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Title page

A randomized, double-blind, parallel group, placebo-controlled, multi-center study to assess the safety and tolerability of monthly subcutaneous administrations of a low and high dose cohort of osocimab to ESRD patients on regular hemodialysis

Osocimab in ESRD Phase 2b study

Bayer study drug	BAY 1213790 / Osocimab		
[Study purpose:]	Dose finding		
Clinical study phase:	IIb	**Date:**	23 JUN 2022
Study No.:	20115	**Version:**	4.0
Author:	PPD PPD		

This Statistical Analysis Plan is produced on a word-processing system and bears no signatures.

The approval of the Statistical Analysis Plan is documented in a separate Signature Document.

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Abbreviations

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
AP	Asia Pacific
aPTT	activated Partial Thromboplastin Time
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AV	Arteriovenous
BMI	Body mass index
CARURS	Covariate Adaptive Randomization User Requirements Specification
CI	Confidence interval
CIAC	Central Independent Adjudication Committee
CIF	Cumulative incidence function
CRF	Case report form
CRNMB	Clinically relevant non-major bleeding
cs	cause specific
CSR	Clinical Study Report
CV	Cardiovascular
DMC	Data monitoring committee
eCRF	Electronic case report form
EOMT	End of main treatment phase
EOET	End of extension treatment phase
ESRD	End Stage Renal Disease
FAS	Full Analysis Set
F1.2	Prothrombin fragment 1.2
GCP	Good Clinical Practice
HEOR	Health Economics and Outcome Research
HR	Hazard ratio
ICF	Informed consent form
ICH	International Council for Harmonization
ISTH	International Society on Thrombosis and Haemostasis
IwRS	Interactive web response system
LD	Loading dose
LMWH	Low molecular weight heparin
LOS	Listing only set

LTFU	Lost to follow-up
MACE	Major adverse cardiovascular event
MD	Maintenance/ monthly dose
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NAB	Neutralizing Antibody
N/A	Not applicable
PD	Pharmacodynamic(s)
PE	Pulmonary embolism
PK	Pharmacokinetic(s)
PPS	Per-protocol set
PT	Preferred term
RBC	Red blood cell
RHR	Relative hazard reduction
RRR	Relative risk reduction
SAC	Statistical Analysis Center
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SE	Systemic embolism
SOC	System organ class
SQCS	Semi-quantitative clotting score
TAT	Thrombin-antithrombin complex
TE	Thromboembolic
UFH	Unfractionated heparin
VTE	Venous thromboembolism
WBC	White blood cell

1. Introduction

Osocimab is a novel long-acting anticoagulant targeting the activated form of FXI with the potential to exhibit lower risk of bleeding events than currently available anticoagulants.

It is well known that ESRD patients on dialysis are at high risk for cardiovascular diseases. By targeting FXI, osocimab has the potential to provide an efficacious treatment for the prevention of thromboembolic events like MI, stroke, and cardiovascular death with a favorable risk profile for unwanted bleeding. This Phase 2b trial will assess the safety and characterize the PK/PD profile of two different dose cohorts of osocimab given subcutaneously once a month to subjects with ESRD.

Further information can be found in the clinical study protocol.

2. Study Objectives

Objectives and endpoints are listed in the table below:

Objectives	Endpoints
Primary	
• To clinically assess the safety and tolerability of different doses of osocimab administered subcutaneously once a month during main treatment period as compared to placebo	• Composite of major and clinically relevant non-major bleeding events (in alignment with the ISTH guidelines) as assessed by blinded central independent adjudication committee (CIAC) • Composite of moderate and severe AEs and SAEs
Secondary	
• To assess the change of key PD parameter from baseline	• aPTT, FXIa activity at trough levels after 6 months
Tertiary/Exploratory	
• To clinically assess the efficacy of osocimab during main treatment period	• Composite endpoint consisting of: vascular death [due to MI, stroke, PE, and SE], non-fatal stroke, non-fatal MI, major amputation of vascular etiology, acute limb ischemia, symptomatic VTE and systemic embolism as assessed by blinded central independent adjudication committee (CIAC) • Incidence of thrombosis of the arterio-venous grafts or fistulas
• To evaluate the anticoagulant effect of osocimab on the extracorporeal blood circuit by the assessment of a semi-quantitative clotting score (SQCS)	• Semi-quantitative clotting score
• To evaluate the impact of osocimab on the AV access for subjects with fistulas or grafts	• AV access bleeding score
• To assess key PK parameter	• Osocimab trough levels
• To explore additional PK/PD parameters, biomarkers, and biomarker genetics • To further investigate the study intervention (i.e. mode-of-action-related effects and / or safety) and to further investigate pathomechanisms deemed relevant to cardiovascular diseases and associated health problems	• Various biomarkers and biomarker genetics may be explored (e.g. diagnostic, safety, population PK, PD, monitoring, or potentially predictive biomarkers)

Abbreviations: AE = adverse event, aPTT = activated partial thromboplastin time, AV = arteriovenous, CIAC = Central Independent Adjudication Committee, ISTH = International Society on Thrombosis and Hemostasis, MI = myocardial infarction, PD = pharmacodynamic(s), PE = pulmonary embolism, PK = pharmacokinetic(s), SAEs = serious adverse events, SE = systemic embolism, SQCS = semi-quantitative clotting score, VTE = venous thromboembolism

The primary objective is to assess the safety under an osocimab concentration which is expected to be maintained during a chronic treatment. Thus, the attributes constituting the primary estimand are the following:

Population: The population consists of ESRD patients, further defined by the in- and exclusion criteria, who received assigned treatment at least once.

Variable:

- Time from first dose of assigned treatment to treatment emergent major and clinically relevant non-major bleeding events (in alignment with ISTH guidelines) up until 30 days after the last administration of assigned treatment
- Time from first dose of assigned treatment to moderate or severe AEs and SAEs up until 30 days after the last administration of assigned treatment

Treatment: Low/high-dose osocimab or matching placebo on top of standard of care

Intercurrent events: Of interest is the response to treatment while the subject is

- alive (intercurrent event "death") and
- exposed to assigned treatment (intercurrent event "premature discontinuation of treatment". Rationale: The primary objective is to assess the safety under an osocimab concentration which is expected to be maintained during a chronic treatment.),

i.e. both intercurrent events are handled using the same strategy "while alive" or "while on treatment".

Changes in the background therapy etc. will be handled following the treatment policy strategy. Other potential intercurrent events are not anticipated.

Population-level summary: (Cause-specific) hazard ratios comparing each of the osocimab dose groups with the placebo group as estimated from cause-specific Cox proportional hazards models.

Of note, based on the current expert assessment of the COVID-19 Public Health Emergency, it was to be expected that a low number of patients will suffer from (symptomatic) COVID-19. In addition, as ESRD patients visit dialysis centers on a regular basis anyway, no increase in missing data is to be expected. This is why no intercurrent event linked to the COVID-19 Public Health Emergency was accounted for. However, any premature discontinuation will be summarized, and selected analyses will be repeated by (symptomatic) COVID-19 (Yes/No). Also, if occurred, number of missed visits related to the COVID-19 pandemic will be summarized.

3. Study Design

Study 20115 is a covariate-adaptive randomization, double-blind, parallel group, placebo controlled, multi-center study to assess the safety and tolerability of monthly administrations of a low and high dose cohort of osocimab given subcutaneously in ESRD patients on hemodialysis. Here the term hemodialysis includes hemodiafiltration. The overall study design is depicted in the figure below.

Approximately 600 subjects (up to 750) from approximately 150 sites are planned to be randomized and will receive either osocimab (200 subjects on each dose arm), or placebo (200 subjects, i.e. 100 subjects receiving low dose volume placebo and 100 subjects receiving high dose volume placebo).

The following regions are planned to be included: North America, Europe, Asia Pacific.

The planned study will consist of:

- Screening period (visit 1): up to 14 days

- Randomization (visit 2): 1 day
- Pre-treatment period (from visit 2 until visit 4): 7 days
- Main treatment period (from visit 5 until EOMT visit): 6 months
- Extension treatment period (from visit 19 until EOET visit): up to 12 months
- Follow-up period (from visit 32 until visit 35): 4 months after end of treatment (EOMT or EOET)

Informed consent form will be obtained at the beginning of the screening period. During the screening period, subject's eligibility evaluations will be performed. Subjects will be randomized either to osocimab or to placebo using a covariate-adaptive randomization technique (minimization methods) (for details see Section 6.3).

During the pre-treatment period, which will serve as a baseline period, a series of 3 hemodialysis sessions will be performed. Unfractionated or low molecular weight heparin (UFH/LMWH) is allowed as anticoagulation for maintenance of hemodialysis treatment during the whole study duration.

