**Clinical Trial Protocol:** AMAG-977-213

**Study Title:** A Phase 2 Randomized, Double-blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Ciraparantag for Reversal of Anticoagulation in Healthy Adults

**Document:** Statistical Analysis Plan

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# Statistical Analysis Plan

AMAG-977-213, Protocol Version 4.0

**A Phase 2 Randomized, Double-blind, Placebo-Controlled, Study to Assess the Efficacy and Safety of Ciraparantag for Reversal of Anticoagulation in Healthy Adults**

Sponsor: AMAG Pharmaceutical, Inc.*
[redacted]

Prepared by:
[redacted]

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*Note: AMAG Pharmaceuticals, Inc. was acquired by Covis Pharma GmbH in November 2020. To prevent confusion at the site/investigator level, the Sponsor name will remain as above so long as there are active protocols listing AMAG as the Sponsor.

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## Signature Page

| Authors: | |
|---|---|
| [redacted]<br>Senior Director, Biostatistics<br>[redacted] | Signature: [redacted]<br>Date: [redacted] |
| **Sponsor Representative:** | |
| [redacted]<br>Associate Director, Clinical Operations<br>Covis Pharma GmbH | Signatur [redacted]<br>Date: [redacted] |

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**Glossary and Abbreviations**

| ABBREVIATION | DEFINITION |
|---|---|
| AE | Adverse Event |
| AESI | Adverse Event of Special Interest |
| ANCOVA | Analysis of Covariance |
| ATC | Anatomic Therapeutic Chemical |
| AUC | Area under the plasma concentration-time curve |
| BAP | 1,4-bis (3- aminopropyl) piperazine |
| BL | baseline |
| CL | Total plasma clearance (IV administration) |
| CL/F | Total plasma clearance uncorrected for bioavailability (F) |
| $C_{max}$ | Maximum plasma concentration |
| $C_{24}$ | Concentration 24 hours after dosing |
| ECG | electrocardiogram |
| F | Bioavailability |
| FDA | US Food and Drug Administration |
| HIV | human immunodeficiency virus |
| IV | intravenous |
| IWRS | Interactive Web Response System |
| $\lambda z$ | Elimination rate constant |
| $MR_{Cmax}$ | Metabolite to parent ratio of $C_{max}$ |
| $MR_{AUC(0\text{-}last)}$ | Metabolite to parent ratio of $AUC_{(0\text{-}last)}$ |
| $MR_{AUC(0\text{-}inf)}$ | Metabolite to parent ratio of $AUC_{(0\text{-}inf)}$ |
| NOACs | non-vitamin K oral anticoagulants |
| PBO | Placebo |
| PK | pharmacokinetic |
| SAE | serious adverse event |

| ABBREVIATION | DEFINITION |
|---|---|
| SOC | System Organ Class |
| $t_{1/2}$ | Apparent terminal half-life |
| TAP | Test Article Preparer |
| TEAE | Treatment-emergent adverse event |
| TESAE | Treatment-emergent serious adverse event |
| $t_{max}$ | Time of $C_{max}$ |
| $V_{ss}$ | Steady-state volume of distribution after IV dosing |
| $V_z$ | Apparent volume of distribution |
| WBCT | whole blood clotting time |

# 1 Introduction

This document details the analysis plan for the study entitled “A Phase 2 Randomized, Double-blind, Placebo Controlled Study to Assess the Efficacy and Safety of Ciraparantag for Reversal of Anticoagulation in Healthy Adults". It describes the proposed efficacy and safety analyses, including planned summary tables and by-subject data listings.

Anticoagulant medications remain the cornerstone of therapy for the prevention and treatment of thrombosis. Anticoagulants have been approved for indications such as prevention of stroke in patients with nonvalvular atrial fibrillation, prevention and treatment of deep vein thrombosis and pulmonary embolism, and reduction in the risk of myocardial infarction or other cardiovascular events in certain patients (Boehringer Ingelheim Pharmaceuticals, 2018a; Bristol-Myers Squibb Company, 2016; Daiichi Sankyo, 2017; Janssen Pharmaceuticals, 2016; Sanofi-Aventis U.S., 2018). Newer anticoagulants are being evaluated for additional indications that could substantially broaden their use.

The traditional anticoagulants (heparin and warfarin) have a long history of successful clinical use, although the dosing and monitoring of these drugs can be time consuming and problematic for both physicians and patients. Challenges associated with these traditional anticoagulants include the need for parenteral administration of heparin, variable efficacy of warfarin that can be affected by diet, and the need for close monitoring of coagulation status. More recently, non-vitamin K oral anticoagulants (NOACs) have been developed that have several advantages, including rapid therapeutic effectiveness, ease of dosing, and lack of monitoring requirements (Alquwaizani, 2013). However, despite the advantages of NOACs, all anticoagulants are associated with some risk of major bleeding (Lip, 2016).

Across the various indications of the currently available anticoagulant medications, the risk of major bleeding typically ranges from 1% to 5% annually, although individual patient risk can vary substantially based on numerous factors including age, co-morbidities, and concomitant medications (Bristol-Myers Squibb Company, 2016; Daiichi Sankyo, 2017; Janssen Pharmaceuticals, 2016; Lip, 2016; Tepper, 2018; Yao, 2016). A study from the US Centers for Disease Control and Prevention evaluated emergency department visits associated with adverse drug events from 2013 to 2014. This study showed that anticoagulants accounted for 17.6% of all emergency department visits for outpatient adverse drug effects, more than any other class of drugs. These anticoagulant events occurred almost exclusively among adults, with increasing risk in successively older age groups. Further, these events were mostly severe, with nearly half requiring hospitalization (Shehab, 2016).

Based on adverse drug event reports submitted to the US Food and Drug Administration (FDA) Adverse Event Reporting System during 2016, the US Institute for Safe Medication Practices ranked harm from oral anticoagulant drugs as one of the highest priority drug safety problems in

2016. Practically all reported anticoagulant-associated injuries or deaths were from hemorrhage (ISMP, 2017). Therefore, a major concern regarding the use of any anticoagulant, including the NOACs, is how to manage major bleeding in patients who are receiving anticoagulant therapy. In some cases, discontinuation of the anticoagulant, transfusion, and/or other supportive care measures may be sufficient. However, the availability of an anticoagulant reversal agent that is safe, effective and convenient to use may be critical in cases such as serious/life-threating bleeding, prior to urgent or emergency surgery, after major trauma, or in cases of anticoagulant overdose.

Ciraparantag is a small, synthetic, cationic, water-soluble molecule composed of amino acid derivatives with short-linking elements that physically associate with certain anticoagulant drugs and reverses their effect in order to re-establish a normal blood coagulation state. This is mediated through direct non-covalent binding to the anticoagulant molecule, with no binding to blood coagulation factors or proteins in the blood. Based on available preclinical and clinical data, ciraparantag has the potential to reverse anticoagulation caused by rivaroxaban, apixaban, edoxaban, dabigatran, and heparins, with:

- A single IV dose (administered over approximately 10 minutes) that provides a sustained effect through at least 6 hours
- A ready-to-use solution
- A favorable safety profile and no prothrombotic signal to date

This statistical analysis plan (SAP) covers the detailed procedures for performing statistical analyses and for producing tables, listings, and figures (TLFs) in the study. Due to the observed lack of efficacy in ciraparantag relative to Placebo in the Cohort 1 (Edoxaban) and Cohort 3 (Rivaroxaban) Group 1 subjects, the study was terminated. The scope of the analyses has been revised and is reflected in this SAP. There will be one final CSR produced for the study including all applicable analyses.

