal severity of the other occurrences. If the severity is missing for all the occurrences, the severity will be left as missing.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase.

The AE tables will be sorted as indicated in Table 4.

Table 4 - Sorting of AE tables

AE presentation	Sorting rules
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]

a Sorting will be based on the overall incidence.
b The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any TE SAE
- Any TEAE leading to death
- Any TEAE leading to permanent discontinuation of caplacizumab
- Any TEAE leading to caplacizumab interruption
- Any AESI
- Any AESI related to IMP
- Any TEAE related to IMP
- Any SAE related to IMP
- Any severe TEAEs
- Any severe TEAEs related to IMP
- Any bleeding event, based on the Standardized MedDRA Query (SMQ) ‘Haemorrhage terms (excluding laboratory terms)’
- Any hypersensitivity reaction, based on the SMQs 'Hypersensitivity' [Narrow], 'Anaphylactic reaction' [Narrow], and 'Angioedema' [Narrow]

The AE summaries of Table 5 will be generated with number (%) of participants experiencing at least one event.

Table 5 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC and PT
Common TEAE (with incidence PT rate ≥5%)	Primary SOC and PT
TEAE related to IMP (caplacizumab) as per Investigator's judgment	Primary SOC and PT
TEAE related to Corticosteroids as per Investigator's judgment	Primary SOC and PT
TEAE related to Rituximab or Biosimilar therapy as per Investigator's judgment	Primary SOC and PT
TEAE related to TPE as per Investigator's judgment	Primary SOC and PT
TEAE by maximal intensity	Primary SOC and PT
Treatment-emergent SAE	Primary SOC and PT
Treatment-emergent SAE related to IMP (caplacizumab) as per Investigator's judgment	Primary SOC and PT
Treatment-emergent SAE related to Corticosteroids as per Investigator's judgment	Primary SOC and PT
Treatment-emergent SAE related to Rituximab or Biosimilar therapy as per Investigator's judgment	Primary SOC and PT
TEAE leading to permanent discontinuation of IMP (caplacizumab)	Primary SOC and PT
Treatment-emergent Bleeding event	Primary SOC and PT
Treatment-emergent Hypersensitivity reaction	Primary SOC and PT
Pretreatment AE	Overview[a] Primary SOC and PT
Post-treatment AE	Overview[a] Primary SOC and PT
Post-treatment SAE	Primary SOC and PT

a Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent discontinuation of IMP (caplacizumab)

Analysis of deaths

In addition to the analyses of deaths included in Table 5, the number (%) of participants in the following categories will be provided:

- Deaths during the TE and post-treatment periods by reason for death (primary cause, and secondary cause if any)
- Deaths in enrolled participants but not treated participants, if any

Analysis of adverse events of special interest (AESIs)

AESIs will be selected from the electronic case report form (e-CRF) specific tick box on the AE page and will include:

- 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.
- Symptomatic overdose (serious or nonserious) with IMP
- Increase in alanine transaminase (ALT) >3 × ULN
- All major bleeding events, including bleeding into a critical organ, life threatening or fatal bleeding.

Number (%) of participants experiencing at least 1 event as well as the number of events by SOC and PT will be provided for each event of interest. Tables will be sorted as indicated in Table 4.

Analysis of Bleeding Events

Treatment-emergent bleeding events, based on SMQ 'Haemorrhage terms (excluding laboratory terms)', will be summarized by SOC and PT.

Number (%) of participants experiencing at least 1 event as well as the number of events by SOC and PT will be provided for each event of interest. Tables will be sorted as indicated in Table 4.

Analysis of Hypersensitivity Reaction events

Treatment-emergent hypersensitivity reaction events, based on SMQs 'Hypersensitivity' [Narrow], 'Anaphylactic reaction' [Narrow], and 'Angioedema' [Narrow], will be summarized by SOC and PT.

Number (%) of participants experiencing at least 1 event as well as the number of events by SOC and PT will be provided for each event of interest. Tables will be sorted as indicated in Table 4.

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs, and electrocardiograms

The following laboratory variables, vital signs, and ECG variables will be analyzed on the safety population. They will be converted into standard international units.

- Blood smear
- Hematology:
  - Platelet count, 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 cells (WBC) count with differential: neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Coagulation parameters
  - prothrombin time, activated partial thromboplastin time (aPTT)
- Clinical chemistry:
  - blood urea nitrogen (BUN), creatinine, glucose, chloride, potassium, sodium, calcium, aspartate aminotransferase (AST), ALT, alkaline phosphatase, total and direct bilirubin, total protein
- Vital signs: weight, body surface area (BSA), body mass index (BMI), heart rate, systolic and diastolic blood pressure, respiratory rate, temperature (oral or tympanic).
- ECG variables: Investigator's interpretation of the ECG performed in supine position.

- Other screening tests
  - Coronavirus disease 2019 (COVID-19) test: SARS-CoV-2 RT-PCR or antigen test
  - Serology: human immunodeficiency virus (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 (cTnl), LDH
- ADAMTS13: ADAMTS13 activity and anti-ADAMTS13 antibody

If any, data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification (ULOQ) will be replaced by ULOQ value.

Quantitative analyses

For all laboratory variables and vital signs variables above, descriptive statistics for results and changes from baseline will be provided by scheduled timepoint.

These analyses will be performed using both local and central measurements separately when both are available, otherwise using either local or central measurements when only one measurement has been performed.

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range.

For laboratory parameters, local laboratory normal ranges (LLN, ULN) will be used with the local assessments, and central normal ranges with the central laboratory assessments.

Analyses according to PCSA will be performed based on the worst value, from the first study IMP to last IMP + 28 days, using all measurements (either local or central, either scheduled, non-scheduled or repeated).

