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Study Title: A Multicenter, Randomized, Subject- and Investigator-blinded, Placebo-controlled, Parallel-group, Dose-range Finding Study to Assess the Pharmacokinetic and Pharmacodynamic Parameters, Safety, Tolerability, and Immunogenicity of MAA868 in Patients with Atrial Fibrillation

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Statistical Analysis Plan

Anthos

ANT-004

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Reviewers

The following reviews of the SAP were conducted:

Name and Title	Role	Version Last Reviewed	Company/ Organization
[redacted] Biostatistician	Peer Review Statistician	Draft 1	[redacted]

Glossary of Abbreviations

Abbreviation	Term
AE	Adverse Event
AESI	Adver e Event of Special Intere t
AF	Atrial fibrillation
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
bpm	Beats per Minute
°C	Celsius
CK	Creatine Kinase
CRNM	Clinically relevant nonmajor
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EoS	End of study
FAS	Full Analysis Set
FXI	Factor XI
GGT	Gamma-Glutamyltransferase
kg	Kilograms
LC-MS	Liquid Chromatography-Mass Spectrometry
LDH	Lactate Dehydrogenase
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mmHg	Millimeters of Mercury
msec	Millisecond
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per-protocol
PT	Preferred Term
QTcB	Bazett corrected QT interval
QTcF	Fridericia corrected QT interval
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software

Abbreviation	Term
SBP	Systolic Blood Pressure
s.c.	Subcutaneous
SD	Standard Deviation
SI	International System of Units
SOC	System Organ Class
TBD	To be Determined
TD	Treatment Discontinuation
TEAE	Treatment-emergent Adverse Event
TFLs	Tables, Figures, and Listings
VTE	Venous Thromboembolic Events
WHO	World Health Organization

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	01-November-2019	Version 2.0
Electronic Case Report Form (eCRF)	27-March-2020	Version 1.0

2. Protocol Details

2.1 Study Objectives

- Primary:
  To evaluate the proportion of subjects that achieve ≥50%, ≥80%, or ≥90% Factor XI (FXI) inhibition at trough after the third dose (Day 91) at different dose levels of MAA868.
- Secondary:
  1. To evaluate the proportion of subjects achieving FXI inhibition ≥50%, ≥80%, and ≥90% at trough after the first and second dose (Day 31 and Day 61) at different dose levels of MAA868.
  2. To evaluate the safety and tolerability following multiple s.c. administration of MAA868 compared to placebo in subjects with AF.
  3. To evaluate the incidence of major bleeding events, clinically relevant non-major bleeding events, and total bleeding with MAA868 relative to placebo during the treatment period.
  4. To evaluate the immunogenicity of MAA868 compared to placebo.
- Exploratory:
  1. To evaluate the effect of MAA868 compared to placebo on the incidence of major cardiovascular, cerebrovascular, and venous thromboembolic events.
  2. To evaluate the change from baseline in D-dimer and other thrombogenesis markers with MAA868 relative to placebo during the treatment period.

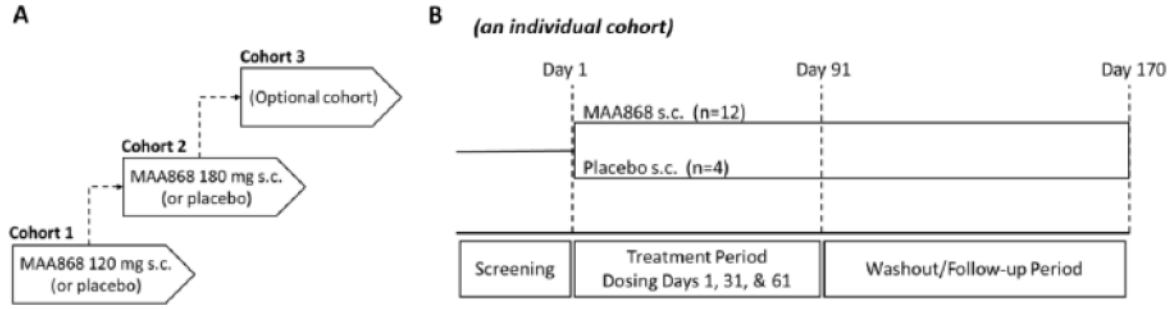
2.2 Overall Study Design

This is a phase 2a, randomized, double-blind, placebo-controlled, multiple ascending dose-ranging study to assess the pharmacokinetics, pharmacodynamics, safety, tolerability, and immunogenicity of MAA868 in subjects with AF or flutter.