# 2 Study Objectives

## 2.1 Primary Objective

The primary objective of this study is to demonstrate that a single IV administration of ciraparantag is superior to placebo (PBO) in the reversal of anticoagulation induced by each of the evaluated anticoagulant drugs (edoxaban, apixaban or rivaroxaban) in healthy adults, as assessed by whole blood clotting time (WBCT) measured with Perosphere Technologies' POC Coagulometer.

## 2.2 Secondary Objectives

The secondary objectives of this study are as follows:

- To evaluate the safety and tolerability of ciraparantag in this population.

- To evaluate the pharmacokinetics (PK) of ciraparantag and the evaluated anticoagulant drugs in this population.
- To describe the correlation between WBCT measured with Perosphere Technologies' POC Coagulometer and with a manual testing method.

## 3 Study Design and Methods

This is a randomized, double-blind, PBO-controlled study to evaluate the efficacy and safety of ciraparantag for reversal of anticoagulation induced by different anticoagulant drugs (edoxaban, apixaban, or rivaroxaban) in generally healthy adults. Throughout the study, coagulation status will be determined by WBCT, which will be measured primarily by the Perosphere Technologies' PoC Coagulometer (hereafter referred to as the "coagulometer") and at selected timepoints using a manual testing method.

The study was planned to be conducted in three separate cohorts; each cohort will evaluate the reversal of a different anticoagulant drug. Within each cohort, an initial group of subjects (Group 1) will be enrolled for evaluation of a target dose of ciraparantag (180 mg IV). Depending on the efficacy and safety results from Group 1, a second group (Group 2) may be enrolled to evaluate a different dose of ciraparantag for that cohort.

Since the study has been terminated, no subjects will be enrolled for Cohort 2 or Group 2. The analyses will be based on the available data from Group 1 subjects in Cohorts 1 and 3.

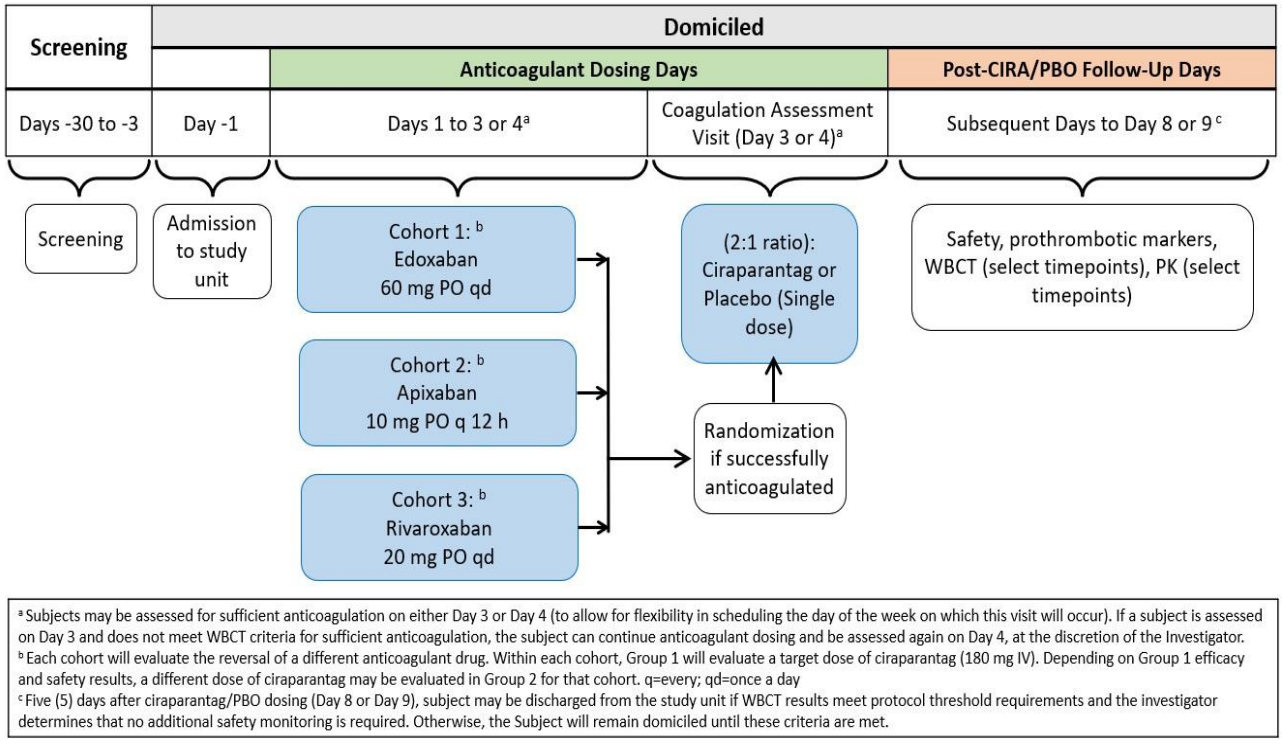
**Table 1: Anticoagulation Regimen by Cohort**

| Cohort | Anticoagulant | Regimen |
|---|---|---|
| 1 | Edoxaban | 60 mg PO once daily in the morning on Days 1 to 4 |
| 2 | Apixaban | 10 mg PO every 12 hours on Days 1 to 3, with a final dose in the morning on Day 4 |
| 3 | Rivaroxaban | 20 mg PO once daily in the morning on Days 1 to 4 |

PO=orally

An overview of the study design is provided in Figure 1.

**Figure 1: Study Design for AMAG-977-213**




[a] Subjects may be assessed for sufficient anticoagulation on either Day 3 or Day 4 (to allow for flexibility in scheduling the day of the week on which this visit will occur). If a subject is assessed on Day 3 and does not meet WBCT criteria for sufficient anticoagulation, the subject can continue anticoagulant dosing and be assessed again on Day 4, at the discretion of the Investigator.
[b] Each cohort will evaluate the reversal of a different anticoagulant drug. Within each cohort, Group 1 will evaluate a target dose of ciraparantag (180 mg IV). Depending on Group 1 efficacy and safety results, a different dose of ciraparantag may be evaluated in Group 2 for that cohort. q=every; qd=once a day
[c] Five (5) days after ciraparantag/PBO dosing (Day 8 or Day 9), subject may be discharged from the study unit if WBCT results meet protocol threshold requirements and the investigator determines that no additional safety monitoring is required. Otherwise, the Subject will remain domiciled until these criteria are met.

An Interactive Web Response System (IWRS) will determine the cohort into which a subject is enrolled. Enrollment will begin with Cohort 1, but cohorts may be enrolled in parallel, depending on the availability of qualified subjects (e.g., if the stratum of younger subjects is fully enrolled in Cohort 1, further eligible subjects in that stratum may be enrolled in Cohort 2). Within a cohort subjects will be randomized in only one group at a time. Individual subjects may only participate in one cohort or group in this study. If a subject is enrolled but does not achieve sufficient anticoagulation in one cohort (and is not randomized), the subject may be re-screened for potential enrollment in a different cohort (i.e., a different anticoagulant drug). For a given cohort, study treatments and assessments through discharge (Day 8 or 9) will be completed for all subjects in Group 1 before deciding to proceed with Group 2. This determination, and the ciraparantag dose to be evaluated in Group 2, will be made by a data review team.