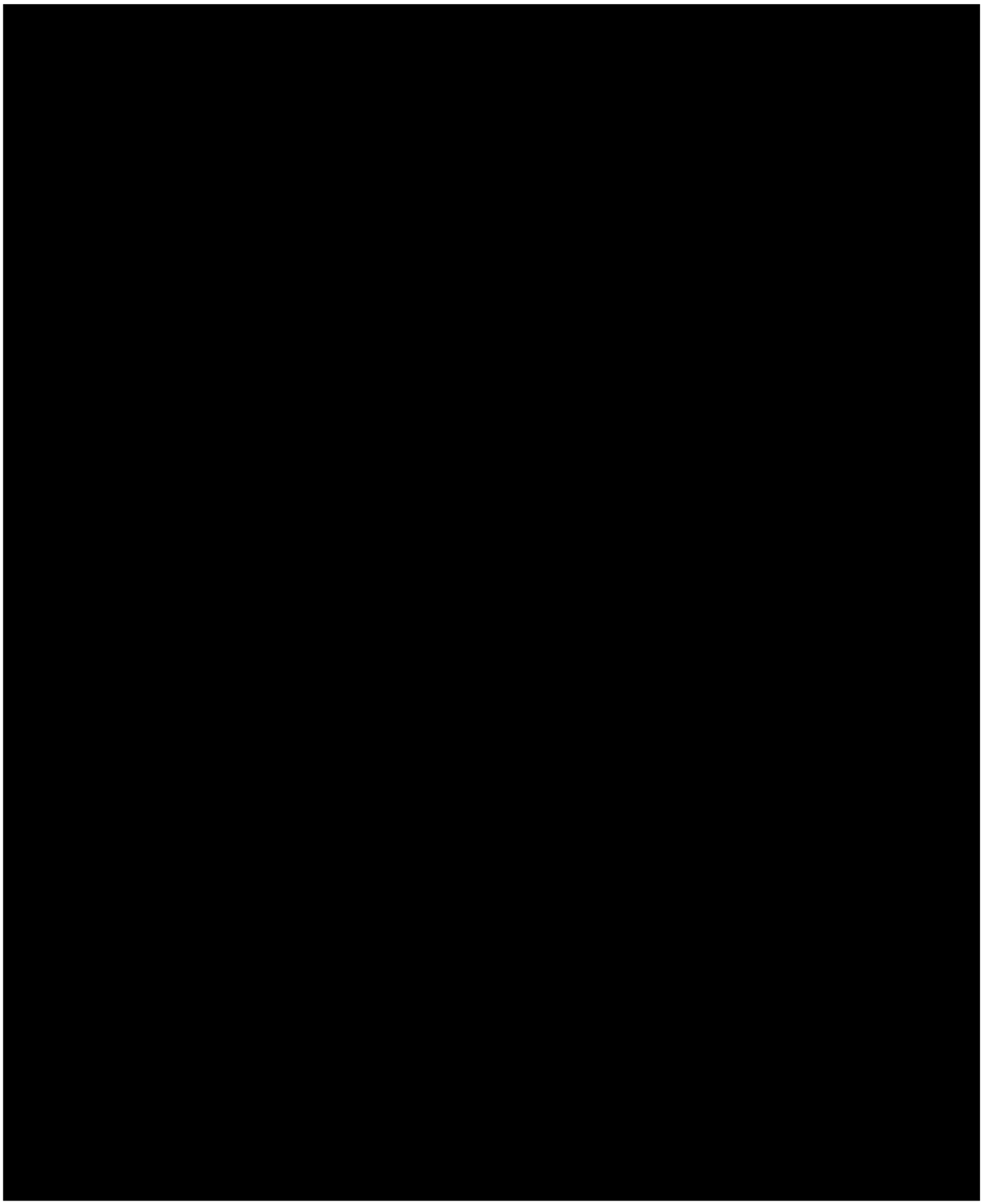
For laboratory variables and vital signs variables above, the incidence of participants with at least one PCSA, will be summarized regardless of the baseline level and according to the following baseline status categories:

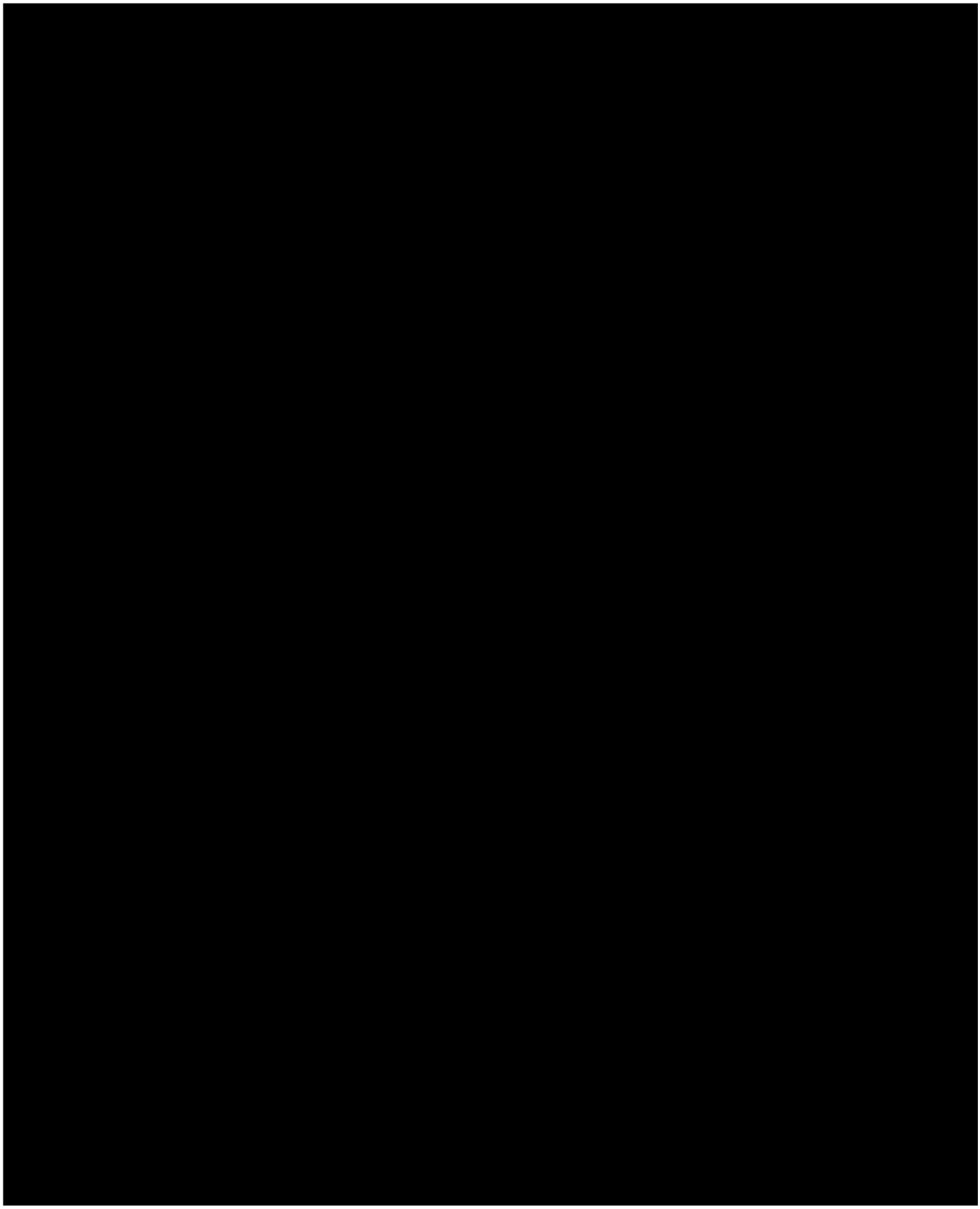
- Normal/missing
- Abnormal according to PCSA criterion or criteria