The study intervention will be administered subcutaneously abdominal with one single loading dose at visit 5 and monthly maintenance doses from visit 8 onwards until the end of the extension treatment period with an overall maximum of 18 months of treatment. The main treatment period consists of 6 months of treatment as this time frame is deemed to be the minimum clinically relevant treatment time to assess osocimab as chronic life-time treatment in an appropriate manner and in preparation for Phase 3.

Study intervention will be administered during the extension treatment period for up to a maximum of 12 months or until the last subject randomized to the study has performed the EOMT visit (whichever comes first).

The treatment period (main or extension) will end with the study assessments performed 30 days after the last study intervention administration.

The follow-up period is an observational period of 4 months, i.e. ends approximately 5 months after the administration of the last dose of osocimab.

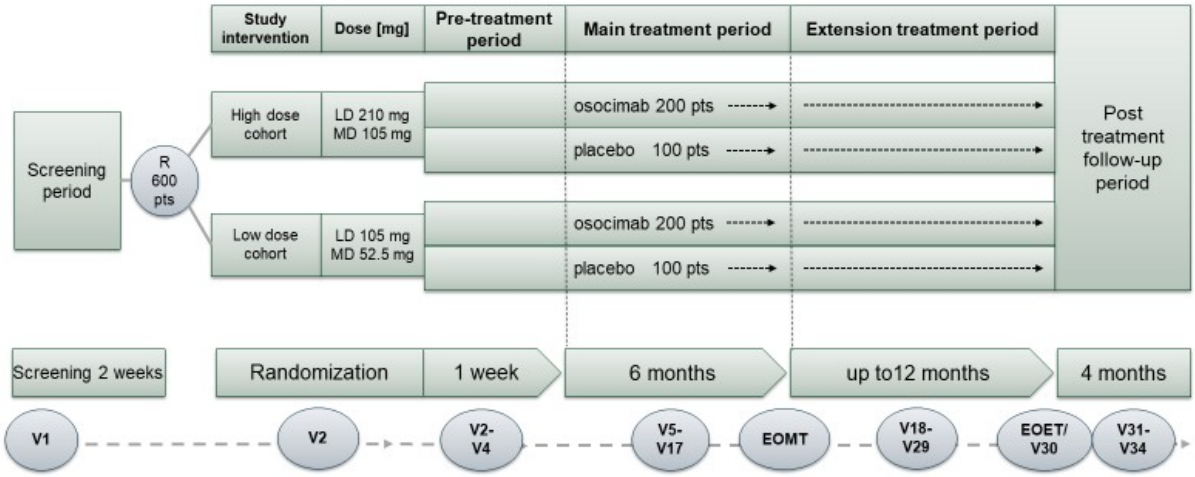
All suspected bleeding and cardiovascular (CV) or thromboembolic (TE) events occurring after signing informed consent (randomized subjects only) will be adjudicated by the CIAC in a blinded fashion; blinded to treatment allocation and dose cohort (details are described in the CIAC charter).

The procedures followed by the CIAC are detailed in the CIAC charter. Detailed instructions regarding documentation, reporting and transferal of adjudication dossiers will be provided in a study specific guidance document.

A DMC will frequently review safety data to ensure the safety of the subjects in the ongoing study. Further details can be found in the DMC charter.

Details of study procedures and their timing are summarized in the clinical study protocol.

Figure 3–1: Study design review



Abbreviations: EOET = end of extension treatment phase, EOMT = end of main treatment phase, LD = loading dose, MD = maintenance/ monthly dose, pts = participants, R = randomization, V = visit

The Follow-up ends 5 months after last study intervention and 4 months after EOMT or EOET.

3.1 Randomization and Blinding

Subjects will be randomized between osocimab low dose and placebo low dose and osocimab high dose and placebo high dose in a ratio of 2:1:2:1. Covariate-adaptive randomization techniques, or better the Pocock and Simon Minimization with Biased-coin Assignment methodology (Pocock, SJ, R Simon. 'Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial', Biometrics, 31, pp 103–115, 1975) will be utilized to perform subject randomization for this study.

In brief, each subject's randomization is performed by calculating the imbalance that will exist by assigning each treatment group in turn – by considering the previous treatment assignments to pre-specified balancing factor levels corresponding to the subject being randomized, and summing the individual factor level imbalances to determine which treatment(s) have minimal imbalance. The treatment assignment for this subject is then performed in a non-deterministic manner, by assigning probabilities of treatment assignment to each of the treatment arms based on the calculated treatment imbalances.

More detailed information can be found in sections 9.2, 9.3 and in the Covariate Adaptive Randomization User Requirements Specification (CARURS) as provided by the IwRS provider ALMAC Clinical Technologies.

The following baseline covariates will be taken into account:

- Region (categorical)
- Age (<50yrs/>=50-<60yrs/>=60-<65yrs/>=65-<70yrs/>=70-<80yrs/>=80yrs)
- Prior major adverse cardiovascular event (MACE) (Yes/No)
- Dialysis access via catheter (Yes/No)
- Low-dose ASA use (Yes/No)

- Diabetes (Yes/No)
- Atrial fibrillation (Yes/No)

The first five covariates will have twice the factor weight then the latter two.

Sponsor, subjects, and investigators are being blinded with respect to active treatment versus placebo, but not blinded to dose cohort (low or high dose). In order to reduce any risk which could be associated with the open-label nature of the dose cohort, the final SAP will be available before first patient first visit. No ad hoc interim analyses comparing the treatment effect of the two dose cohorts will be performed. Aggregation of treatment-specific interim results will only be performed for safety measures in the context of DMC meetings.

The CIAC will remain blinded to the subject's treatment allocation and dose cohort throughout the course of the study. The DMC is unblinded.

4. General Statistical Considerations

4.1 General Principles

The statistical evaluation will be performed by using the software package SAS release 9.2 or higher (SAS Institute Inc., Cary, NC, USA) or other software if applicable. All variables will be analyzed by descriptive statistical methods. The number of data available and missing data, mean, standard deviation, minimum, quartiles, median, and maximum will be calculated for metric data. Frequency tables will be generated for categorical data.

In general, subjects receiving placebo in either the low dose or the high dose cohort will be analyzed in a pooled manner. This group will be referred to as placebo group. The group of subjects receiving osocimab in the high dose cohort (or low dose cohort) will be referred to as high dose (or low dose) osocimab group.

4.2 Handling of Dropouts

A subject 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, compliance, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. The subject will be permanently discontinued both from the study intervention and from the study at that time. If a subject permanently discontinues/withdraws from the study and is unwilling or unable to attend regular study visits at the study site, all possible efforts should be made to obtain information on the health status of the subject.

A subject will be considered lost to follow-up if he/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 subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

In both cases, when the subject permanently discontinues/withdraws from the study or the subject is lost to follow-up, he/she is considered a dropout. The number of dropouts for any reason, as well as the reasons for dropout, will be displayed by treatment arm. Baseline characteristics will be displayed by dropout (yes/no). All data collected until the dropout will be analysed. Of note, subjects who drop out because they suffer from COVID-19 will be displayed here with the corresponding reason.

In rare instances, it may be necessary for a subject to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the subject will remain in the study to be evaluated until the end of the follow-up period. If a subject permanently discontinues study intervention and is unwilling or unable to attend regular study visits at the study site, all possible efforts should be made to obtain information on the health status of the subject. The reason for discontinuation of study intervention must be recorded in the eCRF and source documentation.

The number of subjects who permanently discontinue (definitive discontinuation) study intervention and the reason for discontinuation will be displayed by treatment arm. Baseline characteristics will be displayed by permanently discontinue study intervention (yes/no). All data collected until the discontinuation will be analysed according to the treatment emergent definition.

4.3 Handling of Missing Data

All missing or partial data will be presented in the subject data listing as they are recorded on the Case Report Form (CRF).

General rules

When appropriate, the following rules will be implemented so as not to exclude subjects from statistical analyses due to missing or incomplete data:

- **Efficacy and Safety clinical variables, adverse events**
  For cases where start month and year are reported but day is missing, impute the maximum of (date of randomization + 1 week, first date of study intervention, 01.month.year). For cases where only start year is reported, impute the maximum of (date of randomization + 1 week, first date of study intervention, 01.01.year), but not later than death date if the patient died.
- **PD variables**

  No imputation will be done for pharmacodynamic parameters.
- **Study intervention start date**
  If the start date and time is missing it will be imputed with the randomization date + 1

week and time. If start date and time is recorded as earlier than randomization and cannot be clarified, date and time of randomization will be used for the statistical analysis.

- **Study intervention stop date**
  If the stop day is missing, but the stop month and stop year are available then the stop date will be imputed as minimum of (15.month.year and last study visit date in main treatment or extension treatment period and death date).
  If the stop day and month are missing then the stop date will be imputed as minimum of (the last study visit date before the post treatment follow-up period and death date).

4.4 Interim Analyses and Data Monitoring

No formal interim analysis is planned.

The primary analysis will be performed after all subjects have completed the main treatment period (primary completion).