Subjects who remain eligible after the Day -1 assessments and who are admitted to the study unit will be considered enrolled in the study. Only those subjects who achieve sufficient anticoagulation on Day 3 or Day 4 will be randomized. The randomization target is 18 subjects (12 ciraparantag: 6 PBO) in each group of each cohort. Assuming full enrollment of two dose groups for each of the three cohorts, a total of approximately 108 subjects will be randomized in the study.

The study will be conducted at a minimum of two and up to four study sites. For a given cohort, at least two sites will contribute subjects to each group of that cohort, and no site will contribute more than 70% of the subjects randomized to any group of that cohort.

The study's schedule of events is shown in Table 2.

**Table 2: Schedule of Events**

| Study Procedure | Screening Period [a] | Domiciled Period | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Anticoagulant Dosing Days | | | | | Post-CIRA/PBO Follow-up Days | | |
| | | Day -1 [b] | Day 1 | Day 2 | *Day 3* [u] | Coagulation Assessment Visit [v] (Day 3 and/or 4) Pre-Randomization | Coagulation Assessment Visit [v] (Day 3 and/or 4) Post-Randomization | FU-1 | FU-2, FU-3, FU-4 | FU-5 [c] |
| Informed consent | X | | | | | | | | | |
| Medical/medication history | X | X | | | | | | | | |
| Physical examination [d,e] | X | X | | | | | | X | | X |
| Height | X | | | | | | | | | |
| Weight | X | X | | | | | | | | |
| Vital signs [d, f] | X | X | X | X | *X* | X | X | X | | X |
| 12-lead ECG [d, g] | X | X | | | | | | | | |
| Blood Chemistry/Urinalysis [d] | X | X | | | | X [h] | | X | | X |
| Triglycerides & Cholesterol [d, i] | X | X | | | | | | | | |
| Hematology [d] | X | X | | | | X [h] | | X | X | X |
| PT/INR & aPTT | X | X | | | | X [h] | | X | | X |
| Fibrinogen | X | X | | | | X [h] | | X | X | X |
| Anti-fXa activity | | | X [t] | | | X [h] | | X | | X |
| Prothrombotic markers [j] | | X | | | | X | X | X | X | X |
| Pregnancy test [k] | X | X | | | | | | | | X |
| Viral hepatitis/HIV serology | X | | | | | | | | | |
| Drug/tobacco/alcohol screen [l] | X | X | | | | | | | | |
| Fecal occult blood [m] | | X | | | | | | | | |
| Randomization | | | | | | | X | | | |
| Anticoagulant administration [n] | | | X | X | *X* | X | | | | |
| Ciraparantag/PBO administration [o] | | | | | | | X | | | |
| WBCT measurements [d, p] | | | X | | | X | X | X | X [q] | X [q] |
| PK sample collections [d, r] | | | | | | X | X | X | | |
| Adverse event monitoring [s] | X | X | X | X | *X* | X | X | X | X | X |
| Prior/concomitant medications | X | X | X | X | *X* | X | X | X | X | X |
| Discharge from study unit [c] | | | | | | | | | | X |

ECG=electrocardiogram; HIV=human immunodeficiency virus; IV=intravenous; PK=pharmacokinetic; SAE=serious adverse event; WBCT=whole blood clotting time.

a. Informed consent must be obtained before any study-specific procedure is performed. All Screening procedures are to be performed between Day -30 and Day -3 (inclusive), with Screening test results available no later than Day -1 to determine eligibility. Subjects will be provided with lifestyle and dietary guidelines appropriate for an anticoagulant study and for fecal occult blood testing.
b. After completion of all Day -1 assessments, subjects who remain eligible per entry criteria will begin their domiciled period in the study unit.
c. Subject may be discharged from the study unit after completion of all procedures if WBCT results meet protocol threshold requirements (Section 3.1) and the Investigator determines that no additional safety monitoring is required. Otherwise the subject will remain domiciled until these criteria are met.
d. When timing for assessments coincide, WBCT testing (coagulometer and manual) will be performed first, followed by PK and safety laboratory samples, then other safety assessments (physical examinations, vital signs, and ECG).
e. A complete physical examination will be performed at Screening. An abbreviated physical examination will be performed on the subsequent designated days.
f. Temperature will be measured at Screening and Day -1. Blood pressure, heart rate, and respiration rate will be measured at Screening, Day -1 and subsequently as follows: on all anticoagulant dosing days within 30 minutes prior to anticoagulant dosing; the ciraparantag/PBO dosing day within 30 minutes prior to anticoagulant dosing, within 30 minutes prior to ciraparantag/PBO dosing and at 1 hour (±10 minutes), 4 hours (±10 minutes), and 8 hours (±10 minutes) after the end of ciraparantag/PBO infusion; Day FU-1 at 24 hours (±1 hour) after the end of ciraparantag/PBO infusion; Day FU-5 prior to discharge from the study unit. Additional vital sign measurements may be performed during the study if clinically indicated.
g. Additional ECGs may be performed during the study if clinically indicated.
h. For Cohort 1 these blood samples will be collected on coagulation assessment day(s) at 2.75 hours (±10 minutes) after anticoagulant, and for Cohorts 2 and 3 these blood samples will be collected at 3.75 hours (±10 minutes) after anticoagulant. Urinalysis may be performed at any time of day prior to dose of ciraparantag/PBO.
i. Blood samples for triglycerides & cholesterol will be collected after at least 8 hours of fasting (except water *ad libitum*).
j. Prothrombotic marker (D-dimer, prothrombin fragment 1.2, and tissue factor pathway inhibitor) blood samples will be collected on Day -1, coagulation assessment day(s) at 2.75 hours (±10 minutes) after anticoagulant for Cohort 1 and 3.75 hours (±10 minutes) after anticoagulant for Cohorts 2 and 3, ciraparantag/PBO dosing day at 6 hours (±10 minutes) after the end of ciraparantag/PBO infusion, Day FU-1 at 24 hours (±30 minutes) after the end of ciraparantag/PBO infusion, and on Days FU-2 through FU-5 (blood draws at a time of day ±2 hours of the time of day of the end of ciraparantag/PBO infusion). Testing for these markers will be performed at a central laboratory.
k. For female subjects, serum pregnancy tests will be performed, except a urine pregnancy test also may be performed at the study site on Day -1 to ensure that results will be available before Day 1.
l. A urine sample will be taken for drug and tobacco screening. Alcohol screening will be performed via breath or saliva testing performed at the study site.
m. Fecal occult blood kits will be given to subjects at Screening with instructions on their use. A sample should be obtained at a time as close as possible prior to the Day -1 visit, and the kit returned to the study site on Day -1. If a kit is not returned, on Day -1 at the study site the subject must provide a stool sample, or a rectal exam for a stool sample will be required. Fecal occult blood test results must be negative for a subject to continue study participation and proceed to Study Day 1.
n. Anticoagulant morning doses after Day 1 will be administered at a time of day within ±1 hour of the time of morning dose on Day 1.
o. For sufficiently anticoagulated subjects, ciraparantag/PBO IV dose will be administered at 3 hours (±5 minutes) after the anticoagulant dose for Cohort 1 and 4 hours (±5 minutes) after the anticoagulant dose for Cohorts 2 and 3 (Section 3.1).
p. Blood samples for WBCT for coagulometer assessment will be collected as follows: Day 1 prior to the first dose of anticoagulant*; coagulation assessment day(s) at 2.75 hours (±10 minutes) after anticoagulant for Cohort 1* and 3.75 hours (±10 minutes) after anticoagulant for Cohorts 2 and 3*. For sufficiently anticoagulated subjects, blood samples for WBCT will be collected at 15 minutes (±5 minutes), 30 minutes (±5 minutes), 1 hour (±5 minutes)*, 3 hours (±10 minutes), 6 hours (±10 minutes) and 8 hours (±10 minutes) after the end of ciraparantag/PBO infusion; Day FU-1 at 24 hours (±30 minutes)* after the end of ciraparantag/PBO infusion, and on subsequent study days* as needed until protocol threshold criteria are met (Section 3.1). Blood samples for simultaneous testing using the manual method also will be collected at the timepoints designated with the asterisk (*).
q. Any subject with WBCT >120% of BL on Day FU-1 (based on the coagulometer) or >110% of BL (based on the manual method) will have both WBCT measurements repeated on subsequent days as required until WBCT protocol threshold requirements are met.
r. Blood samples for PK assessment for ciraparantag, ciraparantag metabolite(s) and anticoagulant will be collected on the ciraparantag/PBO dosing day and Day FU-1 at the same timepoints as WBCT blood collections (for coagulometer assessment), with the following exceptions: PK also will be assessed on coagulation assessment day(s) prior to