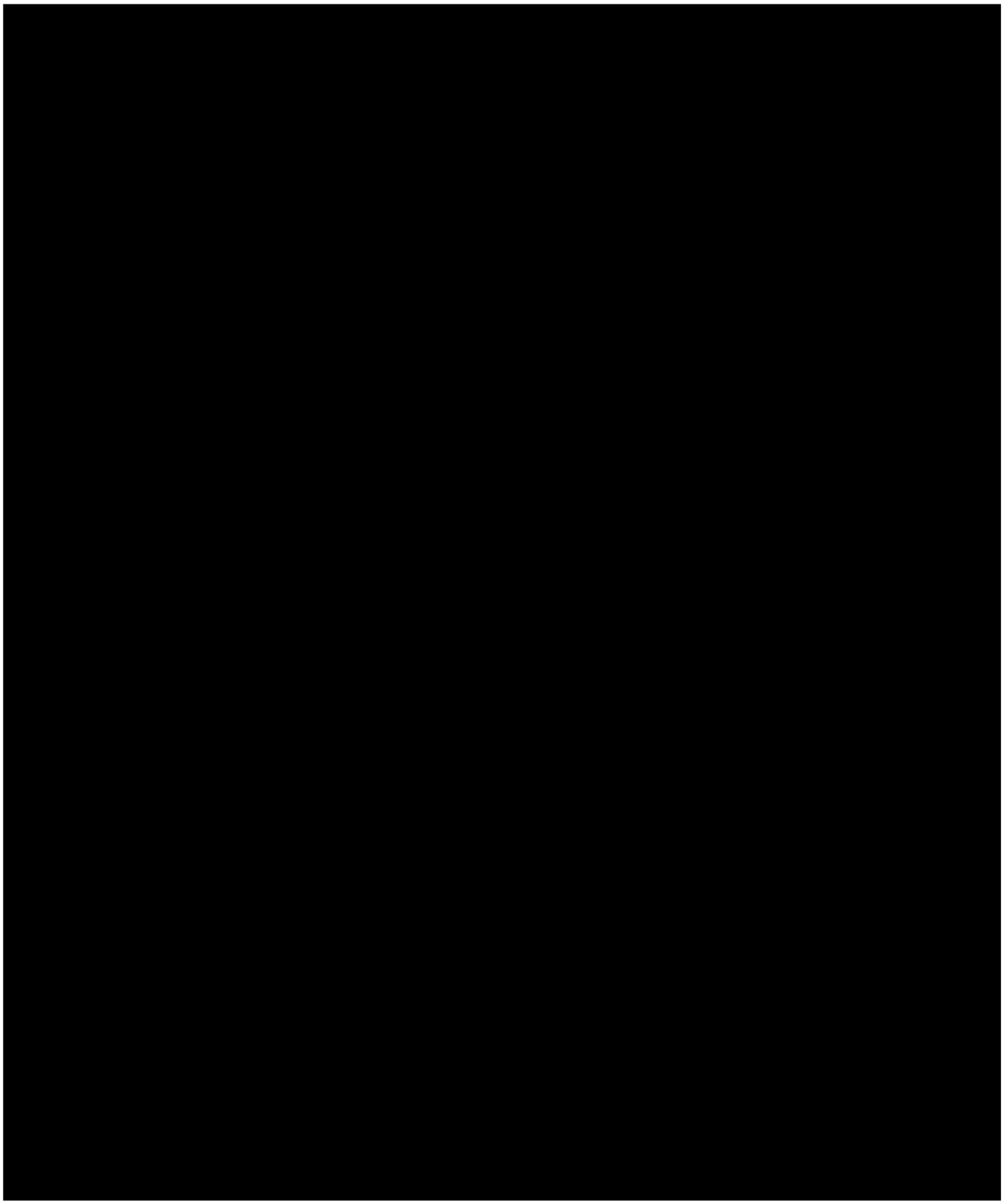
For ECG, the incidence of participants with at least one abnormal ECG, from the first study IMP to last IMP + 28 days, will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing
- Abnormal

3.7 OTHER ANALYSES







Participants **who received TPE** will be classified as follows based on the ADA assay results:

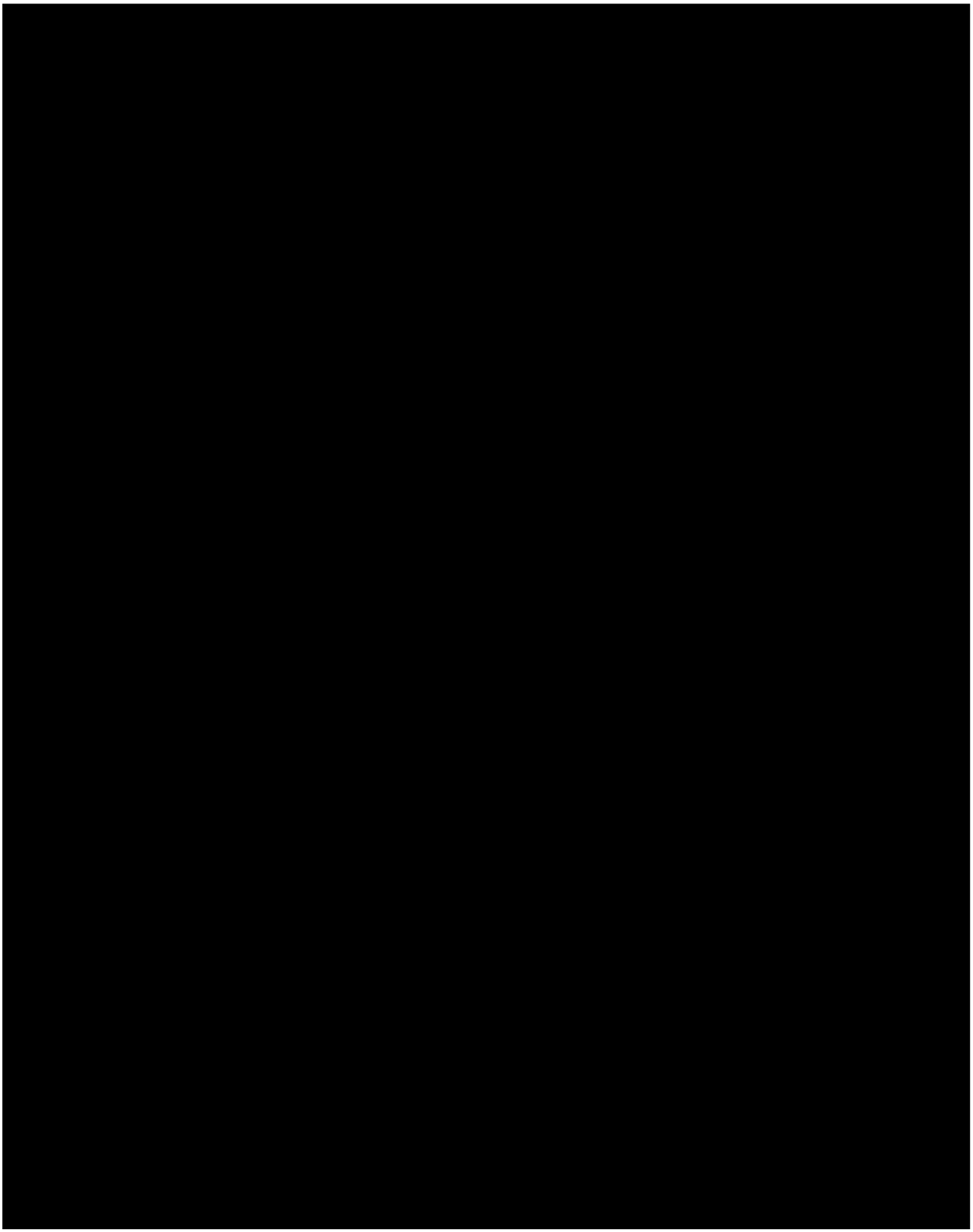
- ADA negative: no positive ADA samples at any of the sampling timepoints.
- ADA positive: positive ADA samples at one or more sampling timepoints.
- Inconclusive: no positive ADA samples and drug/target is present at levels higher than the drug/target tolerance characteristics of the assay. Drug tolerance limit is 5µg/mL and the target tolerance limit is 10µg/mL (at screening level).
- Missing: will be used if the outcome for relevant samples is missing and no clear statement can be made.

Participants **without TPE** will be classified as follows based on the ADA assay results and will not be further analyzed in the mADA assay:

- Pre-Ab negative – Drug-induced TE ADA negative: no positive ADA samples at any of the sampling timepoints.
- Pre-Ab positive – Drug-induced TE ADA negative: No significant titer increase post-dose.
- If a positive pre-dose titer is reported, the titer is considered to be significantly increased post-dose, if the highest post-dose titer compared to the pre-dose titer is higher than the minimum significant ratio (MSR) value ie, the increase of the $\log_{10}$ (titer) post versus pre-dose should be $>\log_{10}$ (MSR).
- Pre-Ab negative – Drug-induced TE ADA positive: positive ADA samples at one or more post-dose sampling timepoints.
- Pre-Ab positive – Drug-induced TE ADA positive: Significant increase in titer post-dose.
- If a positive pre-dose titer is reported, the titer is considered to be significantly increased post-dose, if the highest post-dose titer compared to the pre-dose titer is higher than the minimum significant ratio (MSR) value ie, the increase of the $\log_{10}$ (titer) post versus pre-dose should be $>\log_{10}$ (MSR).
- Inconclusive: no positive ADA samples and drug/target is present at levels higher than the drug/target tolerance characteristics of the assay. Drug tolerance limit is 5µg/mL and the target tolerance limit is 10µg/mL (at screening level).
- Missing: will be used if the outcome for relevant samples is missing and no clear statement can be made.