A full analysis will be performed after the last subject has completed the follow-up of 4 months (study completion). Of note, the full analysis, or better the evaluation of the data collected after the main treatment period will be considered open-label due to the unblinding caused by the primary analysis.

Furthermore, the DMC will frequently review safety data to ensure the safety of the subjects in the ongoing study. The required tables and listings will be created by an independent Statistical Analysis Center (SAC). Only the open session of the DMC meetings may be attended by representatives of the Sponsor. Overall treatment data presented here may include enrollment data, adverse event data, baseline characteristics, update on study status or any potential issues, outcome data. More details can be found in the Data Monitoring Committee Charter.

4.5 Data Rules

The pre-treatment period serves as baseline period and takes place before first study intervention was given. If there is more than one measurement, the mean of the respective measures will serve as baseline.
Baseline for PD will be visit 5 data prior to dosing.

The primary analysis will be based on all respective events that occurred during the scheduled main treatment period.

Additional analyses may be based on all respective events that occurred during the overall study period, consisting of both the main treatment and extension treatment period.

In addition, further analyses may be based on all events occurring during the full study period consisting of the main treatment, extension treatment and post-treatment follow-up period.

These time scopes are summarized in the table below.

An event is considered treatment emergent if it occurred between start of treatment and not later than 30 days after last administration of study intervention.

An event is considered as full study treatment emergent if it occurred between first study intervention and not later than 5 months after last administration of study intervention.

Additional analysis may be performed post-hoc.

Time scope definition:

Overall study period	Main treatment phase + extension treatment phase
Full study period	Main treatment phase, extension treatment phase + follow up

4.5.1 Laboratory measurements

Numeric laboratory measurements outside the calibration range, marked by "<x" (<LLOQ) or ">x" (>ULOQ) will be replaced by LLOQ/2 or ULOQ, respectively, in the statistical analysis.

For the analysis of PD, means and standard deviation will only be calculated if at least 2/3 of the individual data were measured and were within the calibration range.

Laboratory records without a RAVE Datapage ID (corresponding record in the electronic case report form is missing) will be excluded from the analysis.

4.6 Blind Review

There will be two data assessment lists. The first one will occur after primary completion and the second one will occur after end of study. The results of both data lists will be documented in separate lists of important deviations, validity findings and assignment to analysis set(s). Any changes to the statistical analysis prompted by the results of the review of study data will be documented in an amendment and, if applicable, in a supplement to this SAP.

The results of the final data assessment will be documented in the final list of important deviations, validity findings and assignment to analysis sets. Pharmacodynamic values to be excluded from statistical analysis will be documented in the list of pharmacodynamic values to be flagged as invalid.

5. Analysis Sets

Final decisions regarding the assignment of subjects to analysis sets will be made during the review of study data and documented in the final list of important deviations, validity findings and assignment to analysis set(s) (see section 4.6).

The following populations are defined:

Population	Description
Enrolled	All subjects who sign the ICF
Full Analysis Set	All subjects randomly assigned to study intervention.
Safety Analysis Set	All subjects randomly assigned to study intervention and who took at least 1 dose of study intervention. Subjects will be analyzed according to the intervention they actually received.
Pharmacokinetic analysis set	All osocimab-treated subjects with at least 1 PK sample in accordance with the PK sampling schedule (Section 1.3 and Section 8.5 of the study protocol) and without deviation from the protocol that would interfere with the evaluation of the PK data will be included in the PK analysis.
Pharmacodynamic analysis set	All subjects with at least 1 PD sample in accordance with the PD sampling schedule and without deviation from the protocol that would interfere with the evaluation of the PD data will be included in the PD analysis.
Listing only set	All subjects who signed ICF but are not randomized.

In accordance with the "population" attribute of the primary estimand, the primary analysis set is the safety analysis set.

Supplementary analyses of the efficacy variables will be performed on the full analysis set.

6. Statistical Methodology

In general, the evaluations will be conducted on each osocimab group and on the placebo group.

In addition, the primary safety and efficacy variables will be analysed descriptively for the following groups:

- each osocimab group, placebo high dose group, placebo low dose group,
- pooled osocimab group, pooled placebo group.

For the primary analysis and all analyses conducted at primary completion which will occur once the last patient completed the end of main treatment phase visit, only the main treatment period will be considered. The partial data of a subject's extended treatment period up until primary completion may be presented in separate tables.

At full study completion, also the extension treatment and follow-up period will be considered.

Incidence rates and cumulative incidences will be calculated only for endpoints with at least 3 events in at least one treatment arm. Hazard ratios (cause specific and subdistribution) will be calculated only if in addition at least 1 event in each of the compared treatment arm occur.

6.1 Population characteristics

6.1.1 Demography and baseline characteristics

Demographic and baseline data will be evaluated descriptively for the SAF as well as for the FAS, by treatment groups and overall. No statistical tests will be performed to compare these characteristics across treatment groups.

Descriptive statistics (such as mean, standard deviation, median, quartiles (inter quartile range), minimum and maximum) will be provided for continuous variables such as

- Age at Screening
- Year of birth
- Body weight
- Body height
- Calculated BMI
- Hemoglobin level
- Platelet count
- Dialysis vintage (time since start of chronic dialysis)
- aPTT

Counts and (appropriate) percentages will be provided for categorical variables such as

- Sex (male/female)
- Race (American Indian or Alaska Native, Asian, Black or African American, Multiple, Native Hawaiian or Other Pacific Islander, Not Reported, White)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported)
- Low dose ASA use (yes/no)
- Dialysis access via catheter (yes/no)
- Diabetes mellitus (yes/no)
- Atrial Fibrillation (AF) (yes/no)
- Prior CV events (Stroke, TIA, MI, DVT, PE) (yes/no)
- Hemodiafiltration (yes/no)

Reasons for exclusion from analysis populations will be summarized.

6.1.2 Medical history

Medical history data will be evaluated by frequency tables, showing the number and percentage of subjects with medical history findings (i.e. previous diagnoses, diseases or surgeries) that started before signing of the informed consent and that are considered relevant to the study using MedDRA Primary System Organ Class / Preferred Term.

6.1.3 Prior and Concomitant Medication

The dictionary used for coding concomitant medications is the World Health Organization Drug Registration and Listing. Frequency tables displaying frequency of subjects for each drug category summarized by Anatomical Therapeutic Chemical (ATC) and coded terms will

be used to summarize the number and percentage of subjects with prior and concomitant medications. The following time windows will be used:

- Prior medication: medication stopped prior to randomization
- Concomitant medication present in pre-treatment, main treatment, extension period, follow-up period, overall study period, full study period (i.e administered at least one dose within the respective period)
- Concomitant medication started in pre-treatment, main treatment, extension period, follow-up period, overall study period, full study period

Frequency tables of subjects taking prohibited concomitant medications (see study protocol section 6.5) are considered as well as by categories: anticoagulants, antiplatelets (incl. ASA), thrombolytic medication.

6.1.4 Renal Replacement Therapy Baseline Information

Information of the renal replacement therapy at baseline will be evaluated similar to the other baseline characteristics. In this context the use of unfractionated heparins and LMWH for dialysis maintenance at baseline will be descriptively summarized by treatment groups and overall.

6.2 Efficacy

6.2.1 Main efficacy analysis

Two main efficacy variables will be considered. The first is the composite endpoint consisting of the following components:

- Death due to MI, ischemic stroke, pulmonary embolism (PE),non-CNS systemic embolism (SE) and undetermined - presumed cardiovascular death
- Stroke (ischemic stroke or undetermined type)
- MI
- Major amputation of vascular etiology
- Acute limb ischemia
- Symptomatic VTE
- Systemic embolism

The second variable is the thrombosis of the arteriovenous fistulas or grafts.

The analysis for both main efficacy variables is a descriptive time to first event analysis which will be conducted separately for the osocimab low and high dose group similar to the primary safety analysis (i.e. only treatment emergent efficacy events which occurred during the main treatment period will be considered), see section 6.4.1. Thus, the descriptive analysis focuses on estimating the efficacy under constant osocimab concentration during chronic treatment.

6.2.2 Supplementary Analyses

Efficacy Analysis for the overall study period and full study period in SAF

Treatment emergent efficacy events occurring in the overall study period (main and extension treatment period) and the full study period (main, extension and follow-up period) will be analysed similarly as the main efficacy analysis.

Efficacy Analysis in FAS

All efficacy events of the main efficacy variables occuring from randomization until the respective periods (main treatment period, overall treatment period and full study period) will be considered. Similar statistical methods will be applied as for the main efficacy analyses, but the intercurrent event "premature discontinuation of treatment" will be handled following the treatment policy strategy.

6.2.3 Other efficacy analyses

Efficacy Analysis by Component

The main efficacy analysis will be repeated for all single components of the main efficacy variable (MI, stroke (ischemic and undetermined type), major amputation of vascular etiology, acute limb ischemia, symptomatic VTE, systemic embolism).