There will be two cohorts (with an optional third) consisting of 16 subjects each. Each cohort will be randomized 3:1 to receive MAA868 or placebo, respectively, on day 1 and will receive two subsequent monthly injections on day 31 and 61. Subjects in cohort 1 randomized to MAA868 will receive a dose of 120 mg. After approximately 10 of the subjects in cohort 1 have received their second dose of study drug and have been followed for at least an additional 14 days, an interim analysis (detailed in section 7.9) of emerging safety and tolerability data from cohort 1 will be carried out. Cohort 2 will be initiated after it is confirmed that the cohort 1 dose was safe and tolerated and at least half of the subjects in cohort 1 have been randomized. Subjects in cohort 2 randomized to MAA868 will receive a dose of 180 mg. Likewise, after 10 of the subjects in cohort 2 have received their second dose and have been followed for at least an additional 14 days, a second interim safety and tolerability analysis will be conducted. Based on emerging data, the Sponsor may elect to enroll cohort 3 to evaluate a new dosage of MAA868 or terminate the study.

The overall study design is presented in Figure 1 below.

Figure 1: Overall Study Design



The study is comprised of 3 periods: screening period, treatment period, and follow-up period. The screening period may last up to 4 weeks. The treatment period is 91 days and consists of 3 monthly subcutaneous doses of MAA868 (or matching placebo). Study drug is administered at the study site on day 1 (visit 2), day 31 (visit 4), and day 61 (visit 6). During the treatment period, subjects will return to the study site on day 11, day 31, day 41, day 61, day 71, and day 91 for safety assessments. The follow-up period is 79 days and continues to day 170, allowing a 110-day washout period from the last study drug administration. During the follow-up period, subjects will return to the study site on day 101, day 121, and day 170 (EoS) for additional safety evaluations.

2.3 Sample Size and Power

A sample size of 16 subjects per treatment dose cohort with a ratio of 3:1 for MAA868 and placebo treatment assignment is based on historic data considerations. For

example, if the observed proportion of subjects in a cohort achieving target levels of inhibition is 11/12, the exact 90% confidence interval would be 0.661 to 0.996.

3. Study Endpoints

3.1 Primary Endpoint

The primary efficacy endpoint is the proportion of subjects achieving ≥50%, ≥80%, or ≥90% inhibition of FXI (<50%, <20%, or <10% free FXI) at trough on Day 91 at different dose levels of MAA868.

3.2 Secondary Endpoints

Efficacy

- The proportion of subjects achieving ≥50%, ≥80%, or ≥90% inhibition of FXI (<50%, <20%, or <10% free FXI) at trough on Day 31 and Day 61 at different dose levels of MAA868.

Safety

- All safety assessment results during the treatment and follow-up periods. Safety endpoints include:
  - Adverse Events (AE)
  - Physical exam
  - Laboratory parameters
  - Vital Signs
  - Electrocardiogram (ECG)
  - Hypersensitivity reactions
  - Injection site reactions

- Occurrence of confirmed major bleeding events, clinically relevant non-major (CRNM) bleeding events, and total bleeding events during the treatment period.

- Identification of anti-drug (MAA868) antibodies using a ligand-binding assay.

3.3 Exploratory Endpoints

Safety

- Occurrence of major cardiovascular, cerebrovascular, systemic arterial, and venous thromboembolic events (VTEs).

- Concentrations of D-dimer and other exploratory thrombogenesis markers during the treatment period.

4. Pharmacokinetic/Pharmacodynamic Variables

4.1 Pharmacokinetic Analysis

PK samples will be obtained and evaluated at all post-screening visits (where data permit) in all subjects at all dose levels using the actual recorded sampling times. Untreated (placebo) samples will not be analyzed. All concentrations below the lower limit of quantitation (LLOQ) or missing data will be labeled as such in the concentration data listings.