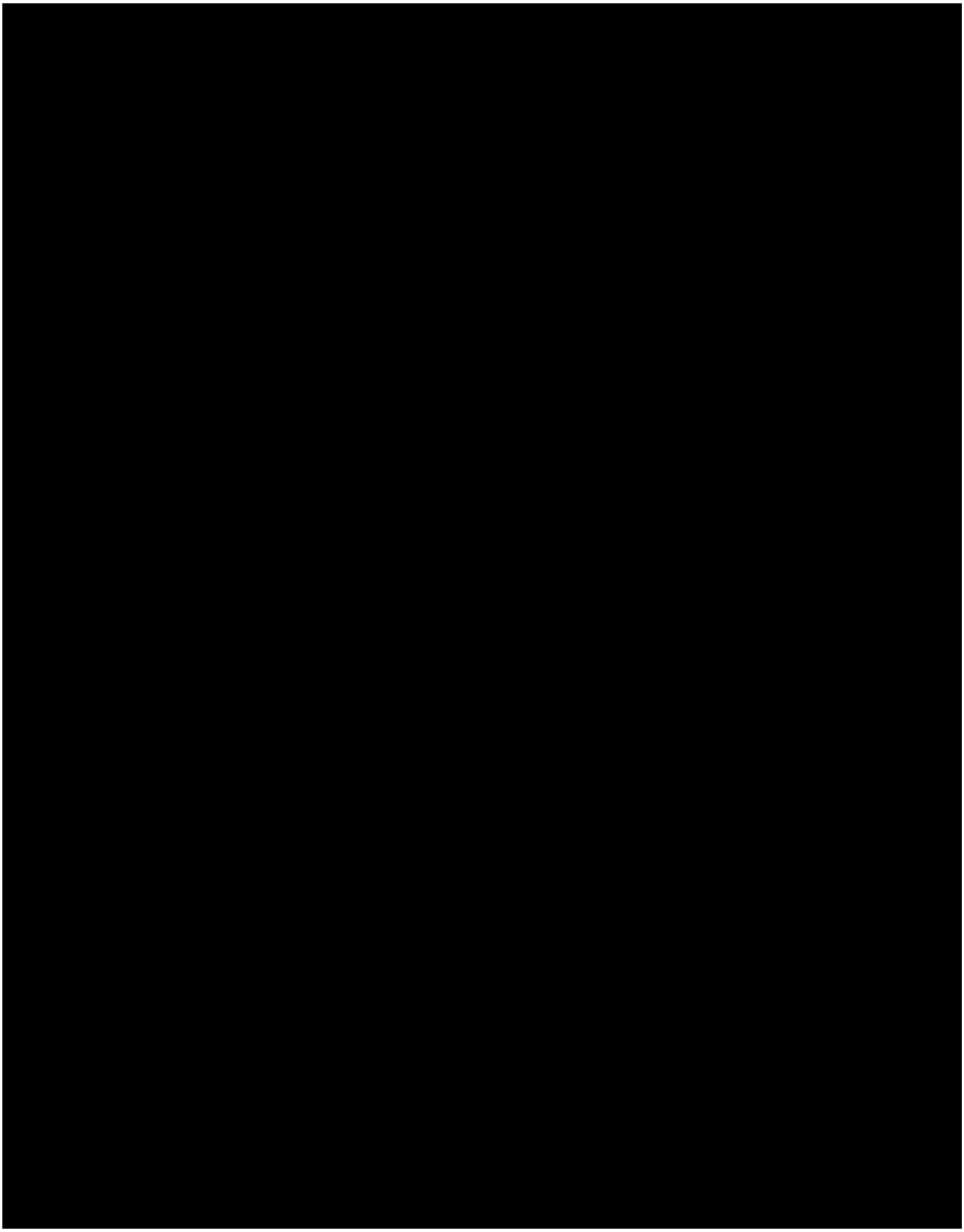
mADA

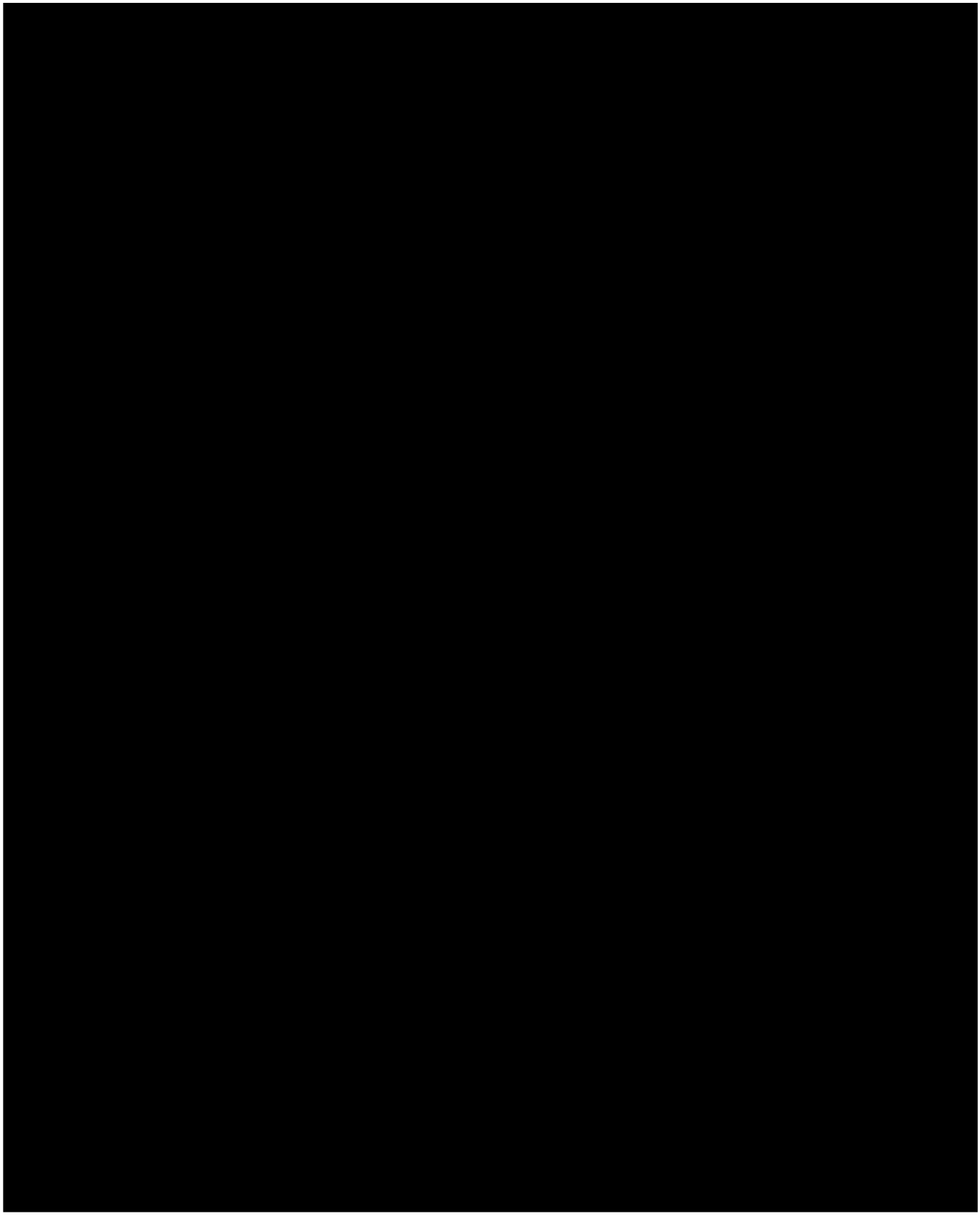
All positive ADA samples **from participants who received TPE** will be further evaluated using the mADA assay. This method employs a modified caplacizumab molecule as detection reagent in the bridging format, ie, caplacizumab-Ala variant. The modification constitutes of a single alanine extension at the C-terminus of caplacizumab. The mADA assay allows detection of drug-induced treatment-emergent (TE) ADA, whereas pre-Ab directed against the C-terminus of the compound is not detected. In other words, drug-induced TE ADA will score positive in the mADA assay. Only TE ADA responses with a restricted repertoire, directed against the C-terminal part of the Nanobody (ie, C-terminal part of the last Nanobody domain), which might be shielded by the presence of the additional alanine on the detector reagent might be left undetected using this mADA assay. All samples confirmed positive in the mADA assay will be titrated and reported as a $\log_{10}$ (titer). Samples scoring negative in the mADA assay are not titrated and the respective