anticoagulant (within 30 minutes) and for sufficiently anticoagulated subjects at 45 minutes (±5 minutes) and 1.5 hours (±5 minutes) after the end of ciraparantag/PBO infusion; PK will not be assessed at 8 hours after the end of ciraparantag/PBO infusion.

s. AEs will be monitored from the time the informed consent is signed through Day FU-5 (or the day the subject is discharged from the study unit, whichever is later. SAEs will be reported through 30 days after the last dose of study drug.
t. On Day 1, these blood samples will be collected prior to the first dose of anticoagulant.
u. These assessments will be performed only if the subject will NOT be assessed for sufficient anticoagulation on Day 3.
v. The coagulation assessment visit (CAV) may occur on Day 3 and/or Day 4 as described below (to allow for flexibility in scheduling the day of the week on which this visit will occur). The post-randomization procedures shown are for subjects who are sufficiently anticoagulated and are randomized, and will occur on the calendar day of the CAV.
   - For CAV on Day 3, if subject does not meet WBCT criteria for sufficient anticoagulation, one of the following will occur:
     — At the discretion of the Investigator the subject can continue anticoagulant dosing and repeat the CAV again on Day 4 (all CAV pre-randomization procedures will be repeated on Day 4); or
     — The subject will be discontinued (CAV post-randomization procedures will not occur); see Section 6.11.3 for discontinuation instructions
   - For CAV on Day 4, if subject does not meet WBCT criteria for sufficient anticoagulation, the subject will be discontinued (CAV post-randomization procedures will not occur); see Section 6.11.3 for discontinuation instructions.

## 3.1 Efficacy and Safety Endpoints

WBCT Testing will be performed using the Perosphere Technologies' PoC Coagulometer at all planned WBCT timepoints. At selected timepoints, WBCT also will be assessed simultaneously using the manual WBCT method. Blood sample collection timepoints are shown below (Table 3).

**Table 3: Blood Sample Collection Timepoints for WBCT**

| WBCT Method | Day 1[c] | Day of CIRA/PBO dose (time relative to CIRA/PBO dose) [a] | | | | | | | Day after CIRA/ PBO dose | Subsequent days until criteria met |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Pre-dose[d] | 0.25 h | 0.5 h | 1 h | 3 h | 6 h | 8 h | 24 h | |
| Coagulometer | X | X | X | X | X | X | X | X | X | X [b] |
| Manual | X | X | | | X | | | | X | X [b] |

[a] Day 3 or Day 4, as per Section 3.1. Timing for samples collected after ciraparantag/PBO are determined relative to the *end* of study drug infusion.

[b] WBCT testing to continue daily as needed until protocol threshold criteria are met (Section 3.1).

[c] WBCT testing on Day 1 to occur prior to first dose of anticoagulant.

[d] Pre-dose WBCT testing on day of ciraparantag/PBO dosing to occur at 2.75 hrs after anticoagulant for Cohort 1 and 3.75 hrs after anticoagulant for Cohorts 2 and 3.

For all efficacy endpoints listed below, analyses will be based on WBCT results obtained with the coagulometer unless otherwise specified.

### 3.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is achieving a WBCT ≤120% of BL within 1 hour after administration of ciraparantag/PBO, which is subsequently sustained after 1 hour through at least 6 hours after ciraparantag/PBO dosing.

### 3.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

1. Achieving WBCT ≤115% of BL within 1 hour after administration of ciraparantag/PBO, which is subsequently sustained after 1 hour through at least 6 hours after ciraparantag/PBO dosing.
2. Achieving a WBCT ≤110% of BL within 1 hour after administration of ciraparantag/PBO which is subsequently sustained after 1 hour through at least 6 hours after ciraparantag/PBO dosing.

3. Achieving a WBCT ≤120% of BL within 30 minutes after administration of ciraparantag/PBO which is subsequently sustained after 30 minutes through at least 6 hours after ciraparantag/PBO dosing.

4. Achieving WBCT ≤115% of BL within 30 minutes after administration of ciraparantag/PBO, which is subsequently sustained after 30 minutes through at least 6 hours after ciraparantag/PBO dosing.

5. Achieving a WBCT ≤110% of BL within 30 minutes after administration of ciraparantag/PBO which is subsequently sustained after 30 minutes through at least 6 hours after ciraparantag/PBO dosing.

6. Achieving a WBCT ≤120% of BL within 15 minutes after administration of ciraparantag/PBO which is subsequently sustained after 15 minutes through at least 6 hours after ciraparantag/PBO dosing.

7. Achieving a WBCT ≤115% of BL within 15 minutes after administration of ciraparantag/PBO, which is subsequently sustained after 15 minutes through at least 6 hours after ciraparantag/PBO dosing.

8. Achieving a WBCT ≤110% of BL within 15 minutes after administration of ciraparantag/PBO which is subsequently sustained after 15 minutes through at least 6 hours after ciraparantag/PBO dosing.

### 3.1.3 Tertiary Efficacy Endpoints

The tertiary efficacy endpoints are as follows:

1. Achieving a WBCT ≤120% of BL at each of the planned WBCT assessment timepoints: 15 minutes, 30 minutes, 1 hour, 3 hours, 6 hours, 8 hours, and 24 hours after administration of ciraparantag/PBO (7 endpoints).

2. Achieving a WBCT ≤115% of BL at each of the planned WBCT assessment timepoints: 15 minutes, 30 minutes, 1 hour, 3 hours, 6 hours, 8 hours, and 24 hours after administration of ciraparantag/PBO (7 endpoints).

3. Achieving a WBCT ≤110% of BL at each of the planned WBCT assessment timepoints: 15 minutes, 30 minutes, 1 hour, 3 hours, 6 hours, 8 hours, and 24 hours after administration of ciraparantag/PBO (7 endpoints).

4. Achieving a WBCT ≤120%, ≤115%, or ≤110% of BL at 1 hour after administration of ciraparantag/PBO by the manual method.

5. WBCT (as a percentage of BL) at each of the planned WBCT assessment timepoints: 15 minutes, 30 minutes, 1 hour, 3 hours, 6 hours, 8 hours, and 24 hours after administration of ciraparantag/PBO (7 endpoints).