Analysis of Death Events

The main efficacy analysis will be repeated for all-cause death and for vascular death (Death due to MI, ischemic stroke, pulmonary embolism (PE) and non-CNS systemic embolism (SE)). In addition, frequencies of other reasons (including COVID-19 related) will be displayed by the categories as adjudicated by the CIAC.

Pre-Treatment Efficacy Summary

All efficacy events that started after randomization and before first dose of study intervention will be summarized by presenting counts and percentages of subjects by treatment group.

SQCS Analysis

The effect of osocimab on the clotting in the dialysis circuit will be assessed by the SQCS. Clotting scores will be assigned as follows:

- "0" clean filter and no visible clots in the drip chamber/air trap
- "1" traces of coagulation in the filter and/or in the drip chamber/air trap
- "2" intermediate state between "1" and "3"
- "3" fully clotted extracorporeal system resulting in an interruption of the hemodialysis session

Adequate anticoagulation is defined by a SQCS of less or equal "1".

The mean difference of SQCS values during main treatment period and baseline between each of the osocimab groups and the placebo group by visit will be displayed together with the corresponding 90% (and 95%) confidence intervals applying ANOVA with treatment group as factor. This will also be repeated for the overall study period. The distribution of SQCS between each of the osocimab groups and the placebo group by visit will be compared using

the Wilcoxon Rank sum test. Change in SQCS scores from baseline per visit will be also calculated. Baseline will be the median of all pre-treatment values.

Percentage of subjects with adequate anticoagulation (SQCS "0" or "1") by visit will be presented.

Additionally, a table will be created showing SQCS categories over time per visit, at pre-treatment all values will be shown. This will be done for the full study period. Figures will be provided.

6.2.4 Subgroup analysis

The time to event analysis for the efficacy variables will be repeated by the following subgroups:

- Age group 1 (<60 years, 60-75, >75years)
- Age group 2 (<50yrs/>=50-<60yrs/>=60-<65yrs/>=65-<70yrs/>=70-<80yrs/>=80yrs)
- Sex (male, female)
- Patients with AF (Yes/No)
- Patients with diabetes mellitus (Yes/No)
- Patients with prior CV events (Stroke, TIA, MI, DVT, PE) (Yes/No)
- Patients with prior MACE (Yes/No)
- Patients with ASA / non-ASA
- History of (symptomatic) COVID-19 (Yes/No)
- Symptomatic COVID-19 during the study (Yes/No)

Forest plots showing incidences and hazard ratios will be provided for the comparison of high dose osocimab and placebo and for low dose osocimab versus placebo.

6.3 Pharmacokinetics/pharmacodynamics

There might be some inaccuracies in the actual sampling times compared to planned sampling times due to the fact, that the study procedures orientate on the dialysis schedule rather than specifiying exact days for the study procedures. These deviations can be relevant for the interpretation of pharmacokinetic and pharmacodynamic data. Accepted time windows were prespecified in the guidance document for PD validity for study #20115 and will be referenced in the final blind review report. Accepted time windows for the assessment of pharmacokinetic concentrations will be handled analoguously.

All valid results will be included in the listings and graphical displays of individual data, which are displayed using actual times. Measurements taken outside the predefined time windows will be flagged by the pharmacokinetic and pharmacodynamic experts to be excluded from the calculation of summary statistics (with respect to planned times) in order to avoid biased results.

For the primary completion analyses all duplicates at the same visit will be excluded for the statistical analyses in section 14 by programming algorithm, and they will be listed only in section 16.2.

For the final analyses all PK data and PD data (aPTT, FXIa activity, FXI activity) flagged as invalid will not be used for the analyses. Duplicates in other PD data at the same visit will be excluded for the statistical analyses in section 14 by programming algorithm, and they will be listed only in section 16.2.

PK variables

Osocimab concentrations will be summarized by visit, separated according to actual dose cohort. Descriptive statistics of plasma concentrations [geometric mean and percent coefficient of variation (%CV), arithmetic mean and %CV, median and range] will be presented by treatment group and time in tabular form. Means at any time will only be calculated if at least 2/3 of the individual data were measured and were above the lower limit of quantification (LLOQ). For the calculation of the mean value, a data point below LLOQ will be substituted by one half of this limit. In tables showing mean values, where values below LLOQ are included in the calculation of mean values, these means will be marked. Box plots for osocimab trough levels will be provided by treatment.

For all treatments where at least one subject with at least one confirmed ADA formation is included, the individual concentrations of osocimab in plasma will be displayed including supplemental information about the ADA titer. Individual subjects with confirmed ADA formation will be indicated by different colors and symbols. Filled symbols will indicate neutralizing characteristics.

Pharmacokinetic and exposure-response analysis using population approaches (popPK and popPK/PD, e.g., by non-linear mixed effect modeling) will be reported under separate cover, if applicable.

Bioanalysis and population PK (popPK) evaluation might be started prior to database lock: if this is applicable, appropriate measures will be taken to maintain blinding of the study team.

PD variables

All PD analyses will be conducted in the pharmacodynamic analysis set.

The activated partial thromboplastin time (aPTT) and FXIa activity at trough levels after 6 months will be analyzed as ratio to baseline by providing the mean and median, together with the standard deviation and quantiles, respectively.

Results of the additional pharmacodynamics parameters will be displayed utilizing appropriate summary statistics and figures. The parameters will be described by the following summary statistics: arithmetic mean, standard deviation, median, minimum, and maximum. These summary statistics will be presented by actual dose group for the original data as well as for the absolute and relative changes from baseline as ratio to baseline. In addition, for each subject the maximum and minimum relative change from baseline will be determined and presented by appropriate summary statistics and figure.

In addition, a scatter plot of the following pairs of parameters by time point is provided to evaluate the correlation, the first parameter on the y-axis and the second parameter on the x-axis:

Parameter on y-axis	Parameter on x-axis
aPTT	FXIa activity (AXIA assay)

aPTT	FXI activity (clotting assay)
aPTT	FXI concentration
aPTT	Plasma concentration of osocimab
FXIa activity (AXIA assay)	FXI activity (clotting assay)
FXIa activity (AXIA assay)	FXI concentration
FXIa activity (AXIA assay)	Plasma concentration of osocimab
FXI activity (clotting assay)	FXI concentration
FXI activity (clotting assay)	Plasma concentration of osocimab
FXI concentration	Plasma concentration of osocimab
D-dimer	aPTT
D-dimer	FXIa activity (AXIA assay
D-dimer	FXI activity (clotting assay)
D-dimer	Plasma concentration of osocimab
TAT	aPTT
TAT	FXIa activity (AXIA assay)
TAT	FXI activity (clotting assay)
TAT	FXI concentration
TAT	Plasma concentration of osocimab
F1.2	aPTT
F1.2	FXIa activity (AXIA assay)
F1.2	FXI activity (clotting assay)
F1.2	FXI concentration
F1.2	Plasma concentration of osocimab

These plots will be repeated using a semi-logarithmic scale.

It is important to present the PD tables and figures in the following order:

- aPTT,
- FXIa activity (AXIA),
- FXI activity (clotting assay),
- FXI concentration,
- D-dimer,
- TAT,
- F1.2

The scatterplots will be sorted by the parameter on the y-axis.

The exploratory PD marker results may be reported separately.

6.4 Safety

6.4.1 Primary safety variables

The composite of major bleeding (MB) and clinically relevant non-major bleeding (CRNMB) events, as assessed by CIAC, and the composite of moderate and severe AEs and SAEs will

be the primary safety endpoints in this study. Only events that started after the first dose of study treatment and during the main treatment period are considered for the primary analysis.

For the primary safety analysis descriptive time to first primary safety event (both treatment emergent AEs and composite of treatment emergent major and CRNMB events [in alignment with ISTH guidelines]) analyses will be performed.

According to the description of the primary estimand, the following events will be considered as competing events for the respective safety endpoint:

- death
- premature end of exposure to assigned treatment (last administration of assigned treatment plus 30 days).

For the primary analysis, the time to event for a subject will be censored at the date of the EOMT visit or after no further data collection happened for a subject (e.g. lost to follow-up).

According to the study protocol (section 7.1.1) one maintenance dose can be missed. If a subject misses a maintenance dose, has a so called administration gap, that lasts longer than 30 days, the subject is not considered at risk for treatment-emergent events during this time until the next dose. When the subject then takes a maintenance dose again, he/she is at risk again. Accordingly there will be additional analyses, where the time not under exposure between two doses will be ignored and events during that time will not be counted. The time under risk will be calculated by removing time between the interrupted dose + 30 days and the next dose and the time more than 30 days after permanent discontinuation to study drug and if occurred the 1st event per patient will be counted. For the primary analysis in this data scope, the time to event for a subject will be censored at the date of the EOMT visit or after no further data collection happened for a subject (e.g. lost to follow-up).