No records will be reported for samples not evaluated in the mADA assay.

[redacted]





3.8 INTERIM ANALYSES

An interim analysis will be performed after the first 30 participants with baseline ADAMTS13 activity of <10% have completed treatment period per protocol and 12 weeks of follow-up. The participants who have completed the study at the time of IA will be included in the interim analysis.

The IA will provide a preliminary assessment of the efficacy and safety of Caplacizumab and immunosuppression without first-line TPE in adults with iTTP. The study will continue enrollment through this IA and the interim results should not alter the study conduct, ie, there is not a plan for early termination of the study based on this IA.

In addition, a DMC will be appointed to monitor the safety of the patients enrolled in the study on an ongoing basis in order to provide timely recommendations to the Sponsor. The purpose of this is to ensure the clinical data integrity and the appropriate final interpretation of the study results. At each DMC meeting during the conduct of the trial (approximately every 6 months), the DMC makes a recommendation to the Sponsor to continue the trial as planned, or with an amendment, or to terminate the trial. Further details regarding the DMC are included in the DMC charter.

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 of <10% at baseline is available for analysis of the primary endpoint (mITT analysis).

With the sample size of 55 participants, 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%.

Table 6 - 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% Confidence Interval of responder rate*
65% or below	At most 52%
70%	58%
75%	64%
80%	68%
85% or greater	At least 74%

* In post-hoc analysis of HERCULES, the upper confidence limit of remission rate for the placebo arm (placebo + IST + TPE) was 54%. HERCULES (ALX0681-C301) was a Phase III, randomized, double-blind, placebo-controlled, study to evaluate the efficacy and safety of caplacizumab when administered in addition to standard of care treatment in subjects with an acute episode of acquired TTP.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

[redacted]

ADAMTS13:	disintegrin and metalloproteinase with a thrombospondin type 1 motif13
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine transaminase
aPTT:	activated partial thromboplastin time
AST:	aspartate aminotransferase
ATC:	anatomical therapeutic chemical
BMI:	body mass index
BSA:	body surface area
BUN:	blood urea nitrogen
CDR:	complementary determining region
CI:	confidence interval
COVID:	coronavirus disease
cTnl:	cardiac troponin I
DMC:	data monitoring committee
ECG:	electrocardiogram
e-CRF:	electronic case report form

[redacted]

FAS:	full analysis set
FU:	follow-up
HBsAg:	hepatitis B surface antigen
hCG:	human chorionic gonadotropin

[redacted]

HIV:	human immunodeficiency virus
HLGT:	high-level group term
HLT:	high level term
IA:	interim analysis
ICF:	inform consent form
ICU:	intensive care unit
IMP:	investigational medicinal product
IST:	immunosuppressive therapy
iTTP:	immune mediated thrombotic thrombocytopenic purpura
LDH:	lactate dehydrogenase
LLN:	lower limit of normal
LLOQ:	lower limit of quantitation/detection limit
LLT:	lower-level term
mADA:	modified anti-drug antibody
MCH:	mean corpuscular hemoglobin
MCHC:	mean corpuscular hemoglobin concentration

MCS: mental component summary
MCV: mean corpuscular volume
MedDRA: medical dictionary for regulatory activities
mITT: modified ITT
MRD: minimal required dilution
MSR: minimum significant ratio
NAb: alternative neutralizing antibody
[redacted]
PCS: physical component summary
PCSA: potentially clinically significant abnormality
PD: pharmacodynamic
PK: pharmacokinetic
PQAT: patient's qualitative assessment of treatment
pre-Ab: pre-existing antibody
PT: preferred term
Q1: first interquartile range 1
Q3: third interquartile range
RBC: red blood cell
RICO: ristocetin cofactor
SAE: serious adverse event
SAP: statistical analysis plan
SD: standard deviation
SF-12: short form 12-item survey
SMQ: standardized MedDRA query
SOC: system organ class
TCP: titration cut-point
TE: treatment-emergent
TEAE: treatment-emergent adverse event
TPE: therapeutic plasma exchange
TTP: thrombotic thrombocytopenic purpura
ULN: upper limit of normal
ULOQ: upper limit of quantitation/detection limit
WBC: white blood cells
WHO-DD: world health organization-drug dictionary

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently enrolled. The number (%) of screen failures and reasons for screen failures (ie, eligibility criteria not met) will be provided on the screened population (participants who did the screening visit).