The concentration-times courses of abelacimab will be tabulated for each sampling interval. Individual and geometric mean concentration vs time curves of MAA868 (using the actual sampling times for individual plots and the planned sampling intervals for mean plots) will be plotted using both linear and semilogarithmic scale.

The following pharmacokinetic parameters will be estimated, where data permit, from the plasma concentrations of total MAA868 following the Day 61 dose administration using noncompartmental methods in validated software program Phoenix WinNonlin (Certara, Version 8.1 or higher):

Parameter	Units[a]	Definition
AUC_{last}	h*µg/mL	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration[b]
C_{max}	µg/mL	maximum observed concentration within the postdose concentration-time profile[c]
C_{min}	µg/mL	minimum observed concentration within the postdose concentration-time profile
$DAUC_{last}$	h*µg/mL/mg	AUC_{last} normalized by dose administered[d]
DC_{max}	µg/mL/mg	C_{max} normalized by dose administered[d]

[a] Units are based on concentration units (provided by the bioanalytical lab or preferred units for presentation of PK parameters) and dose units used in the study.
[b] Area under the concentration-time curve will be calculated using the linear trapezoidal rule for increasing and decreasing concentrations
[c] Due to the sparse sampling, this may not directly correspond to the C_{max} of MAA868 determined with intensive sampling schemes.
[d] Calculated by dividing the parameter by the dose (mg)

Additional PK parameters may be determined where appropriate.

Pharmacokinetic analysis will be carried out where possible using actual blood sampling times postdose. If an actual time is missing, the sample concentration result will be treated as missing unless there is scientific justification to include the result using the nominal time.

The parameters C_{max} and C_{min} will be obtained directly from the concentration-time profiles.

4.1.1 Criteria for Calculation and Reporting of Area Under the Concentration-time Curve

The minimum requirement for the calculation of area under the concentration-time curve (AUC) will be the inclusion of at least 3 consecutive concentrations above the lower limit of quantification. If there are only 3 consecutive concentrations, at least 1 should follow C_{max}.

4.1.2 Criteria for Handling Missing or Concentrations Below the Limit of Quantification in Pharmacokinetic Analysis

Plasma concentrations below the limit of quantification (BLQ) will be assigned a value of 0 before the first measurable concentration and thereafter BLQs will be treated as missing. The following rules apply with special situations defined below:

- If an entire concentration-time profile is BLQ, it will be excluded from PK analysis.
- Where 2 or more consecutive concentrations are BLQ at the end of a profile, the profile will be deemed to have terminated and any further quantifiable concentrations will be set to missing for the calculation of the PK parameters, unless they are considered to be a true characteristic of the profile of the drug.

4.1.3 Treatment of Outliers in Pharmacokinetic Analysis

If a value is considered to be anomalous due to being inconsistent with the expected PK profile, it may be appropriate to exclude the value from the PK analysis. However, the exclusion of any data must have strong justification and will be documented in the CSR.

4.2 Pharmacodynamic Variables

The following Pharmacodynamic (PD) parameters will be estimated:

- Free FXI
- Activated partial thromboplastin time (aPTT)
- Total FXI
- FXI coagulation activity (FXI:C)

PD parameters are used in the primary endpoint analysis. PD samples will be obtained and evaluated in all subjects at all dose levels. PD parameters aPTT, Free FXI, and Total FXI are collected at all visits. FXI coagulation activity is collected at day 1, day 61, day 91, and EoS. Concentrations of plasma total MAA868 (i.e., MAA868 that is bound to FXI or not bound to FXI) will be measured in plasma and determined by a validated LC-MS/MS method.

5. Analysis Populations/Sets

5.1 All Randomized Set

The all randomized set will include all subjects who are randomized.

5.2 Safety Set

The safety set will include randomized subjects who received at least one dose of study drug. Subjects will be analyzed based on the actual treatment taken.

5.3 Full Analysis Set (FAS)

The full analysis set will include all randomized subjects who had at least one dose of study drug and at least one post-baseline assessment. This set excludes subjects who are randomized into the study in error and did not receive study drug. Subjects will be analyzed based on the assigned treatment at the randomization.

5.4 Per Protocol Set

The per-protocol set will include subjects in Full Analysis Set that have no important protocol deviations after randomization.