6. Change from Day 4 pre-ciraparantag/PBO in WBCT (as a percentage of BL) to each of the planned WBCT assessment timepoints: 15 minutes, 30 minutes, 1 hour, 3 hours, 6 hours, 8 hours, and 24 hours after administration of ciraparantag/PBO (7 endpoints).

### 3.1.4 Safety Endpoints

The safety endpoints are as follows:

- Treatment-emergent AEs (TEAEs)
- Treatment-emergent serious adverse events (TESAEs)
- Changes from BL in vital signs
- Changes from BL in clinical laboratory evaluations

AEs with onset during the anticoagulant administration period also will be summarized.

### 3.1.5 Pharmacokinetic (PK) Parameters

The PK parameters are listed in Table 4.

**Table 4: PK Parameters**

| Parameter | Units | Description | Ciraparantag/BAP | Anticoagulant |
|---|---|---|---|---|
| $C_{max}$ | ng/mL | Maximum concentration in sampled matrix, obtained directly from observed concentration versus time data, typically observed at 0.25 hour (i.e., at the first post-dose time point). | X | X |
| $C_{12}/C_{24}$ | ng/mL | Estimated analyte concentration in at 12-hour time point for Apixiban, and at 24-hour time point for Edoxaban and Rivaroxaban | | X |
| $t_{max}$ | h | Time of $C_{max}$, obtained directly from the observed concentration vs time data, typically observed at 0.25 hour (i.e., at the first post-dose time point). | X | X |
| $AUC_{(0\text{-last})}$ | ng·h/mL | Area under the concentration-time curve, from time zero to the last quantifiable concentration ($C_{last}$) | X | |
| $AUC_{(0\text{-inf})}$ | ng·h/mL | Area under the concentration-time curve in the sampled matrix from time zero (predose) extrapolated to infinite time by addition of the last quantifiable concentration divided by the elimination rate constant: $AUC_{(0\text{-last})} + C_{last}/\lambda_z$ | X | |
| $AUC_{(0\text{-24})}$ | ng·h/mL | Area under the concentration-time curve in sampled matrix over a 24-hour dosing interval for Edoxaban and Rivaroxaban. The concentration at 24-hour time point will be estimated and used for analysis. | | X |
| $AUC_{(0\text{-12})}$ | ng·h/mL | Area under the concentration-time curve in sampled matrix over a 12-hour dosing interval for Apixaban. The concentration at 12-hour time point will be estimated and used for analysis. | | X |
| $\lambda_z$ | 1/h | Apparent terminal rate constant | X | |
| $t_{1/2}$ | h | Apparent terminal half-life, determined as $\ln(2)/\lambda_z$ | X | |
| CL | L/h | Systemic clearance after IV dosing | X | |
| CL/F | L/h | Systemic clearance after oral dosing | | X |
| $V_z$ | L | Volume of distribution after IV dosing | X | |
| $MR_{Cmax}$ | | Metabolite to parent ratio of $C_{max}$ | X | |
| $MR_{AUC(0\text{-last})}$ | | Metabolite to parent ratio of $AUC_{(0\text{-last})}$ | X | |
| $MR_{AUC(0\text{-inf})}$ | | Metabolite to parent ratio of $AUC_{(0\text{-inf})}$ | X | |

### 3.2 Blinding

Anticoagulant drugs will be administered in an open-label manner.

Ciraparantag or PBO will be administered in a double-blind manner. Subjects and all study site personnel (except the Test Article Preparer [TAP]) will be blinded to individual subject treatment assignment (ciraparantag or PBO). In particular, study site personnel who perform or record safety assessments and WBCT testing must be blinded to individual treatment assignment. The Sponsor will be unblinded to individual treatment assignments in order to monitor efficacy and safety data and compile results for the data review team.

At the conclusion of each dose group in each cohort (i.e., after study treatments and assessment through Day 8 or 9 are completed for subjects in that group), available data for that group will be reviewed as follows:

- Investigators will receive results that are unblinded at group level (not individual subject level) as part of data review for Group 2 dose determinations.
- Subjects and study site personnel (except the TAP) will remain blinded to individual subject treatment assignment throughout the study.

### 3.3 Randomization

Subjects will be randomized via Interactive Web Response System (IWRS) to study treatment in a 2:1 ratio (ciraparantag vs. PBO). Randomization will be stratified by age group (18 to <50 years vs. ≥50 to 75 years) within each group of each cohort.

Each cohort will have a different, independently generated randomization schedule.

### 3.4 Sample Size Justification

Assuming true response rates for the primary efficacy endpoint of 78% and 5% in the first active dose group and the placebo group, respectively, 18 subjects with a 2:1 randomization ratio will have 91% power at 0.05 two-sided significance level based on the Boschloo's test. Assuming true response rates of 66% and 5% in the second active dose group and the placebo group, respectively, 12 subjects in each group will have 94% power. Note: For the second active dose group, the treatment allocation ratio will be 2:1 (ciraparantag:placebo), but placebo subjects will be pooled within each cohort, so the analyses will be comparisons of two groups of 12 subjects each.

### 3.5 Data Handling

Summaries for continuous variables will include the descriptive statistics for number of subjects (n), mean (arithmetic and/or geometric), standard deviation (SD), minimum (min), median, and maximum (max). For plasmas concentrations and PK parameters, the geometric mean and coefficient of variation (CV%) will also be presented. Values below

the quantification limit (BQL) will be treated as "0" in the summary statistics. Descriptive statistics that are not quantifiable will be designated as 'NC' in the summaries and a footnote, NC = not calculable, added. Summaries for categorical (discrete) variables will include the number of subjects and/or percentage of subjects in a particular category.

Conventions for presentation of numerical data:

Min and max values will be presented to the same number of decimal places as the Electronic case report form (eCRF) data. Means and medians will be presented to one more decimal place than the eCRF data. Standard deviations will be presented to two more decimal places than the eCRF data.

All evaluable data from subjects in the analysis sets will be included in the analyses.

Baseline values will be defined as the last assessment prior to administration of ciraparantag/PBO. However, BL WBCT will be defined as the result of the test performed on Day 1 (prior to the first dose of anticoagulant).

Change from Baseline is defined as [Post-baseline Value – Baseline Value].

### 3.6 Handling of Missing Data

For the primary efficacy endpoint, i.e. achieving a WBCT ≤120% of BL within 1 hour after administration of ciraparantag/PBO, which is subsequently sustained after 1 hour through at least 6 hours after ciraparantag/PBO dosing, the subject must have non-missing WBCT ≤120% of BL at all scheduled time points in the 1-6 hours assessment window to be a responder, otherwise the subject will be deemed a non-responder, including subjects with any missing data in this window. Missing data at time points earlier than 1 hour (i.e. 0.25 hour and 0.5 hour) will not affect the primary efficacy responder status determination. The secondary efficacy endpoints will be analyzed in the same manner. For the tertiary efficacy endpoints that evaluate responder status at each time point, a subject with a missing WBCT value will be considered as a non-responder for the specific time point.

For the other endpoints including the pharmacokinetic analysis, missing data will not be imputed.

### 3.7 Adjustment for Multiple Comparison

Each group in each cohort will be treated as a standalone sub-study and analyzed separately. Within each group in each cohort, if the primary efficacy endpoint is positive, i.e., p-value < 0.05, the study will be declared positive, and we will test the secondary efficacy endpoints in three reversal target clusters in parallel as shown in Table 5. Because a goal of the study is to verify the dose and the endpoints for future evaluations of ciraparantag, we don't plan to control the multiplicity for the entire set of 8 secondary

endpoints. Instead, the testing approach controls the multiplicity for each reversal target cluster separately.