The cumulative incidence function for the event-of-interest as well as the associated competing event(s) together with the corresponding confidence interval will be estimated for each treatment arm using Aalen-Johansen estimators.

The competing event for the primary safety endpoint is death and premature discontinuation of exposure to assigned treatment.

The cumulative incidence, i.e. the probability of having a specific event E at or before a timepoint t, $P(T \leq t, E = 1)$, will be estimated for time-to-event endpoints by Aalen-Johansen estimators with the competing event.

The difference of the Aalen-Johansen estimators between high dose osocimab and placebo and low dose osocimab and placebo will be presented with a 90% confidence interval.

As the Aalen-Johansen estimator is approximately normal distributed (Aalen, Borgan and Gjessing 2008), the difference of Aalen-Johansen estimators is approximately normal distributed. Thus, the two-sided 90% confidence interval is obtained via:

$$\left[(\widehat{AJ}^{TRT}(day) - \widehat{AJ}^{CON}(day)) \pm z_{0.95} \sqrt{\sigma^2(\widehat{AJ}^{TRT}(day)) + \sigma^2(\widehat{AJ}^{CON}(day))} \right],$$

with $\widehat{AJ}^{TRT}(day) / \widehat{AJ}^{CON}(day)$ the Aalen-Johansen estimator for treatment TRT/ control CON at study day, $z_{0.95}$ the 90% quantile of the standard normal distribution and $\sigma^2(\widehat{AJ}^{TRT}(day))$ and $\sigma^2(\widehat{AJ}^{CON}(day))$ the estimated variance of the Aalen-Johansen

estimator for osocimab (treatment, TRT) and placebo (control, CON) at study day, estimated with the Aalen method.

Rates

Cause-specific incidence rates will be calculated for each treatment arm with an 90% confidence interval.

The exposure-adjusted incidence rate will be expressed a "subjects with an event – per 100 participant years". For that the following formula is used:

$$IR_{adj} = \frac{\#Participants\ with\ an\ event}{\sum time\ under\ treatment\ (in\ days)/(100 * 365.25)}$$

The 90% confidence interval for the exposure-adjusted IR will be computed as

$$\left[\frac{IR_{adj} * \chi^2(0.05; 2e)}{2e}; \frac{IR_{adj} * \chi^2(0.95; 2e)}{2e}\right],$$

with $\chi^2(q; 2e)$ the q quantile of a chi square distribution with 2e degrees of freedoms and e the number of participants with an event. (Nelson 1982)

With respect to the cause-specific hazards for the respective safety variable, each of the osocimab groups will be compared to the placebo group using two-sided log-rank tests at a type I error rate of α=10%. Due to the explorative nature of these analyses, no multiplicity adjustment will be done.

Cause-specific hazard ratios, cause-specific relative hazard reduction (csRHR; csRHR = 100 × [1 – cause-specific hazard ratio]%), and corresponding 2-sided 90% and 95% confidence intervals, comparing the hazards for the event-of-interest in each of the osocimab groups with the placebo group will be estimated based on two separate cause-specific Cox proportional hazards models. Censoring will be assumed independent of the randomized group assignment.

To complete the analysis, cause-specific HRs will be estimated for (each of) the competing events.

For the analysis of the primary endpoint in this study, the cause-specific hazard function $h_k(t)$ is the chance that an individual experiences an event of the primary safety outcome in the next instant in time, given that the individual has not had such an event or a competing event up to time t. For example, for the comparison of the osocimab high dose group with the placebo group, the corresponding cause-specific Cox proportional hazards model can be described by the following equation:

$$H_k(t,x_i) = h_{0,k}(t) \exp(\beta_k x_i),$$

where

$h_k(.)$ cause-specific hazard function for primary safety outcome, as a function of time and subject's covariates

$h_{0,k}(.)$ unspecified underlying baseline hazard function for primary safety outcome; hazard of an individual with $x_i = 0$

t time (in days) relative to the date of first administration

x_i treatment group of subject i
(0 corresponds to “placebo group” and
1 corresponds to “osocimab high dose group”)

β_k unknown parameter (to be estimated); cause-specific hazard ratio = $\exp(\beta_k)$

k type of event

Probability

As a supportive analysis, the cumulative incidence functions for the respective event-of-interest will be compared using the Fine and Grays subdistribution hazards model as well as using the Gray’s test.

6.4.2 Supplementary Safety Analysis

The primary safety analyses will be repeated for the overall treatment period for the safety analysis set. Here, all events which occurred during the main and extension treatment period will be taken into account. Therefore, a subject will be censored after a primary safety event occurred, or after the date of the EOET visit, or 30 days after study drug discontinuation or after no further data collection happened for a subject (e.g. lost to follow-up).

6.4.3 Other safety analyses

All Bleedings Analysis

The primary safety analyses will be repeated for all bleedings (defined as the composite of MB, CRNMB and minor bleedings) and its components for the safety analysis set.

Bleeding analysis by ISTH category

The descriptive primary safety analysis will be repeated for all major bleedings and their respective ISTH categorization.

BARC Bleedings Analysis

The descriptive primary safety analyses will be repeated for bleeding types 1 to 5, including any sub types, according to the BARC Bleeding Criteria. These are defined as follows:

- Type 0:
  - No bleeding
- Type 1:
  - Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health-care professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health-care professional.
- Type 2:
  - Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging

alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:

- requiring nonsurgical, medical intervention by a health-care professional,
- leading to hospitalization or increased level of care, or
- prompting evaluation

- Type 3:
  - Type 3a:
    - Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL* (provided hemoglobin drop is related to bleed)
    - Any transfusion with overt bleeding
  - Type 3b:
    - Overt bleeding plus hemoglobin drop ⩾5 g/dL* (provided hemoglobin drop is related to bleed),
    - Cardiac tamponade,
    - Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid),
    - Bleeding requiring intravenous vasoactive agents
  - Type 3c:
    - Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal),
    - Subcategories confirmed by autopsy or imaging or lumbar puncture,
    - Intraocular bleed compromising vision.
- Type 4:
  - CABG-related bleeding,
  - Perioperative intracranial bleeding within 48 h,
  - Reoperation after closure of sternotomy for the purpose of controlling bleeding
  - Transfusion of ⩾ 5 U whole blood or packed red blood cells within a 48-h period,
  - Chest tube output more than or equal to 2L within a 24-h period
- Type 5:
  - Fatal bleeding
  - Type 5a:
    - Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

- Type 5b:
  - Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Bleeding Characteristics Summary

The characteristics of all bleedings will be summarized by presenting counts and percentages of events with a certain attribute separated by treatment group.

Pre-Treatment Safety Summary

All safety events that started after randomization and before first dose of study intervention will be summarized by presenting counts and percentages of subjects with efficacy event before start of treatment separated by treatment group.

AV Access Bleeding Score Analysis

Severity of bleeding at the dialysis access will be assessed approx. 15 minutes after removal of the dialysis needle(s) from the AV access according to the following categories (exploratory bleeding score):

- "0" no access bleeding
- "1" slow oozing
- "2" overt bleeding

The mean difference of AV access bleeding score during main treatment period and baseline between each of the osocimab groups and the placebo group by visit will be displayed with the corresponding 90% (and 95%) confidence intervals applying ANOVA with treatment group as factor. The distribution of AV access bleeding score between each of the osocimab groups and the placebo group by visit will be compared using the Wilcoxon Rank sum test. Change in AV accesss bleeding scores from baseline per visit will be also calculated. Baseline will be the median of all pre-treatment values.

Additionally, a table will be created showing AV access bleeding categories over time per visit, at pre-treatment all values will be shown. Change from baseline per visit will be calculated. This will be done for the full study period. Figures will be provided.

Furthermore, the difference of the proportion of hemodialysis sessions with no AV access bleeding during main treatment period and baseline between each of the osocimab groups and the placebo group will be summarized with the corresponding 90% (and 95%) confidence intervals based on the score method as described by Newcombe (1998).

6.4.4 Subgroup analysis

The time to event analysis for the safety variable (composite of major bleeding (MB) and clinically relevant non-major bleeding (CRNMB) events, as assessed by CIAC) will be repeated by the following subgroups:

- Age group 1 (<60 years, 60-75, >75years)
- Age group 2 (<50yrs/>=50-<60yrs/>=60-<65yrs/>=65-<70yrs/>=70-<80yrs/>=80yrs)
- Sex (male, female)

- Patients with AF (Yes/No)
- Patients with diabetes mellitus
- Patients with prior CV events (Stroke, TIA, MI, DVT, PE) (Yes/No)
- Patients with prior MACE
- Patients with ASA / non-ASA
- History of (symptomatic) COVID-19 (Yes/No)
- Symptomatic COVID-19 during the study (Yes/No)

Forest plots showing incidences and hazard ratios will be provided for the comparison of high dose osocimab and placebo and low dose osocimab and placebo, respectively.