Protocol deviations are defined as any change, divergence, or departure from the study design or procedures defined in the study protocol. Important protocol deviations are a subset of protocol deviations and may significantly impact the correctness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

5.4.1 Important Protocol Deviations Leading to Exclusion from the PP

Only those important protocol deviations considered to have a major effect on efficacy will lead to complete exclusion of the subject from the PP. For the purposes

of this study, the list of subjects that have been identified as important protocol deviations leading to exclusion from the PP set is listed below. It is considered that the occurrences of any of these criteria might have an important influence on the primary efficacy endpoint.

Missed IMP dose

Missed FXI collection at V8, D91

Missed FXI collection at V2, Randomization

Out of window visit greater than 30 days

Most of the important protocol deviations leading to exclusion from the PP set require clinical or medical monitoring interpretation. These criteria will be reviewed prior to database lock. Important protocol deviations leading to exclusion from the PP set occurring during the study will be reviewed and approved by Anthos prior to database lock. Should additional important protocol deviations leading to exclusion from the PP set, not anticipated at the time of preparing this SAP, be identified during the study they will be documented in a SAP amendment and included in all relevant protocol deviation reviews and approvals.

5.5 PK/PD Analysis Set

The PK/PD analysis set will include all subjects who received at least one dose of study drug and have at least one PK/PD assessment.

6. Data Handling

6.1 Time points and Visit Windows

Day 1 is defined as the day subjects receive the first dose of study drug. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1.

Baseline is defined as the most recent result obtained prior to first administration of study medication. This occurs at visit 2 (day 1 pre-dose). If the assessment is not performed at visit 2, the value from visit 1 (screening) will be used. If this value is not present, there will be no baseline value.

Trough FXI levels will only be used if they are considered "on treatment". A measurement is considered "on treatment" if it is collected within 30 (±5) days after the last administration of MAA868.

All data will be analyzed using nominal study visits as defined in the schedule of assessments and eCRF. Unscheduled visits will be listed but not tabulated. No visit windows will be applied for summary and analysis.

6.2 Handling of Dropouts, Missing Data, and Outliers

6.2.1 Study Discontinuation

Subjects who prematurely discontinue the study will undergo a study treatment discontinuation (TD) visit. Assessments performed at the TD visit are defined in appendix 4 of the protocol.

6.2.2 Missing Data

The occurrence of missing data related to the primary endpoint is considered a protocol deviation. Endpoint analyses will use observed data only – no imputation methods are planned.

Imputations of missing and partial dates are given below and to be used only for the following: assessment of treatment emergence status of an AE; determination of study day/time of onset and duration of an AE; definitions of prior and concomitant medications.

Missing or Partial Start Dates

- Missing time – the minimum possible onset time will be calculated and presented in '≥DD:HH:MM' format
- Missing day – impute the 1st of the month unless month is same as month of first dose of study drug then impute first dose date.
- Missing day and month – impute 1st January unless year is the same as first dose date then impute first dose date.
- Completely missing – impute first dose date unless the end date suggests it could have started prior to this in which case impute the 1st of January of the same year as the end date.

Missing or Partial End Dates

- Missing time – the maximum possible duration will be calculated and presented in '≤DD:HH:MM' format
- Missing day – impute the last day of the month unless month is same as month of first dose of study drug then impute last dose date.
- Missing day and month – impute 31st December unless year is the same as first dose date then impute last dose date.

- Completely Missing – need to look at whether the AE/medication is still ongoing before imputing a date and when it started in relation to study drug. If the ongoing flag is missing, then assume that AE is still present / medication is still being taken (i.e., do not impute a date). If the AE/medication has stopped and start date is prior to first dose date then impute the 1st dose date, if it started on or after first dose date then impute a date that is after the last dose date.

6.2.3 Outliers

No rules for outlier detection are planned.

7. Statistical Methods

7.1 General Principles

All data processing, summarization and analyses will be performed using Covance's SAS Environment / Version 9.3 (or later) of the SAS® statistical software package.