**Table 5: Hypothesis Testing Paradigm of The Secondary Efficacy Endpoints For Each Dose Group Within Each Cohort**

| **120% Reversal Target Cluster** | **115% Reversal Target Cluster** | **110% Reversal Target Cluster** |
|---|---|---|
| Achieved within 30 minutes hour and subsequently sustained from 30 minutes to 6 hours | Achieved within 1 hour and subsequently sustained from 1 hour to 6 hours | Achieved within 1 hour and subsequently sustained from 1 hour to 6 hours |
| | if p-value <0.05 ↓ | if p-value <0.05 ↓ |
| | Achieved within 30 minutes and subsequently sustained from 30 minutes to 6 hours | Achieved within 30 minutes and subsequently sustained from 30 minutes to 6 hours |
| if p-value <0.05 ↓ | if p-value <0.05 ↓ | if p-value <0.05 ↓ |
| Achieved within 15 minutes and subsequently sustained from 15 minutes to 6 hours | Achieved within 15 minutes and subsequently sustained from 15 minutes to 6 hours | Achieved within 15 minutes and subsequently sustained from 15 minutes to 6 hours |

## 4 Data Analysis

The analysis of both efficacy and safety parameters will be conducted for each cohort (i.e., each anticoagulant drug) separately. Each cohort consists of up to three treatment groups, i.e., one or two active doses, and one PBO group including all subjects randomized to PBO.

### 4.1 Analysis Populations

The analysis populations that will be used to summarize the results from this study are defined below.

**Enrolled Population:** The Enrolled Population will include all subjects who remain eligible after the Day -1 assessments (i.e., are not Screen failures) and are admitted to the study unit for the domiciled study period.

**Safety Population**: The Safety Population will include all subjects who receive at least one dose of ciraparantag/PBO. Subjects will be analyzed based on the actual treatment they received. Full safety analyses will be performed on this population.

**Efficacy Population**: The Efficacy Population will include those randomized subjects who receive the planned single dose of ciraparantag/PBO and have at least one subsequent WBCT measurement. Subjects will be analyzed based on their randomized treatment assignment. Efficacy analyses will be performed on this population.

**Pharmacokinetic (PK) Population:** The PK Populations (separately for ciraparantag and each anticoagulant) will include all subjects who receive at least one administration of ciraparantag or anticoagulant, respectively, and provide sufficient data to estimate at least one PK parameter without any protocol deviations with the potential to affect these measurements. These populations will be used for PK analyses.

**Anticoagulant Population:** The Anticoagulant Population will include all subjects in the Enrolled Population who receive at least one dose of anticoagulant (apixaban or rivaroxaban). Limited safety analyses will be performed on this population.

The frequency and percentage of subjects in each population will be summarized by cohort and treatment group. Subjects who are excluded from the analysis populations will be listed.

## 4.2 Study Subjects

### 4.2.1 Subject Disposition

The number of subjects who were screened, failed screening, enrolled, received anticoagulant treatment, randomized along with the reason for not being randomized, and the number of subjects who received ciraparantag/PBO treatment will be presented. For each treatment group and overall, the number and percentage (of randomized subjects) who complete the study, and the number and percentage (or randomized subjects) who discontinue early from the study and the reason for discontinuation will be presented.

Eligibility status for the study will be listed for all screened subjects.

### 4.2.2 Protocol Deviations

Protocol deviations will be identified prior to database lock and may include but are not limited to: significant violations of inclusion/exclusion criteria, noncompliance with the study treatment taken, the use of prohibited medications or not following clinical trial protocol procedures that may affect evaluation of the primary or secondary efficacy endpoints.

All protocol deviations will be listed by subject and summarized by deviation type and treatment group.

### 4.3 Subject Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by each treatment and cohort for the Efficacy Population, and as applicable for the Anticoagulant Population. The demographic and baseline characteristics will consist of age, age group (18 to <50 years vs. ≥50 to 75 years; <65 years vs. ≥65 years ), gender, race, ethnicity, height (cm), weight (kg), body mass index (BMI) ($kg/m^2$), BL WBCT (seconds), WBCT on Day 4 pre-ciraparantag/PBO (seconds) and the percentage of BL (%). Counts and percentage of subjects with Day 4 pre-ciraparantag/PBO WBCT ≥120% of BL, ≥130% of BL, ≥140% of BL, and ≥150% of BL will also be tabulated. Individual demographic and baseline characteristics will be listed by subject.

The age is a calculated parameter. Age will be calculated using the subject's date of birth and the subject's informed consent date. Continuous variables (age, height, weight, BMI, BL WBCT, Day 4 pre- ciraparantag/PBO WBCT, and Day 4 pre- ciraparantag/PBO WBCT percentage of BL) will be summarized by n, mean, SD, min, median, and max. Number of subjects and percentages will be used to describe categorical variables (age group, gender, race, ethnicity and WBCT (as a percentage of BL) categories). No statistical hypothesis tests will be performed on these characteristics.

### 4.4 Medical/Surgical History and Procedures/Non-Drug Therapies

The presence/absence of any current medical condition and/or other significant medical/surgical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0, or higher. Any procedures/non-drug therapies will also be coded using MedDRA or World Health Organization (WHO) Drug Enhanced Dictionary (March 2017 or later), as appropriate.

Medical/surgical history will be summarized by treatment and cohort, and listed by subject. Procedures/non-drug therapies will be summarized by treatment and cohort, and listed by subject.

### 4.5 Prior and Concomitant Medications

All prescription medications and over-the-counter (OTC) products, including herbal products, taken within 14 days prior to Day 1 or during the study period will be documented in the subject's source documentation and the eCRF.

Details of all medications must be recorded at trial entry. Any changes in concomitant medications must be recorded at each visit. The information collected for each concomitant medication includes dosage, route, start date, stop date (or continuing) and indication. Prior medications will be recorded at the screening visit and will be defined as those medications with start prior to the first dose of anticoagulant on Day 1. Concomitant medications will be defined as those medications with a stop date after the

first dose of anticoagulant or with a missing stop date. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Enhanced Dictionary (March 2017 or later).

Prior and concomitant medications will be summarized by treatment including Anatomical Therapeutic Chemical (ATC) classification level 3, preferred term and reported term. Medications will also be listed by subject.

## 4.6 Efficacy Analyses

### 4.6.1 Primary Efficacy Endpoint

The primary efficacy endpoint is achieving WBCT ≤120% of BL (as measured by coagulometer) within 1 hour after administration of ciraparantag/PBO which is subsequently sustained after 1 hour through at least 6 hours after ciraparantag/PBO dosing. The null hypothesis for this endpoint is that the true (success) proportions of subjects meeting the primary efficacy endpoint are equal for the two treatments, and the alternative hypothesis is that they are unequal. The statistical hypotheses are as follows:

$H0: \pi 1 = \pi 2$

and

$H1: \pi 1 \neq \pi 2,$

where $\pi 1$ and $\pi 2$ are the true success proportions for ciraparantag and PBO, respectively.

This endpoint will be summarized by cohort and treatment group (ciraparantag dose vs. PBO) using frequencies and percentages and an exact (Clopper-Pearson) 95% confidence interval (CI) for the true percentage based on the binomial distribution. The difference in percentages between treatments (ciraparantag dose vs. PBO) will be tested using Boschloo's test (Boschloo 1970). A 95% CI for the difference in percentages will be constructed by the Miettinen and Nurminen method (Newcombe 1998).

