

**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:** Protocol

**Document Date:** Version 4, 14 Oct 2022

**NCT:** NCT04593784

## **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:** Perosphere Pharmaceuticals, Inc.\*  
a wholly owned subsidiary of AMAG Pharmaceuticals, Inc.



**Drug Product:** Ciraparantag

**Protocol Number:** AMAG-977-213

**Phase:** 2

**Protocol Version:** Version 4.0

**Version Date:** 14 Oct 2022

\*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/Perosphere as the Sponsor.

This study will be conducted in accordance with the Protocol and in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki, and any other applicable regulatory requirements. Perosphere Pharmaceuticals, Inc., a wholly owned subsidiary of AMAG Pharmaceuticals, Inc., will also continue to support the principles of the Declaration of Helsinki.

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## **CONTACTS**

### **Emergency Contacts**

**Emergency contacts will be listed in the Procedures Manual**

## PROTOCOL APPROVAL SIGNATURE PAGE

**Protocol 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

**Protocol Number:** AMAG-977-213

### Authorized Sponsor Representative Signature

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

Name: \_\_\_\_\_

Title: Vice President, Clinical Development

Department: Clinical Development

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

Name: \_\_\_\_\_

Title: Medical Monitor

Department: Clinical Development

## INVESTIGATOR PROTOCOL AGREEMENT

**Protocol 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

**Protocol Number:** AMAG-977-213

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I will provide copies of the study protocol and access to all study-related information to the study personnel at my site who are involved with this protocol. I will discuss with them this material and the material in the Investigator's Brochure to ensure that they are fully informed about the investigational drug and understand the protocol. All documents will be kept in the strictest confidence.

I confirm that my staff and I have carefully read and understand this protocol. I agree to conduct this study according to the attached protocol. I also agree to conduct this study in compliance with Good Clinical Practice and all applicable national and local laws and regulations, as well as with the requirements of the appropriate Institutional Review Board or Independent Ethics Committee (IRB/EC) and any other institutional requirements. No changes will be made to the study protocol without prior written approval of the Sponsor and the IRB/EC.

I have read, understand, and agree to abide by all conditions and instructions contained in this protocol.

---

Principal Investigator's Signature

---

Date

Name (print): \_\_\_\_\_

Clinical Site/Institution: \_\_\_\_\_

Address: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

## PROTOCOL VERSION HISTORY

### Version 4.0 – 14 Oct 2022

This amendment consists of two changes:

- This amendment allows for subjects to be assessed for sufficient anticoagulation on either Day 3 or Day 4 of anticoagulant dosing (prior versions indicated assessment only on Day 4). Because of the intensity of testing and number of site personnel required on the day of ciraparantag/placebo dosing, this Day 3/Day 4 option is provided to allow for flexibility in scheduling the day of the week on which this visit will occur. For the anticoagulant dosing regimens used in this study, the anticoagulants are expected to be at steady state by Day 3, and, per the study design, subjects are only randomized if they achieve sufficient anticoagulation, so providing this option is not expected to impact subject safety or study findings. All subjects will continue to be followed for 5 days following ciraparantag/PBO dosing. The associated changes apply predominantly to the Synopsis, Section 3.1, Section 6.6.2, Section 6.11.3, and the Schedule of Events in Appendix A.
- Individual subjects who do not achieve sufficient anticoagulation in one cohort (and are not randomized), will now be allowed to be re-screened for potential enrollment in a different cohort. This change is being implemented because of challenges with identifying volunteers that meet all entry criteria, and because subjects who do not achieve the threshold for sufficient anticoagulation with one anticoagulant drug may achieve it with a different anticoagulant drug. As before, a subject may only be randomized and treated with ciraparantag/placebo once. This change applies to Section 3.1 and Section 6.1.

### Version 3.0 – 12 APR 2021

This amendment provided for evaluation of an additional cohort of subjects to evaluate ciraparantag for reversal of edoxaban, which has been inserted as Cohort 1. Key changes made to the protocol are described below.

- Changes were made throughout the protocol to indicate the addition of the edoxaban cohort, most notably in the Synopsis, Section 3.1, and Section 5.4.1.
- Study procedures for the edoxaban cohort (Cohort 1) are nearly identical to those of other cohorts, except for Cohort 1 the time interval between the last dose of edoxaban and the single dose of ciraparantag/placebo is 3 hours, whereas this interval is 4 hours for the apixaban and rivaroxaban cohorts. This is because maximum plasma concentrations of edoxaban are achieved more rapidly. This timing for each cohort is detailed in the Synopsis and Section 3.1, and the timing for associated blood draws is detailed in the Schedule of Events in Appendix A.
- Assuming full enrollment of all cohorts/groups as outlined in the protocol below, the maximum number of subjects randomized will increase to 108 (Synopsis and Section 3.1).
- Final results for two recently completed clinical studies (Studies 02-011 and 02-012) were added. This update was made to Section 1.2.2.

## **Version 2.0 – 11 DEC 2020**

This amendment consisted primarily of additions to blood testing requirements, in accordance with discussions between the sponsor and the United States Food and Drug Administration (FDA). Key changes made to the protocol are described below.

- Per FDA feedback, subjects with serum total cholesterol outside the normal range are to be excluded. This change was made to Exclusion criterion 1 in the Synopsis and Section 4.2 . In addition, total cholesterol was added to the laboratory testing list in Section 6.6 and to the Schedule of Events in [Appendix A](#).
- Per FDA feedback, blood testing for anti-fXa activity was added to the study at selected timepoints, and hematology and fibrinogen testing was expanded to additional study days. These changes are detailed in Schedule of Events in [Appendix A](#), and anti-fXa activity was added to the laboratory testing list in Section 6.6 .
- To further assess the duration of effect of ciraparantag after a single IV dose, a WBCT test was added at 8 hours after the end of study drug infusion. This change was made in the Synopsis, Section 6.6.2, and in Schedule of Events in [Appendix A](#).
- The total estimated blood volume to be collected per subject was updated in Section 6.8.