The following principles will be applied to all TFLs unless otherwise stated:

Table 1: General Principles for the Presentation of Results

Principle	Value
Significant tests and confidence intervals	No significance tests will be conducted for the purpose of this analysis. For the primary efficacy endpoint, a 2-sided 90% confidence interval for the responder rate (%) at trough on Day 91 will be presented by treatment group for MAA868 arms only. For the secondary endpoint, a 2-sided 90% confidence interval for the responder rate (%) at trough on Day 31 and Day 61 will be presented by treatment group for MAA868 arms only.
Treatment group labels and order presented	MAA868 120 mg MAA868 180 mg MAA868 XXX mg (TBD for optional third cohort) Placebo (where applicable) All Subjects (where applicable)
Study phase labels and order presented	Study phase is not relevant to the analysis.
Visit labels and order presented	Listings will present data collected at all visits in the following order:

Principle	Value
	Screening (Visit 1) Visits 2 - 10 TD Visit EoS Visit Unscheduled visits will be included in chronological order. Tables will only present visits that correspond to the specified analysis.
Tables	For endpoints related to inhibition of FXI the data will be tabulated for each trough visit by treatment group. For endpoints related to the occurrence of major bleeding, cardiovascular, cerebrovascular, systemic arterial, and venous thromboembolic events, the data will be tabulated by treatment group. For endpoints related to assessments performed at the study site visits, the data will be tabulated by each treatment group for all applicable scheduled visits.
Listings	All data collected, as well as derived data used in the analyses, will be presented in listings by population/set, treatment group, and visit (where applicable), unless otherwise specified.
Descriptive summary statistics for continuous variables	Non-PK parameters will be summarized by number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max). For a numeric result presented in the database with a "<", "≤", ">", or "≥" preceding the number, the value at the numeric part will be used in the summary. PK Parameters will be summarized by number of subjects (n), mean, standard deviation (SD), median, minimum (min), maximum (max), and Geometric Mean.
Descriptive summary statistics for categorical variables	Categorical variable will be summarized using frequency (N) and percentage (%).
Denominator for percentages	Number of subjects in the analysis population/set, unless stated otherwise in table shell(s).
Display for percentages	If the count is zero, then the percentage will not be presented. Otherwise, percentages will be rounded to 1 decimal place.
Include "Missing" as category	Yes, when the number missing is greater than zero for at least one treatment group.

Principle	Value
Display same number of decimal places as collected value	Minimum Maximum
Display to one more decimal place than collected value	Mean Standard Error Mean Difference Median Confidence Interval
Display to two more decimal places than collected value	Standard Deviation
Date Format	DDMMMYYYY
Source footnotes	Each table will have a footnote that lists the source data listing(s). Each figure will have a footnote that list the source table(s).
Dictionary names and versions	The dictionary names and versions will be included in a footnote in all AE and prior or concomitant medication TFLs that present coded terms from the dictionaries.

7.2 Subject Disposition and Data Sets Analyzed

Subject disposition will be listed and summarized by treatment group and overall and will include the number and percentage of subjects:

- Screened
- Randomized
- Randomized and not treated
- Treated
- Included in each study set (Safety, FAS, PP, PK/PD).

In addition, the number and percentage of subjects who complete the study and who discontinue early, including a breakdown of the primary reasons for discontinuation, will be presented for all screened subjects.

A summary of the reasons for screen failure as well as the number of subjects screened but not randomized will be produced. No other information for screen failures will be presented.

7.3 Protocol Deviations

Both important and non-important protocol deviations will be listed. Important protocol deviations defined in section 5.4.1 will be excluded from PP set, and summarized by treatment group. The deviations will be identified before data are unblinded.

7.4 COVID-19 Impact

All COVID-19 related study disruptions will be listed for each subject by investigational site. Disruptions causing dosing schedule deviations and missing visits will be listed separately for each subject. COVID-19 related protocol deviations will be summarized by treatment for the FAS.

7.5 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment group and overall for the randomized set and FAS. Standard descriptive statistics (see Table 1) will be presented for the continuous variables of:

- Age (years) [calculated as (informed consent date – date of birth)/365.25 and reported as whole years]
- Height (cm)
- Weight (kg)
- Body mass index (kg/m^2)

Standard descriptive statistics (see Table 1) will be presented for the categorical variables of:

- Age group (years) (grouped by decades: 18-20, 21-30, … 81-85)
- Gender
- Race
- Ethnicity

No formal tests of statistical significance will be performed on the demographic and baseline data. The mean of the three screening measurements for SBP and DBP will be used. A listing of subjects with abnormal physical examination findings at screening will be presented. Other baseline measurements will be summarized by treatment group with the post-baseline measurements.