6.4.5 Adverse events

The investigator has to record on the respective CRF pages all adverse events (AEs) occurring in the period between the signing of the informed consent and the end of the post-treatment follow-up period.

The original terms used by investigators to report AEs via the CRFs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All reported adverse events during the main treatment period will be summarized by means of AE tables based on the treatment-emergent approach (see section 4.5).

All AE/SAE/AESI tables will also be provided for the following timeframe named “Full study TE AEs (SAE/AESI)”: AEs occurred after first intake of study intervention up to 5 months after last intake.

If an AESI will be reported, this will always be done separated for the two categories listed below.

For each AE, the number and percentage of subjects who experienced at least 1 occurrence of the given event will be tabulated according to the affected primary system organ class (SOC) and preferred term (PT) by treatment arm. A total column will be included in all safety summaries.

Frequency tables, showing an overall summary of number of subjects with AEs, serious adverse events (SAEs) and adverse events of special interest (AESIs) separated by the two categories will be given, and will include the following information.

- if the AE (/ SAE/AESI) occurred with causal relationship to study drug ,
- if the AE (/SAE/AESI) occurred with causal relationship to study procedures
- reasonable causal relationship to ESRD
- reasonable causal relationship to hemodialysis procedure
- maximum intensity for any AE
- maximum intensity for any study-drug related AE,
- AE related deaths.
- AE resulting in permanent discontinuation of study drug

The two categories of AESI are:

- Decrease in platelets below 75 x 109/L or > 50 % decrease in platelet count from baseline
- Hypersensitivity (i.e. any allergic reactions of ⩾ CTCAE criteria 2 [Common Terminology Criteria for Adverse Events] or anaphylaxis)

A similar table showing overall summary information of AEs (/SAE/AESI) during screening will be given.

Additionally, frequency tables summarizing infection site events will be provided for the SAF.

Injection site event is defined as any AE at the injection site presenting as Injection site erythema, Injection site swelling, Injection site pruritus, or Injection site pain that started on the day of injection.

In addition, frequency tables will summarize the number of subjects with any event occurring during pre-treatment period.

For the full analysis set the event which occurred during the extension treatment period and during the post treatment follow-up period will be considered.

6.4.6 Vital signs

Vital signs will be displayed by means of descriptive statistics and change from baseline by visit and treatment group.

6.4.7 Laboratory parameter

Only centrally analyzed blood samples will be considered for analysis.

Central laboratory parameters will be displayed by means of descriptive statistics and change from baseline by visit and treatment group. High/low abnormalities by laboratory parameter will be presented. This includes various hematology (white blood cell count (WBC), red blood cell count (RBC), …), clinical chemistry (aspartate aminotransferase (AST), alanine aminotransferase (ALT), …) and urinalysis (color, appearance, specific gravity, …) parameters.

All duplicates at the same visit will be excluded from the statistical analyses in section 14 by programming algorithm, and they will be listed only in section 16.2.

6.4.8 Hemodialysis data

Hemodialysis data like heparin dose and Kt/V will be displayed by means of descriptive statistics and change from baseline by visit.

Furthermore, the difference of the proportion of hemodialysis sessions with adequate anticoagulation during main treatment period and baseline between each of the osocimab groups and the placebo group will be summarized with the corresponding 90% (and 95%) confidence intervals based on a proportion test.

Additionally a table will be created showing all heparin values over time per visit, at pre-treatment all values will be shown. Change from baseline per visit will be calculated. Baseline in this case will be the mean of all pre-treatment values. This will be done for the full study period.

Any changes to the dialysis prescription and compliance will be summarized by visit and treatment group.

6.4.9 Pregnancies

Any pregnancy occurring in a study subject (or in partners of study subjects) during the subject's participation in this study will be displayed.

6.5 Data affected by the regional crisis

Data 'affected' by the war in the Ukraine will be assessed during the final Blind Review Meeting and will be documented in the Blind Review Report. As the war started after the primary analysis was completed, it is expected that only data in the post study intervention period will be affected, the impact of the war is considered to be minor/not substantial on the statistical analysis and on interpretation on the study results.

Any missing or invalid (not confirmed) data due to the war is considered as not related to the outcomes of the study i.e. the missingness is likely noninformative. The EMA guidance "Points to consider on the impact of the war in Ukraine on methodological aspects of ongoing clinical trials" released by the Biostatistics Working Party will be taken into account.

7. Document history and changes in the planned statistical analysis

7.1 Version 1.0

Version 1.0 of the SAP was finalized on 26 JUL 2020.

7.2 Version 2.0

Version 2.0 of the SAP was finalized on 26 OCT 2021 with the following edits and additions:

Section 2:

- Add the following sentence "Changes in the background therapy etc. will be handled following the treatment policy strategy. Other potential intercurrent events are not anticipated."
- Change description of the COVID-19 problematic

Section 6.1.1:

- Add categories for demography and baseline characteristics

Section 6.1.3:

- Describe the used time windows in more detail.

Section 6.2.1:

- Change "Death due to MI, stroke, pulmonary embolism (PE) and systemic embolism (SE)" to "Death due to MI, ischemic stroke, pulmonary embolism (PE) and systemic embolism (SE)"
- Change "Non-fatal stroke" to "Non-fatal stroke (ischemic stroke or undetermined type)"

Reordering of sections: former Section 6.2.4 is now section 6.2.2 and was renamed to Supplementary Analysis. Efficacy Analysis for the overall study period and full study period in SAF was added. Sensitivity analyses (stratified analyses) were deleted.

Section 6.2.3:

- Analyses of SQCS as categories and as scores were clarified.

Section 6.2.4:

- Forestplots are descried in more detail

Section 6.4.1:

- The whole analysis is described in more detail regarding the estimand thematic (cause specific inciedence rates). Aalen-Johansen will be used instead of Kaplan-Meier.

Reordering of sections: former Section 6.4.4 is now section 6.4.2 and was renamed to Supplementary Analysis. Sensitivity analysis (stratified analyses) were deleted

Section 6.4.3: Full Safety Analyses was added to this chapter and typo was deleted (Use SAF instead of FAS).

Section 6.4.4:

- Add name of safety variable
- Forestplots are described in more detail.

7.3 Version 3.0

Version 3.0 of the SAP was finalized on 10 JUN 2022 with the following edits and additions:

Section 6.3: Procedure how to deal with the data issue of having duplicates was described in detail for the primary completion analysis and for the final analyses.

Section 6.4.7: Procedure how to deal with the data issue of having duplicates was described in detail.

Section 6.5: Section was added relating to the handling of the data affected by the the war in Ukraine. Corresponding EMA guideline was added to the reference section.

7.4 Version 4.0

Version 4.0 of the SAP was finalized on 23 JUN 2022 with the following edits and additions:

Section 4.5.1: It is given that laboratory records without a RAVE Datapage ID (corresponding record in the electronic case report form is missing) will be excluded from the analysis.

8. References

Aalen O, Borgan O, Gjessing H. *Survival and Event History Analysis*, New York, Springer, 2008.

Biostatistics Working Party, EMA/214249/2022; Points to consider on the impact of the war in Ukraine on methodological aspects of ongoing clinical trials; 13 April 2022.

Nelson W. *Applied Life Data Analysis.* New York: Wiley, 1982.

Newcombe RG. Interval estimation for the difference between independent proportions: comparison of eleven methods. Stat Med. 1998; 17:873-90.

9. Appendix

9.1 Determination of sample size

Assuming 25% screen failure proportion as based on historic operational experience, approximately 800 subjects will be screened to achieve an estimated total of approximately 600 subjects randomly assigned to study intervention. Of those, 555 subjects are expected to complete the main treatment period assuming a true incidence rate of 15 subjects with LTFU (lost to follow-up) (including e.g., withdrawal of consent) per 100 patient-years across all groups.

As a subject will be evaluated once he was randomized and received at least one dose of study intervention, the number of evaluable and randomized subjects can be assumed to be similar.

In case that the observed overall incidence rate of subjects with LTFU after the 400th subjects significantly higher than expected, the number of randomized participants may be increased (max. of 750 subjects) to ensure a sufficient number of subjects completing the main treatment period.

As all analyses will be performed in a descriptive manner, no statistically driven sample size calculation was performed.

The expected 90% confidence interval for the hazard ratio of the primary safety outcome is given by [0.57; 2.28], assuming

- a true incidence rate of 10 subjects with a major or clinically relevant non-major bleeding event (in alignment with ISTH guidelines) per 100 patient-years in the placebo group (see below for definition)
- a true hazard ratio of 1.0 (i.e. no change in relative risk) in both osocimab groups as compared to placebo
- 6 months of treatment with a true incidence rate of 15 subjects with LTFU per 100 patient-years across all groups.