### 4.6.2 Secondary Efficacy Endpoints

The first two secondary efficacy endpoints will be summarized by counts and percentages. No statistical analysis will be performed for the remaining secondary efficacy endpoints.

### 4.6.3 Tertiary Efficacy Endpoints

The tertiary efficacy endpoints are as stated in Section 3.1.3. These endpoints are exploratory in nature and are intended to characterize effects at each of the specified WBCT assessment timepoints.

The first four sets of tertiary efficacy endpoints, achieving a WBCT ≤120%, ≤115% or ≤110% of BL at each of the planned post-BL WBCT assessment timepoints by coagulometer or the manual method, will be tabulated by counts and percentages and no

statistical testing will be performed.

The fifth sets of tertiary efficacy endpoints will be summarized by cohort and treatment using descriptive statistics. The sixth sets of tertiary efficacy endpoints will not be analyzed.

The observed WBCT value, change from baseline, percentage change from baseline, and WBCT as percent of BL assessed using coagulometer or manual method will be summarized and plotted by time point and treatment group for each cohort.

### 4.6.4 Correlations of WBCT Results between Coagulometer and Manual Method

Correlation between WBCT as percent of BL obtained with coagulometer and manual method will be analyzed by fitting a simple linear regression model between these two sets of results. The value of $R^2$ will be presented. Scatter plot of coagulometer results vs. manual method results will be provided along with the regression line.

## 4.7 Safety Analysis

All safety summaries will be presented by cohort and treatment (i.e., ciraparantag doses and PBO), and also by pooled ciraparantag vs pooled PBO across cohorts.

### 4.7.1 Study Product Exposure

Study drug and anticoagulants administration will be listed by subject, indicating date and time of drug dose. The study drug administration diary entries will be listed for all subjects, as applicable. A summary of the exposure will be presented, including total dose (mg) of anticoagulant (apixaban or rivaroxaban) administered, total number of anticoagulant doses taken, compliance of anticoagulant (%), and number of subjects who received the planned ciraparantag / PBO dose.

### 4.7.2 Adverse Events

All AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or later. Treatment-emergent AEs (TEAEs) are defined as those AEs with onset on or after the start of double-blind study drug administration (ciraparantag or PBO) or any adverse event already present at the start of double-blind study drug administration that worsens in severity. For AEs with missing start dates, the AE will be considered treatment-emergent unless there is additional information indicating that the AE started prior to study drug administration.

The number and percentage of subjects with at least one TEAE, at least one serious TEAE, at least one ciraparantag or PBO related TEAE, and at least one TEAE leading to study withdrawal, and at least one TEAE of Special Interest (AESI) will be presented by

cohort and treatment group. AEs that are related or possibly related to study drug, or for which the relationship is missing, will be considered study drug related. AEs of Special Interest include the following categories based on selected preferred terms:

- Altered sensation of temperature: Flushing, Hot flush, Feeling hot, Feeling cold, Feeling of body temperature change, Chills
- Paresthesia or Dysgeusia: Paraesthesia, Dysgeusia

TEAEs, serious TEAEs, TEAEs leading to study discontinuation, ciraparantag or PBO related TEAEs, and TEAE of Special Interest will summarized by SOC and PT for each cohort and treatment group, and also by pooled ciraparantag vs pooled PBO across cohorts. The same summary will also be performed by PT only with decreasing frequency based on the pooled ciraparantag group.

TEAEs will also be summarized by severity, by relationship to anticoagulants, and by relationship to ciraparantag or PBO. If the same AE (SOC/preferred term) is reported more than once for the same subject, the highest severity grade or the strongest relationship to treatment will be counted in the summary table.

All of these AE analyses will be performed on the Safety Population.

AEs with onset on or after the first dose of anticoagulant but prior to the double-blind study drug administration will be considered non-treatment emergent. The numbers and percentages of subjects having such a non-treatment-emergent AE and a non-treatment-emergent SAE in each SOC and Preferred Term will be summarized for the anticoagulant population by cohort and overall across cohorts.

Separate listings will be provided for deaths, SAEs, and AEs leading to study withdrawal. By-subject AE listings will be provided.

### 4.7.3 Clinical Laboratory Assessments

All quantitative laboratory test results, including serum chemistry, hematology, and prothrombotic markers, will be summarized by cohort, treatment, parameter, and time point using descriptive statistics for subjects in the Safety Population. The change from BL to each post-ciraparantag/PBO dose time point will also be summarized. Urinalysis results will be tabulated by counts and percentages. These will also be summarized by pooled ciraparantag vs pooled PBO across cohorts.

Laboratory values will be reported in Système International units.

Clinically notable (CN) laboratory values will be determined based on the criteria in Appendix 1. The number and percentage of subjects with at least 1 CN laboratory value at any post-baseline timepoint will be summarized by cohort, treatment, and parameter.

Percentages for each laboratory test will be based on the number of subjects with at least one post-baseline evaluation for the specific parameter.

In addition to the CN summary, the number and percentage of subjects meeting each of the following criteria at any post-baseline timepoint will be summarized by cohort, treatment, and parameter:

- AST >3 x ULN, >5 x ULN and >10 x ULN
- ALT >3 x ULN, >5 x ULN and >10 x ULN
- Total bilirubin >1.5 x ULN and >2 x ULN

Laboratory values will be listed for each subject. Laboratory values outside normal limits will be identified in the subject data listings with flags for low (L) and high (H) as will laboratory values that meet the CN thresholds. A separate listing will be provided of subjects with values for a laboratory parameter noted as CN.

### 4.7.4 Vital Signs Assessments

Vital signs, including systolic and diastolic blood pressure, heart rate, and respiration rate, will be summarized using descriptive statistics by cohort and treatment group at each time point for subjects in the Safety Population. The change from BL to each post-ciraparantag/PBO dose time point will also be summarized.

Post-baseline vital signs will be defined as Clinically Notable (CN) if they meet 1) the criterion value at the given visit, or 2) meet both the criterion value and the change from baseline criterion listed in Table 6. The number and percentage of subjects with at least 1 CN vital sign at any post-baseline timepoint will be summarized by cohort, treatment, and parameter. Percentages for each vital sign will be based on the number of subjects with a baseline and a post-baseline evaluation for the specific parameter.

A separate listing will be provided of subjects with values for a vital sign noted as CN.

**Table 6. Criteria for Clinically Notable Vital Signs**

| Vital Sign Parameter | Criterion Value | | Change from Baseline |
|---|---|---|---|
| Systolic Blood Pressure (mmHg) | High | ≥180 | Increase of ≥20 |
| | Low | ≤90 | Decrease of ≥20 |
| Diastolic Blood Pressure (mmHg) | High | ≥105 | Increase of ≥15 |
| | Low | ≤50 | Decrease of ≥15 |
| Heart Rate (bpm) | High | ≥120 | Increase of ≥15 |
| | Low | ≤50 | Decrease of ≥15 |

bpm = beats per minute

Vital signs results will be listed for each subject, and summary statistics for vital signs and change from baseline will be displayed by treatment. A separate listing will be provided of subjects with values for a vital sign noted as CN.

### 4.7.5 Resting 12-Lead Electrocardiogram

A resting 12-lead electrocardiogram (ECG) will be performed at screening, Day -1, and at any time during the study if clinically indicated. Parameters assessed will include ventricular rate (beats per minute), RR interval (msec), PR interval (msec), QRS duration (msec), QT interval (msec), and QTc interval (msec), as well as any other observed abnormalities.