7.5.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. All medical history will be listed, and the number and percentage of subjects with any medical history will be summarized separately for the randomized set and FAS by system organ class (SOC) and preferred term (PT) for each treatment group and overall.

7.5.2 Previous and Concomitant Medications

Medications received prior to or concomitantly with study drug will be coded by Covance using the WHO Drug Version March 2019 Global Dictionary Version B3 Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications will be listed and summarized separately for per protocol set and FAS. The number and percentage of subjects using each medication will be displayed together with the number and percentage of subjects using at least one medication within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and generic term.

7.6 Measurements of Compliance

Treatment compliance will not be summarized for this study.

Dose compliance will be calculated for each subject as: (number of doses occurring within protocol-defined study day window within 10% of the planned dose) / (number of doses received), then multiplied by 100.

7.7 Efficacy

All efficacy analysis will be presented by treatment group for MAA868 arms only using the PK/PD set. No comparisons to the placebo or statistical tests will be conducted for efficacy endpoints.

7.7.1 Primary Efficacy Analysis

The primary analysis variable is a binary variable indicating whether a subject will achieve a certain percentage FXI inhibition at trough on Day 91. The response rate per treatment group will be calculated by number of subjects who achieve targeted FXI inhibition rate divided by the total number of subjects with an "on treatment" measurement in the treatment group. The dose regimens and targeted FXI inhibition achievement for Cohorts 1 and 2 are as follows:

Cohort 1 (MAA868 120 mg monthly or placebo): Targeted to achieve ≥ 50% FXI inhibition in 90% of subjects at trough (Day 91).

Cohort 2 (MAA868 180 mg monthly or placebo): Targeted to achieve ≥ 90% FXI inhibition in 90% of subjects at trough (Day 91).

Cohort 3 (MAA868 TBD mg monthly or placebo): Targeted to achieve ≥ TBD% FXI inhibition in 90% of subjects at trough (Day 91).

The "on treatment" trough FXI levels will be used for the primary analysis, where "on treatment" FXI level is defined as a value which is collected within 30 (±5) days after the last administration of MAA868. The estimate of the responder rate (%) at Day 91 will be presented for each dose regimens of MAA868 together with 2-sided 90% confidence intervals computed via the Clopper-Pearson exact binomial method.

7.7.2 Secondary Efficacy Analysis

The secondary efficacy analysis is to evaluate the proportion of subjects achieving FXI inhibition ≥ 50%, ≥80%, and ≥90% at trough after the first and second dose (Day 31 and Day 61) at 3 dose levels of MAA868. The analyses described for the primary endpoint will be repeated for the secondary efficacy variables as follows:

- Cohort 1 (MAA868 120 mg monthly or placebo): at Day 31 and 61.
- Cohort 2 (MAA868 180 mg monthly or placebo): at Day 31 and 61
- Cohort 3 (MAA868 TBD mg monthly or placebo): at Day 31 and 61

No comparisons to the placebo or statistical tests will be conducted for the primary efficacy endpoint.

7.7.3 Sensitivity Analysis

There are no planned sensitivity analyses.

7.7.4 Subgroup Analysis

There are no planned subgroup analyses.

7.7.5 Exploratory Analysis

There are no exploratory efficacy endpoints.

7.8 Safety

All safety analysis will be presented by actual treatment group and overall using the safety set.

7.8.1 Extent of Exposure and Compliance

Study drug exposure will not be summarized for this study. Dose compliance will be summarized by treatment group and overall for the MAA868 arms only.