The corresponding expected 90% confidence interval for the hazard ratio of the primary efficacy outcome is given by [0.44; 1.53]. while additionally assuming

- a true incidence rate of 13 subjects with a main efficacy outcome per 100 patient-years in the placebo group.
- a true hazard ratio of 0.75 in both osocimab groups as compared to placebo

9.2 Randomization Methodology

STEP 1:

Taking each of the balancing (stratification) factors contained in Section 3.4 in turn (with associated factor weight), and only considering the factor level relevant to the current subject being randomized, the following is determined:

- Determine the number of subjects currently assigned to each treatment arm: n_A, n_B, n_C, n_D.
- Obtain the allocation ratios for each treatment arm: r_A, r_B, r_C, r_D.
- Calculate the Treatment Imbalance value for each treatment arm (for that factor level):
  - To calculate the Ranges (as below), the IXRS actually calculates each pairwise imbalance (the range of each pair of values), and then determines which pair of values has the maximum pairwise imbalance – this is exactly equivalent to calculating the range over all applicable values.
  - Factor weights are applied as part of the Treatment imbalance calculations (where a higher factor weight value implies more 'weight' being given to that factor relative to other factor(s)).
  - Calculations also account for associated allocation ratios (for a fair comparison) by multiplying by all 'opposite' allocation ratios (where for A:B:C:D with 2:1:2:1 ratio, values for Treatments=(A, B, C, D) will be multiplied by (x2, x4, x2, x4) respectively):
    - Imbalance_A: Max (Range[r_B * r_C * r_D * (n_A+1),r_A * r_C * r_D * (n_B)],
      Range[r_B * r_C * r_D * (n_A+1), r_A * r_B * r_D * (n_C)],
      Range[r_B * r_C * r_D * (n_A+1), r_A * r_B * r_C * (n_D)],
      Range[r_A * r_C * r_D * (n_B), r_A * r_B * r_D * (n_C)],
      Range[r_A * r_C * r_D * (n_B), r_A * r_B * r_C * (n_D)],
      Range[r_A * r_B * r_D * (n_C), r_A * r_B * r_C * (n_D)]) * <factor weight>
    - Imbalance_B: Max (Range[r_B * r_C * r_D * (n_A), r_A * r_C * r_D * (n_B+1)],
      Range[r_B * r_C * r_D * (n_A), r_A * r_B * r_D * (n_C)],
      Range[r_B * r_C * r_D * (n_A), r_A * r_B * r_C * (n_D)],
      Range[r_A * r_C * r_D * (n_B+1), r_A * r_B * r_D * (n_C)],
      Range[r_A * r_C * r_D * (n_B+1), r_A * r_B * r_C * (n_D)],
      Range[r_A * r_B * r_D * (n_C), r_A * r_B * r_C * (n_D)]) * <factor weight>
    - Imbalance_C: Max (Range[r_B * r_C * r_D * (n_A), r_A * r_C * r_D * (n_B)],
      Range[r_B * r_C * r_D * (n_A), r_A * r_B * r_D * (n_C+1)],
      Range[r_B * r_C * r_D * (n_A), r_A * r_B * r_C * (n_D)],
      Range[r_A * r_C * r_D * (n_B), r_A * r_B * r_D * (n_C+1)],
      Range[r_A * r_C * r_D * (n_B), r_A * r_B * r_C * (n_D)],
      Range[r_A * r_B * r_D * (n_C+1), r_A * r_B * r_C * (n_D)]) * <factor weight>
    - Imbalance_D: Max (Range[r_B * r_C * r_D *(n_A), r_A * r_C * r_D * (n_B)],
      Range[r_B * r_C * r_D * (n_A), r_A * r_B * r_D * (n_C)],
      Range[r_B * r_C * r_D * (n_A), r_A * r_B * r_C * (n_D+1)],
      Range[r_A * r_C * r_D * (n_B), r_A * r_B * r_D * (n_C)],
      Range[r_A * r_C * r_D * (n_B), r_A * r_B * r_C * (n_D+1)],
      Range[r_A * r_B * r_D * (n_C), r_A * r_B * r_C * (n_D+1)]) * <factor weight>

STEP 2:

Calculate the Total Imbalance value for each treatment arm by summing the calculated Treatment Imbalance values for that treatment arm over each of the factor levels.

STEP 3:

Determine the Minimum Imbalance value across the calculated Total Imbalance values for each treatment arm, and which of the treatment arm(s) have this Minimum Imbalance value.

STEP 4:

Based on Table 4.3 (below), assign a Treatment Assignment Probability to each treatment arm; the assigned probabilities are determined by the total number of treatment arms sharing the Minimum Imbalance value and each treatment Total Imbalance value.

The IXRS performs the Probabilistic Treatment Assignment by utilizing a Random Numbers List (generated by Almac – see Section 6) which contains generated random numbers between 0 and 1. For each subject's randomization, the next available random number from the Random Numbers List is allocated to the subject. Based on the associated random number ranges in Table 4.3, the treatment assignment is made by determining the range within which the allocated random number for that subject lies.

9.3 Treatment Assignment Probabilities

Section 9.2 (Step 4) above describes how the IwRS allocates a random number to each subject to perform the probabilistic treatment assignment by comparing the allocated random number with the random number ranges associated with each of the treatment arms.

The IwRS utilizes the following rules when determining the random number ranges to be assigned to each treatment arm:

- Treatment arms with Minimum Imbalance value are sorted alphabetically
- Treatment arms with Total Imbalance value > Minimum Imbalance value are sorted by (a) lowest Total Imbalance value, and (b) alphabetically.

The table below outlines the Treatment Assignment Probabilities and the random number ranges for each treatment group (based on the defined Treatment Assignment Probabilities) that will be utilized for this study.

Treatment Assignment Probabilities and Associated Random Number Ranges

		Treatment Assignment Probabilities [associated random number range to be utilized by the IXRS]			
		Trt A	**Trt B**	**Trt C**	**Trt D**
Minimum Imbalance: 1 arm					
Min. Imbalance = Trt A	Imbalance(Trt B) <= Imbalance(Trt C) <= Imbalance(Trt D)	p=0.85000 [0.00001-0.85000]	p=0.03750 [0.85001-0.88750]	p=0.07500 [0.88751-0.96250]	p=0.03750 [0.96251-0.99999]
	Imbalance(Trt B) <= Imbalance(Trt	p=0.85000 [0.00001-0.85000]	p=0.03750 [0.85001-0.88750]	p=0.07500 [0.92501-0.99999]	p=0.03750 [0.88751-0.92500]

	D) < Imbalance(Trt C)				
	Imbalance(Trt C) < Imbalance(Trt B) <= Imbalance(Trt D)	p=0.85000 [0.00001-0.85000]	p=0.03750 [0.92501-0.96250]	p=0.07500 [0.85001-0.92500]	p=0.03750 [0.96251-0.99999]
	Imbalance(Trt C) <= Imbalance(Trt D) < Imbalance(Trt B)	p=0.85000 [0.00001-0.85000]	p=0.03750 [0.96251-0.99999]	p=0.07500 [0.85001-0.92500]	p=0.03750 [0.92501-0.96250]
	Imbalance(Trt D) < Imbalance(Trt B) <= Imbalance(Trt C)	p=0.85000 [0.00001-0.85000]	p=0.03750 [0.88751-0.92500]	p=0.07500 [0.92501-0.99999]	p=0.03750 [0.85001-0.88750]
	Imbalance(Trt D) < Imbalance(Trt C) < Imbalance(Trt B)	p=0.85000 [0.00001-0.85000]	p=0.03750 [0.96251-0.99999]	p=0.07500 [0.88751-0.96250]	p=0.03750 [0.85001-0.88750]
Min. Imbalance = Trt B	Imbalance(Trt A) <= Imbalance(Trt C) <= Imbalance(Trt D)	p=0.06000 [0.85001-0.91000]	p=0.85000 [0.00001-0.85000]	p=0.06000 [0.91001-0.97000]	p=0.03000 [0.97001-0.99999]
	Imbalance(Trt A) <= Imbalance(Trt D) < Imbalance(Trt C)	p=0.06000 [0.85001-0.91000]	p=0.85000 [0.00001-0.85000]	p=0.06000 [0.94001-0.99999]	p=0.03000 [0.91001-0.94000]
	Imbalance(Trt C) < Imbalance(Trt A) <= Imbalance(Trt D)	p=0.06000 [0.91001-0.97000]	p=0.85000 [0.00001-0.85000]	p=0.06000 [0.85001-0.91000]	p=0.03000 [0.97001-0.99999]
	Imbalance(Trt C) <= Imbalance(Trt D) < Imbalance(Trt A)	p=0.06000 [0.94001-0.99999]	p=0.85000 [0.00001-0.85000]	p=0.06000 [0.85001-0.91000]	p=0.03000 [0.91001-0.94000]
	Imbalance(Trt D) < Imbalance(Trt A) <= Imbalance(Trt	p=0.06000 [0.88001-0.94000]	p=0.85000 [0.00001-0.85000]	p=0.06000 [0.94001-0.99999]	p=0.03000 [0.85001-0.88000]