The number (%) of participants in the following categories will be provided:

- Enrolled participants
- Enrolled but not exposed participants
- Enrolled and exposed participants
- Participants who completed the study treatment period as per protocol
- Participants who did not complete the study treatment period as per protocol and main reason for premature end of treatment
- Participants who completed the study as per protocol (*Completion of End of Study/Follow-up* form: "Did the subject complete the study?" equal to Yes)
- Participants who did not complete the overall study period as per protocol and main reason for premature end of study

In addition, the number (%) of participants screened-failed, enrolled, with premature end of treatment and with early study discontinuation will be provided by country and site.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized on the enrolled population.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

Demographics, baseline characteristics, medical surgical history

The following demographics and baseline characteristics, and medical and surgical history will be summarized using descriptive statistics on the mITT and FAS populations.

Demographic and baseline characteristics:

- age at screening visit in years as quantitative variable and in classes (<65, ≥65 years, and (<75, ≥75 years)
- gender (Male, Female)
- race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Unknown)
- ethnicity (Hispanic or Latino, not Hispanic or Latino, Not Reported, Unknown)

Baseline (see definition in Section 3.1) safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Medical (or surgical) history includes general medical history and iTTP-specific medical history. Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock.

iTTP-specific medical history includes the description of the previous episodes (initial and recurrent), the number of previous episodes, time since iTTP diagnosis defined by date of

iTTP-specific medical history – date of iTTP diagnosis + 1 day (in year) and if the participant was previously exposed to caplacizumab. This includes also the following characteristics assessed at baseline: ADAMTS13 activity (in quantitative and by class: <10/≥10%), platelet count (in quantitative only), LDH, cTnI, and serum creatinine (for these 3 last parameters: in quantitative and by class: ≤ULN/>ULN), and also Glasgow Coma scale assessment.

Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the participant used prior to first study IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any interventions received by the participant concomitantly to the study IMP during the TE period, ie, up to the last IMP administration + 28 days.
- Post-treatment medications are those the participant took in the period running from the end of the concomitant medications period up to the end of the study.

A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant and post-treatment medications will be summarized for the mITT population by anatomic and therapeutic level. The summaries will be sorted by decreasing frequency of Anatomical Therapeutic Chemical (ATC) category. In case of equal frequency, alphabetical order will be used. Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Corticosteroids and anti-CD20 antibody treatments will be described through summaries.

In addition, all TPE will be described using the following variables: number (%) of participants requiring TPE, reason, time since first caplacizumab administration defined by date of TPE – date of first administration of caplacizumab (whatever marketed or study IMP) + 1 day (days), plasma product name, donor specification, plasma exchange technique, amount of plasma exchanged, multiple of plasma volume to be exchanged, and number of sessions for the desired plasma volume.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

Analysis windows for timepoints

For efficacy endpoints, the actual times since first caplacizumab administration will be used, and for by-visit analyses of safety variables only scheduled visits will be used. PCSA analyses include all scheduled or unscheduled or additional visits assessments.

For PROs (during the Treatment Period) and PD parameters, the analysis visit windows are defined in Table 7:

Table 7 - Analyses window definition

Scheduled visit post baseline	Target Study Day	[redacted]
Day 1	1	
Week 1 (Day 2)	2	
Week 1 (Day 3)	3	
Week 2 (Day 8)	8	
Week 3 (Day 15 – Day 21)	15	
Week 4 (Day 22 – Day 28)	22	
Week 5 (Day 29 – Day 35)	29	
Week 6 (Day 36 – Day 42)	36	
Week 7 (Day 43 – Day 49)	43	
Week 8 (Day 50 – Day 56)	50	
Week 9 (Day 57 – Day 63)	57	
Week 10 (Day 64 – Day 70)	64	
Week 11 (Day 71 – Day 77)	71	
Week 12 (Day 78 – Day 84)	78	
EOT (Week 13 (Day 85))	85	
FU 7 days after EOT	7 PT	
Additional FU Visit 1 (14 days after EOT)	14 PT	
Additional FU Visit 2 (21 days after EOT)	21 PT	
FU visit 28 days after EOT	28 PT	
FU visit (EOS) 12 weeks after EOT		

Study days are calculated considering Day 1 as the day of first administration of study IMP for visit on-treatment and considering Day 1 as the day after the last administration of intervention for visit after treatment.

FU=Follow-up; EOT=End of treatment ; PT=Post-treatment

Additional assessments and hospitalization visits

All additional assessments and hospitalization visit measurements of laboratory data, vital signs and ECG will not be included in by-visit analyses. PCSA analyses include all scheduled or unscheduled or additional visits assessments.

Cumulative dose for caplacizumab

In case of missing doses, the minimum cumulative dose calculated from available values will be presented.

Handling missing data

Particular considerations for Platelet, LDH, cTnI, creatinine, ADAMTS13 activity, and anti-ADAMTS13 antibody parameters:

- When used for the efficacy derived endpoints, only **CENTRAL** data will be used. One of the exceptions will be the following:
  - In case of missing CENTRAL record for platelet, LDH, cTnI and creatinine (reported as "NOT DONE" in the rawdata) and a reason given, the missing record will be replaced according the following rule (in this order):
    - If a local record is available with matching sample date and time, the local result will be used to impute central value
    - If only 1 local result is available with same date, the local result will be used to impute central value
    - If multiple local records are available:
      - If central and local records have date and time, the local record with the closest sample time to the missing central record will be used
      - If central record has only sample date and not sample time, the **median** value from the local samples on the same date will be used to impute the missing central record.
    - If duplicates of central records with same date, time and results, only one record will be kept
    - If for the same date and time, one record is "NOT DONE" and one record has a result, the record with the result will be kept
  - In case of missing CENTRAL record for platelet, LDH, cTnI and creatinine (reported as "NOT PERFORMED" in the rawdata), the missing record will be replaced according the following rule (in this order):
    - If a local record is available with matching sample visit, the local result will be used to impute central value
    - If multiple local records are available:
      - the **median** value from the local samples on the same visit will be used to impute the missing central record.
  - If multiple central records are available for the same date, the median value from the central values will be used.
  - For ADAMTS13 activity if a central sample was not done, then a local value, if available, can be substituted for the particular missing value.
  - For antibody titers, only central assessments will be used.