7.8.2 Adverse Events (AE)

All AEs recorded on the eCRF will be coded using the MedDRA dictionary version 22.0. Treatment-emergent Adverse Events (TEAEs) will be of primary interest and are defined as:

- AEs with a start date on or after the date of first dose of study drug and up to the EoS visit
- AEs with start date prior to the date of first dose of study drug whose severity worsens on or after the date of first dose of study drug

TEAEs will be summarized by system organ class (SOC) and preferred term (PT) by treatment group and overall. Subject counts and percentages and event counts will be presented for the following TEAE summaries:

- All TEAEs
- Serious TEAEs
- All TEAEs by severity
- All TEAEs by relationship to study drug
- TEAEs potentially related to study drug
- TEAEs potentially related to study drug by severity
- TEAEs leading to discontinuation of study drug
- TEAEs leading to withdrawal from study

A subject will only be counted once per SOC and once per PT. If a subject reports more than one AE with the same PT, the AE with the maximum severity will be presented. AE severity grades are mild, moderate, or severe. An AEs relationship to study drug is assessed as related, possibly related, or not related.

If the start date/time of an AE is incomplete or missing, the AE will be assumed to be a TEAE, unless the incomplete start date/time or the end date/time indicates an AE started prior to the start of the infusion. AEs with missing causality are assumed

to be related. If the severity of an AE is missing, the AE will be counted under the maximum severity possible.

Listings will be presented by subject for TEAEs, AESIs, serious AEs (SAEs), AEs leading to discontinuation of study drug, and AEs resulting in death.

No statistical comparisons of AEs between treatment groups will be performed.

7.8.3 Laboratory Evaluations

Data for hematology, blood chemistry, and urinalysis analytes received from central laboratory/recorded in the eCRF will be listed and summarized by treatment group and overall for each scheduled collection visit. Standard descriptive statistics (see Table 1) will be presented for the observed values and change from baseline. Baseline definition can be found in section 3.1.

A laboratory value that is within the central laboratory's reference range will be considered normal. A laboratory value that is outside the central laboratory's normal range will be considered abnormal and will be flagged as either high (H) or low (L). The number and percentage of subjects with abnormal laboratory values will be summarized for each analyte for each scheduled visit. Shift tables will be presented to display the shift in the normal range categories (low, normal, high) from baseline to each post-baseline visit for the following laboratory evaluations: hemoglobin, hematocrit, prothrombin time, activated partial thromboplastin time, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and creatinine.

Additionally, the number and percentage of subjects with clinically significant laboratory values will be summarized for each analyte for each scheduled visit.

The following analytes will be included in the analysis:

Hematology	Serum Chemistry	Urinalysis (dipstick)
Hemoglobin	Sodium	Specific Gravity
Hematocrit	Potassium	Protein
Red Blood Cell Count	Creatinine	Glucose
Platelets	Blood Urea Nitrogen	White Blood Cell Count
Neutrophils	Uric acid	Red blood Cell Count
Lymphocytes	Chloride	
Monocytes	Albumin	
Eosinophils	Calcium	
Basophils	Alkaline phosphatase	
Leukocytes	Total Bilirubin	
Activated Partial Thromboplastin Time (aPTT) -FSL	Direct Bilirubin*	
	Indirect Bilirubin*	
Prothrombin Time (PT)	Bicarbonate	
International Normalized Ratio (INR)	Lactate Dehydrogenase (LDH)	
	Gamma-Glutamyltransferase (GGT)	
	Aspartate aminotransferase (AST)	
	Alanine aminotransferase (ALT)	
	Creatine Kinase (CK)	
	Glucose	
	Total Cholesterol	
	Triglycerides	

*if Total Bilirubin >1.5x upper limit of normal

All clinical laboratory data will be presented in listings. Laboratory data will be summarized in SI units.

7.8.4 Vital Signs

The following vital signs will be summarized by treatment group and overall for each scheduled collection visit. Standard descriptive statistics (see Table 1) will be presented for the observed values and change from baseline. Baseline definition can be found in section 3.1. Vital signs results will be listed for each subject by treatment group for each scheduled collection visit.

- Sitting diastolic blood pressure (mmHg)

- Sitting systolic blood pressure (mmHg)
- Heart rate (bpm)
- Temperature (°C)
- Weight (kg)

7.8.5 Electrocardiograms (ECG)

The following ECG measures will be summarized by treatment group and overall for each scheduled collection visit. Standard descriptive statistics (see Table 1) will be presented for the observed values. Baseline definition can be found in section 3.1. ECG results will be listed for each subject by treatment group for each scheduled collection visit.