	C)				
	Imbalance(Trt D) < Imbalance(Trt C) < Imbalance(Trt A)	p=0.06000 [0.94001-0.99999]	p=0.85000 [0.00001-0.85000]	p=0.06000 [0.88001-0.94000]	p=0.03000 [0.85001-0.88000]
		Treatment Assignment Probabilities [associated random number range to be utilized by the IXRS]			
		Trt A	**Trt B**	**Trt C**	**Trt D**
Minimum Imbalance: 1 arm (continued)					
Min. Imbalance = Trt C	Imbalance(Trt A) <= Imbalance(Trt B) <= Imbalance(Trt D)	p=0.07500 [0.85001-0.92500]	p=0.03750 [0.92501-0.96250]	p=0.85000 [0.00001-0.85000]	p=0.03750 [0.96251-0.99999]
	Imbalance(Trt A) <= Imbalance(Trt D) < Imbalance(Trt B)	p=0.07500 [0.85001-0.92500]	p=0.03750 [0.96251-0.99999]	p=0.85000 [0.00001-0.85000]	p=0.03750 [0.92501-0.96250]
	Imbalance(Trt B) < Imbalance(Trt A) <= Imbalance(Trt D)	p=0.07500 [0.88751-0.96250]	p=0.03750 [0.85001-0.88750]	p=0.85000 [0.00001-0.85000]	p=0.03750 [0.96251-0.99999]
	Imbalance(Trt B) <= Imbalance(Trt D) < Imbalance(Trt A)	p=0.07500 [0.92501-0.99999]	p=0.03750 [0.85001-0.88750]	p=0.85000 [0.00001-0.85000]	p=0.03750 [0.88751-0.92500]
	Imbalance(Trt D) < Imbalance(Trt A) <= Imbalance(Trt B)	p=0.07500 [0.88751-0.96250]	p=0.03750 [0.96251-0.99999]	p=0.85000 [0.00001-0.85000]	p=0.03750 [0.85001-0.88750]
	Imbalance(Trt D) < Imbalance(Trt B) < Imbalance(Trt A)	p=0.07500 [0.92501-0.99999]	p=0.03750 [0.88751-0.92500]	p=0.85000 [0.00001-0.85000]	p=0.03750 [0.85001-0.88750]
Min. Imbalance = Trt D	Imbalance(Trt A) <= Imbalance(Trt B) <= Imbalance(Trt C)	p=0.06000 [0.85001-0.91000]	p=0.03000 [0.91001-0.94000]	p=0.06000 [0.94001-0.99999]	p=0.85000 [0.00001-0.85000]
	Imbalance(Trt A) <= Imbalance(Trt	p=0.06000 [0.85001-0.91000]	p=0.03000 [0.97001-0.99999]	p=0.06000 [0.91001-0.97000]	p=0.85000 [0.00001-0.85000]

	C) < Imbalance(Trt B)				
	Imbalance(Trt B) < Imbalance(Trt A) <= Imbalance(Trt C)	p=0.06000 [0.88001-0.94000]	p=0.03000 [0.85001-0.88000]	p=0.06000 [0.94001-0.99999]	p=0.85000 [0.00001-0.85000]
	Imbalance(Trt B) <= Imbalance(Trt C) < Imbalance(Trt A)	p=0.06000 [0.94001-0.99999]	p=0.03000 [0.85001-0.88000]	p=0.06000 [0.88001-0.94000]	p=0.85000 [0.00001-0.85000]
	Imbalance(Trt C) < Imbalance(Trt A) <= Imbalance(Trt B)	p=0.06000 [0.91001-0.97000]	p=0.03000 [0.97001-0.99999]	p=0.06000 [0.85001-0.91000]	p=0.85000 [0.00001-0.85000]
	Imbalance(Trt C) < Imbalance(Trt B) < Imbalance(Trt A)	p=0.06000 [0.94001-0.99999]	p=0.03000 [0.91001-0.94000]	p=0.06000 [0.85001-0.91000]	p=0.85000 [0.00001-0.85000]

		Treatment Assignment Probabilities [associated random number range to be utilized by the IXRS]			
		Trt A	**Trt B**	**Trt C**	**Trt D**
Minimum Imbalance: 2 arms					
Min. Imbalance = Trt A, Trt B	Imbalance(Trt C) <= Imbalance(Trt D)	p=0.56667 [0.00001-0.56667]	p=0.28333 [0.56668-0.85000]	p=0.10000 [0.85001-0.95000]	p=0.05000 [0.95000-0.99999]
	Imbalance(Trt D) < Imbalance(Trt C)	p=0.56667 [0.00001-0.56667]	p=0.28333 [0.56668-0.85000]	p=0.10000 [0.90001-0.99999]	p=0.05000 [0.85001-0.90000]
Min. Imbalance = Trt A, Trt C	Imbalance(Trt B) <= Imbalance(Trt D)	p=0.42500 [0.00001-0.42500]	p=0.07500 [0.85001-0.92500]	p=0.42500 [0.42501-0.85000]	p=0.07500 [0.92501-0.99999]
	Imbalance(Trt D) < Imbalance(Trt B)	p=0.42500 [0.00001-0.42500]	p=0.07500 [0.92501-0.99999]	p=0.42500 [0.42501-0.85000]	p=0.07500 [0.85001-0.92500]
Min. Imbalance = Trt A, Trt D	Imbalance(Trt B) <= Imbalance(Trt C)	p=0.56667 [0.00001-0.56667]	p=0.05000 [0.85001-0.90000]	p=0.10000 [0.90001-0.99999]	p=0.28333 [0.56668-0.85000]
	Imbalance(Trt C) < Imbalance(Trt B)	p=0.56667 [0.00001-0.56667]	p=0.05000 [0.95001-0.99999]	p=0.10000 [0.85001-0.95000]	p=0.28333 [0.56668-0.85000]
Min. Imbalance = Trt B, Trt C	Imbalance(Trt A) <= Imbalance(Trt D)	p=0.10000 [0.85001-0.95000]	p=0.28333 [0.00001-0.28333]	p=0.56667 [0.28334-0.85000]	p=0.05000 [0.95000-0.99999]
	Imbalance(Trt D) < Imbalance(Trt A)	p=0.10000 [0.90001-0.99999]	p=0.28333 [0.00001-0.28333]	p=0.56667 [0.28334-0.85000]	p=0.05000 [0.85001-0.90000]
Min. Imbalance = Trt B, Trt D	Imbalance(Trt A) <= Imbalance(Trt C)	p=0.07500 [0.85001-0.92500]	p=0.42500 [0.00001-0.42500]	p=0.07500 [0.92501-0.99999]	p=0.42500 [0.42501-0.85000]
	Imbalance(Trt C) < Imbalance(Trt A)	p=0.07500 [0.92501-0.99999]	p=0.42500 [0.00001-0.42500]	p=0.07500 [0.85001-0.92500]	p=0.42500 [0.42501-0.85000]
Min. Imbalance = Trt C, Trt D	Imbalance(Trt A) <= Imbalance(Trt B)	p=0.10000 [0.85001-0.95000]	p=0.05000 [0.95000-0.99999]	p=0.56667 [0.00001-0.56667]	p=0.28333 [0.56668-0.85000]
	Imbalance(Trt B) < Imbalance(Trt A)	p=0.10000 [0.90001-0.99999]	p=0.05000 [0.85001-0.90000]	p=0.56667 [0.00001-0.56667]	p=0.28333 [0.56668-0.85000]
Min. Imbalance: 3 arms					
Min. Imbalance = Trt A, Trt B, Trt C		p=0.34000 [0.00001-	p=0.17000 [0.34001-	p=0.34000 [0.51001-0.85000]	p=0.15000 [0.85001-0.99999]

	0.34000]	0.51000]		
Min. Imbalance = Trt A, Trt B, Trt D	p=0.425000 [0.00001-0.42500]	p=0.21250 [0.42501-0.63750]	p=0.15000 [0.85001-0.99999]	p=0.21250 [0.63751-0.85000]
Min. Imbalance = Trt A, Trt C, Trt D	p=0.34000 [0.00001-0.34000]	p=0.15000 [0.85001-0.99999]	p=0.34000 [0.34001-0.68000]	p=0.17000 [0.68001-0.85000]
Min. Imbalance = Trt B, Trt C, Trt D	p=0.15000 [0.85001-0.99999]	p=0.21250 [0.00001-0.21250]	p=0.425000 [0.21251-0.63750]	p=0.21250 [0.63751-0.85000]
Min. Imbalance: 4 arms				
Min. Imbalance = Trt A, Trt B, Trt C, Trt D	p=0.33333 [0.00001-0.33333]	p=0.16667 [0.33334-0.50000]	p=0.33333 [0.50001-0.83333]	p=0.16667 [0.83334-0.99999]