Then, and only after the potential above imputations, to derive the efficacy derived endpoints concerning platelet, LDH, cTnI and creatinine parameters (like Remission, Clinical response, Refractory to therapy, Clinical Relapse, Clinical exacerbation, Time to …), only 1 unique value per day will be retained; this one will correspond to the median value observed among all values recorded on the following time windows:

- [0-24h] according to the actual elapsed time from first dose (1st administration of caplacizumab, whether is the marketed caplacizumab as first dose within 4 hours prior to enrollment or first dose of IMP, and whether the first dose is intravenous or subcutaneous administration, ie, ignoring route of administration for calculation of actual elapsed time from first dose)
- [>24–48h]
- [>48-72h]
- And for the following days >3, by calendar day.
- The values resulting from these derivations will be the values used for the graphical representation of platelet, LDH and ADAMTS13 activity from Day 4.

Consecutive laboratory assessments are considered as 'consecutive visits' for efficacy endpoints.

A participant could potentially have missing laboratory assessment data, however, remission could still be confirmed at a subsequent laboratory value. In the case there is inadequate information to determine the remission status of a participant by the end of the study, the participant will be treated as not having achieved remission.

Clinical evidence of new or progressive ischemic organ injury

Clinical evidence of new or progressive ischemic organ injury is defined as any presence of following clinically significant iTTP event:

- Neurological event
- Elevated cardiac troponins
- Acute myocardial infarction
- Conduction abnormality
- Repolarization abnormality
- Heart failure
- Clinically significant renal event

which will be identified from the checkboxes in the “Clinically Significant TTP Event” eCRF form.

Exacerbation of TTP, *Relapse of TTP* and *Other* event will not be considered as clinical evidence of new or progressive ischemic organ injury.

Sustained Clinical Response

Sustained Clinical response is defined by the concomitance of the 3 following criteria for at least 2 consecutive visits (starting from D2):

- platelet count $\geq 150 \times 10^9$/L
- LDH $<1.5 \times$ ULN
- no clinical evidence of new or progressive ischemic organ injury

Remission

Remission is defined as (1) a sustained Clinical response (see above) associated with (2) Clinical remission or (3) Complete ADAMTS13 Remission, whichever occurs first, and defined as:

- Clinical remission: No TPE (*Plasma Exchange* form) and no anti-VWF therapy (Caplacizumab treatment) for ≥30 days (from the date that Clinical Response is achieved).
- Complete ADAMTS13 Remission: The attainment of ADAMTS13 activity level ≥50% for at least 2 consecutive visits (starting from D2).

Time to event

For each of below time to event, in case of no observation of the event or death, the censoring date will be defined as the last non-missing value of the analyzed parameter (platelet count, LDH….) if any, else as the start date of treatment (defined as first caplacizumab administration [whatever marketed or study IMP]).

- Time to platelet count response will be calculated as follow:

Date of initial day of 2 consecutive days where platelet count ≥150 × 10^9/L - Date of start of treatment

- Time to LDH ≤1 × ULN will be calculated as follow:

  Date where LDH ≤1 × ULN for the first time - Date of start of treatment
- Time to serum creatine ≤1 × ULN will be calculated as follow:

  Date where serum creatine ≤1 × ULN for the first time - Date of start of treatment
- Time to cardiac troponin I ≤1 × ULN will be calculated as follow:

  Date where serum creatine ≤1 × ULN for the first time - Date of start of treatment
- Time to ADAMTS13 partial remission (ADAMTS13 activity between 20% [included] and lower limit of normal [LLN] [excluded]) at 2 consecutive visits after clinical response will be calculated as follow:

  Date of initial day of 2 consecutive visits after clinical response with ADAMTS13 partial remission - Date of start of treatment
- Time to normalization of ADAMTS13 level defined as sustained ADMTS13 level of ≥50% at 2 consecutive visits after clinical response will be calculated as follow:

  Date of initial day of 2 consecutive visits after clinical response with normalization of ADAMTS13 level - Date of start of treatment
- Time to reduction of anti-ADAMTS13 antibodies below the threshold of positivity (12 U/mL) will be calculated as follow:

  Date of reduction of anti-ADAMTS13 antibodies below the threshold of positivity - Date of start of treatment

Refractory to therapy

Refractory to the therapy during the on-treatment period is defined as following:

- Lack of platelet count increment (over 2 consecutive days),

OR

- platelet counts <50 × 10^9/L AND LDH >1.5 × ULN despite 5 days of treatment.

Note: if the 2 consecutive values of platelet are the same, the condition is not met for refractory. Additionally, a patient can become refractory after a sustained platelet count response if he still is on therapy.

iTTP-related death during the on-treatment period and during the overall study period

The iTTP-related deaths will be derived from the ***Clinically Significant iTTP Event*** form with the *Outcome* field filled as Fatal.

Clinical Exacerbation

Clinical exacerbation is defined between a Clinical Response and a Clinical Remission as:

- platelet count decreases to <150 × 10^9/L (note that it is assumed that other causes of thrombocytopenia are excluded from the data collected in the database),
- with or without clinical evidence of new or progressive ischemic organ injury, within 30 days of stopping TPE or anti-vWF therapy.

Clinical Relapse:

Clinical relapse is defined after a Clinical Remission as:

- platelet count decreases to <150×109/L (with other causes of thrombocytopenia excluded)
- with or without clinical evidence of new ischemic organ injury
- confirmed by documentation of severe ADAMTS13 deficiency (<10%)

Number of hospitalization (including hospital and ICU) days during the on-treatment period and during the overall study period

$$\sum_{1}^{\mathrm{x}}(\text{Date of Discharge for hospitalization X} - \text{Date of Admission for hospitalization X} + 1)$$

Number of days in ICU during the on-treatment period and during the overall study period

$$\sum_{1}^{x}(\text{Date of Discharge in ICU X} - \text{Date of Admission in ICU X} + 1)$$

Number of TPE days (if participants started TPE) during the on-treatment and during the overall study period

Number of TPE days will be equal to the number of TPE occurrences/observations in the database during the respective periods.

6 REFERENCES

Not applicable.

Signature Page for VV-CLIN-0674535 v1.0
efc16521-16-1-9-sap

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]