- Heart rate (bpm)
- Fridericia corrected QT (QTcF) interval (msec)
- QT interval (msec)
- RR interval (msec)
- PR interval (msec)
- QRS interval (msec)

An overall investigator interpretation of ECG will be provided (categories "normal", "abnormal, not clinically significant" and "abnormal, clinically significant"). Subjects with abnormal ECG results, as judged by the investigator, will also be listed.

7.8.6 Physical Examination

Physical exams will include assessment of the following body systems:

- General appearance
- Skin
- Lymph nodes
- Head, eyes, ear, nose, and throat
- Neck
- Thorax/lungs
- Cardiovascular
- Abdomen
- Musculoskeletal
- Neurological

Physical examination results (normal/abnormal) and details of abnormalities will be listed for each subject. For each physical examination body system, the number and

percentage of subjects with abnormalities will be summarized by treatment group and overall for each scheduled visit where the examination is performed.

7.8.7 Injection Site Reactions

Injection site inspections evaluate the occurrence, location, severity, and duration of the following reactions:

- Erythema/redness
- Pain/tenderness
- Induration/swelling
- Other sign/symptom

Severity evaluations (mild, moderate, severe) and duration evaluations (<3 days, 3 days to 1 week, >1 week to 1 month, >1 month) will be conducted at each inspection. Reactions will be listed for each injection for each subject by treatment group. The number and percentage of subjects with reactions of each severity and duration will be summarized by treatment group and overall for each scheduled visit where the inspection is performed.

7.8.8 Bleeding Events

Subject counts and percentages and event counts for the number of treatment-emergent adjudicated bleeding events will be summarized by treatment group and overall. The definition of treatment-emergent can be found in section 7.7.2. The following summaries will be presented:

- Major bleeding events
- Clinically relevant non-major bleeding events
- Nuisance (not clinically relevant) bleeding events
- No bleeding event

If a subject has more than one bleeding event in each above category, the subject will be counted only once in the tabulation. All adjudicated bleeding events will be listed.

7.8.9 Immunogenicity

Immunogenicity results will be summarized by treatment group and overall for each scheduled collection visit. Standard descriptive statistics (see Table 1) will be presented for the observed values. Immunogenicity results will be listed for each subject by treatment group for each scheduled collection visit.

7.8.10 Cardiovascular, cerebrovascular, systemic arterial, and VTEs

Subject counts and percentages and event counts for the number of treatment-emergent adjudicated cardiovascular, cerebrovascular, systemic arterial, and venous thromboembolic events will be summarized by treatment group and overall. The definition of treatment-emergent can be found in section 7.7.2. If a subject has more than one event in each above category, the subject will be counted only once in the tabulation. All adjudicated events of these type will be listed.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

Individual MAA868 plasma concentrations and PD parameters are evaluated for the PK/PD set and will be summarized by treatment group for each scheduled collection visit/timepoint. PK parameters (listed in section 4) are evaluated for the PK/PD set and will be summarized by treatment group for the MAA868 arms only. Standard descriptive statistics (see Table 1) will be presented for the observed values. Individual MAA868 plasma concentrations and all PK parameters will be listed for each subject by treatment group.

Concentrations below the LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values.

7.10 Interim Analysis

After approximately 10 of the subjects in cohort 1 have received their second dose of study drug and have been followed for at least an additional 14 days, the safety and tolerability data (AEs, laboratory assessments, vital signs and ECGs) will be evaluated by the Sponsor's Medical Monitor and Covance Lead Project Physician. The decision to proceed to cohort 2 will be made only after:

- It is confirmed that the cohort 1 dose was safe and tolerated
- At least half of the subjects in cohort 1 have been randomized

If notable AEs or safety concerns are found in cohort 1, the study may be terminated.

Likewise, after approximately 10 of the subjects in cohort 2 have received their second dose of study drug and have been followed for at least an additional 14 days, safety, tolerability, and other analyses will be evaluated.

8. Changes in Planned Analysis

There are no changes from planned analyses in the protocol.

9. Data Issues

There are no data issues to report.

10. References

1 ICH. *ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers*, 2012.

2 SAS Institute. SAS/STAT Software: Cary, NC: SAS Institute; 2003.

3 Clopper C, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 1934; 26:404-13

11. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary/Reason for Changes
Version 1, Final, 18 March 2021	SAP draft final review comments