All ECG results will be listed.

## 4.8 Pharmacokinetic (PK) Analysis

### 4.8.1 Plasma and Serum Concentrations

Individual subject plasma concentrations of ciraparantag and its primary metabolite (BAP) and each anticoagulant (apixaban or rivaroxaban) will be listed and summarized using descriptive statistics (n, arithmetic mean, standard deviation, coefficient of variation, minimum, median, maximum, geometric mean and geometric coefficient of variation) for each time point. Values below the quantification limit (BQL) will be treated as “0” in the summary statistics. Descriptive statistics that are not quantifiable will be designated as ‘NC’ in the summaries and a footnote added, NC = not calculable.

Plots of mean concentration levels of ciraparantag and its metabolite, and each anticoagulant versus time will be generated for each cohort and treatment. Plots of individual subject’s concentration levels of ciraparantag and its metabolite, and each anticoagulant versus time will also be generated.

### 4.8.2 Pharmacokinetic Parameters

The PK parameters will be computed using non-compartmental analysis using appropriate software and summarized using descriptive statistics. PK parameters for ciraparantag and BAP, as displayed in Table 7, and key PK parameters for anticoagulants, will be listed by subject and summarized by treatment using descriptive statistics (n, arithmetic mean, standard deviation, coefficient of variation, minimum, median, maximum, geometric mean and geometric coefficient of variation). $T_{max}$ will be described using n, minimum, median, and maximum.

The following PK parameters for ciraparantag and its metabolite, BAP, will be calculated for diagnostic purposes and listed, but will not be summarized.

**Table 7 Listing of Diagnostic Parameters for the Non-Compartmental Analysis of Serum Ciraparantag and BAP**

| | |
|---|---|
| $T_{1/2}$, Interval | The time interval (h) of the log-linear regression to determine $t_{1/2}$ |
| $t_{1/2}$, N | Number of data points included in the log-linear regression analysis |
| $t_{last}$ | Time to the last quantifiable concentration |
| Rsq | Goodness-of-fit statistic for calculation of $\lambda_z$ (regression coefficient) |
| $\%AUC_{ex}$ | Percentage of $AUC_{(0\text{-inf})}$ that is extrapolated from $t_{last}$ to infinity, calculated as: 100 x [1 – ($AUC_{last}/AUC_{0\text{-inf}}$)], where $t_{last}$ is the time of the last measurable plasma drug concentration |

### 4.8.3 Dose Proportionality

Dose proportionality will be examined by a comparison of the geometric means of the ciraparantag and BAP PK parameters AUC(0-inf), AUC(0-last), and Cmax between the two ciraparantag doses using the natural log-transformed values. Confidence intervals (90%) will be constructed for the geometric mean ratios using the log transformed data. The geometric mean ratios and confidence limits will be exponentiated back to the original scale. Dose proportionality will be concluded if the 90% confidence interval includes "the ratio of the doses". For example, if the two ciraparantag doses are 180mg and 360 mg, the ratio of the two doses will be 2.

## 4.9 Interim Analysis

Within each cohort, an initial group of subjects (Group 1) will be enrolled for evaluation of a target dose of ciraparantag (180 mg IV). Depending on the efficacy and safety results from Group 1, a second group (Group 2) may be enrolled to evaluate a different dose of ciraparantag for that cohort, as determined by a data review team. Due to the observed lack of efficacy of ciraparantag in Group 1 subjects of Cohorts 1 and 3, no patients will be enrolled for Group 2.

## 4.10 Statistical Programming and Deliverables

All statistical analyses, tables and listings will be generated in SAS (version 9.4 or later) with appropriate documentation and programming validation. However, the p-value for

Boschloo's test will be obtained using R. The table of contents of all tables, listings, and figures will be presented in a Tables, Listings and Figures shell supplemental document.

### 4.11 Changes from Pre-Specified Analyses

The following changes were made to the protocol-specified efficacy analyses

- For the primary efficacy endpoint, the protocol specified that the Cochran-Mantel-Haenszel Test, with stratification by age group, will be used to compare each active dose with placebo as a sensitivity analysis. This analysis won't be performed.
- For the secondary efficacy endpoints, the protocol specified that they would be analyzed in the same manner as the primary efficacy endpoint. This has been simplified such that the first two secondary efficacy endpoints will be summarized using counts and percentages, and no statistical analysis will be performed for the remaining secondary efficacy endpoints.
- For the first four sets of tertiary efficacy endpoints, the protocol specified that they would be analyzed in the same manner as the primary efficacy endpoint. This has been simplified such that only counts and percentages will be presented.
- For the fifth and the sixth sets of tertiary efficacy endpoint, the Analysis of Covariance (ANCOVA) specified by the protocol will not performed.
- The protocol specified that the agreement between these two methods with respect to the efficacy endpoints at 1 hour after administration of ciraparantag/PBO will be assessed, and this analysis will not be performed.

### 4.12 Changes to the Planned Analysis

Any deviation(s) of consequence from the SAP during the data analysis will be documented and justified in an amended SAP and/or in the final report or addressed in a separate document, as appropriate.

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## Appendix 1. Clinically Notable (CN) Laboratory Criteria

Unless otherwise specified, values in this table correspond to the thresholds for Grade 3 laboratory abnormalities as presented in the U.S. FDA Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials (2007).

| Parameter | | Criterion | |
|---|---|---|---|
| | | Conventional Units | SI Units |
| **Serum chemistry** | | | |
| Alanine aminotransferase (ALT) | | ≥5.1 x ULN | |
| Albumin | | <2.5 g/dL | <25 g/L |
| Aspartate aminotransferase (AST) | | ≥5.1 x ULN | |
| Bilirubin, Total | | ≥2 x ULN | |
| Alkaline phosphatase (ALP) | | ≥3.1 x ULN | |
| Blood urea nitrogen (BUN) | | >31 mg/dL | >11.1 mmol/L |
| Calcium | Low | ≤7.4 mg/dL | ≤1.85 mmol/L |
| | High | ≥11.6 mg/dL | ≥2.9 mmol/L |
| Creatinine | | ≥2.1 mg/dL | ≥160.1 µmol/L |
| Glucose | Low | ≤54 mg/dL | ≤3 mmol/L |
| | High | >200 mg/dL | >11.1 mmol/L |
| Potassium | Low | ≤3.2 mEq/L | ≤3.2 mmol/L |
| | High | ≥5.5 mEq/L | ≥5.5 mmol/L |
| Sodium | Low | ≤129 mEq/L | ≤129 mmol/L |
| | High | ≥148 mEq/L | ≥148 mmol/L |
| **Hematology** | | | |
| Hemoglobin, female | | ≤9.4 g/dL | ≤94 g/L |
| Hemoglobin, male | | ≤10.4 g/dL | ≤104 g/L |
| Platelet count | | <100 x10^3/µL | <100 x10^9/L |
| White blood cell (WBC) count | Low | <1.5 x10^3/µL | <1.5 x10^9/L |
| | High | >20 x10^3/µL | >20 x10^9/L |
| Neutrophils | | <1 x10^3/µL | <1 x10^9/L |
| Eosinophils [a] | | >1 x10^3/µL | >1 x10^9/L |
| Eosinophils [a] | | >10% | |

ULN = upper limit of the normal range
a. Sponsor-defined clinically notable threshold for ciraparantag

**Revision history**

| Version | Date | Comments |
|---|---|---|
| | | |
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