## **Version 1.0 – 04 MAY 2020**

Original

## SYNOPSIS

<b>Protocol Title</b>	A Phase 2 Randomized, Double-blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Ciraparantag for Reversal of Anticoagulation in Healthy Adults
<b>Protocol Number</b>	AMAG-977-213
<b>Study Agent</b>	Ciraparantag
<b>Phase of Development</b>	2
<b>Study Center(s)</b>	2 to 4
<b>Study Objectives</b>	<p><b>Primary Objective:</b></p> <ul style="list-style-type: none"> <li>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' Point-of-Care (PoC) Coagulometer.</li> </ul> <p><b>Secondary Objectives:</b></p> <ul style="list-style-type: none"> <li>To evaluate the safety and tolerability of ciraparantag in this population.</li> <li>To evaluate the pharmacokinetics (PK) of ciraparantag and the evaluated anticoagulant drugs in this population.</li> <li>To describe the correlation between WBCT measured with Perosphere Technologies' POC Coagulometer and with a manual testing method.</li> </ul>
<b>Study Design</b>	<p>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. Coagulation status will be determined by WBCT, which will be measured primarily by the Perosphere Technologies' PoC Coagulometer, and at selected timepoints using a manual testing method.</p> <p>The study will 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</p>

evaluate a different dose of ciraparantag for that cohort, as determined by a data review team.

The Screening period is the same for all cohorts. Eligible subjects will be admitted to the clinical study unit on Day -1. The next day (Day 1), a baseline (BL) WBCT will be determined prior to receiving the anticoagulant based on the cohort to which they were enrolled (Table 1).

**Table 1: Anticoagulation Regimen by Cohort**

Cohort	Anticoagulant	Regimen
1	Edoxaban	60 mg orally (PO) once daily in the morning from Day 1 to Day 3 or Day 4
2	Apixaban	10 mg PO every 12 hours from Day 1 to the morning of Day 3 or Day 4
3	Rivaroxaban	20 mg PO once daily in the morning from Day 1 to Day 3 or Day 4

Within each cohort, subjects will be assessed for sufficient anticoagulation on Day 3 or Day 4 before proceeding further in the study. The Day 3/Day 4 option is provided to allow for flexibility in scheduling the day of the week on which this visit will occur. WBCT will be determined following the morning dose of anticoagulant at the approximate timepoint specified (Table 2) for purposes of determining sufficient anticoagulation. If this WBCT result is  $\geq 130\%$  of BL (based on the coagulometer), the subject will proceed in the study. If testing occurs 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. If testing occurs on Day 4 and does not meet WBCT criteria for sufficient anticoagulation, the subject will be discontinued from the study. Subjects who proceed in the study will be randomized to a single IV dose of ciraparantag or PBO in a 2:1 ratio. Randomization will be stratified by age (18 to <50 years vs.  $\geq 50$  to 75 years). Within each cohort, between 50% to 70% of randomized subjects will be  $\geq 50$  to 75 years of age, and there will be approximately equal numbers of male and female subjects. The ciraparantag/PBO dose will be administered starting at the approximate timepoint specified in Table 2 followed by multiple WBCT and PK measurements.

**Table 2: Timepoints for Assessing Sufficient Anticoagulation and for Ciraparantag/Placebo Dosing (Day 3 or Day 4)**

Cohort	Anticoagulant	Timepoint for assessing sufficient anticoagulation	For sufficiently anticoagulated subjects, timepoint for ciraparantag/PBO dose

	1	Edoxaban	2.75 hours after Day 3 or Day 4 edoxaban dose	3 hours after the last edoxaban dose
	2	Apixaban	3.75 hours after Day 3 or Day 4 apixaban dose	4 hours after the last apixaban dose
	3	Rivaroxaban	3.75 hours after Day 3 or Day 4 rivaroxaban dose	4 hours after the last rivaroxaban dose
	<p>Subjects in all cohorts who receive ciraparantag/PBO will remain domiciled in the clinical study unit for 5 days after dosing (i.e., through Day 8 or Day 9). Evaluations on the day following ciraparantag/PBO dosing will include WBCT, PK, and safety assessments (including testing for prothrombotic markers). On subsequent days, follow-up safety assessments (including testing for prothrombotic markers) will continue. Any subject with WBCT on the day following ciraparantag/PBO dosing that is <math>&gt;120\%</math> of BL (based on the coagulometer) or <math>&gt;110\%</math> of BL (based on the manual method) will have both WBCT repeated on subsequent days as required until WBCT is <math>\leq 120\%</math> of BL (based on the coagulometer) and <math>\leq 110\%</math> of BL (based on the manual method). The differences in these thresholds is based on the differences in assay sensitivity between the two testing methods. Five days after ciraparantag/PBO dosing (Day 8 or Day 9), subjects may be discharged from the study unit, provided that WBCT results are <math>\leq 120\%</math> of BL (based on the coagulometer) and <math>\leq 110\%</math> of BL (based on manual WBCT), and the Investigator determines that no additional safety monitoring is required. Otherwise the subject will remain domiciled until these criteria are met.</p> <p>Subjects who remain eligible after the Day -1 assessments and who are admitted to the study unit will be considered enrolled in the study. As described above, 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.</p> <p>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.</p>			
<b>Planned Number of Subjects</b>	Up to 108			
<b>Duration of Subject Participation</b>	Up to approximately 6 weeks, including a Screening period (up to 30 days) and a domiciled period in the study unit (10 days).			

<b>Subject Population</b>	Healthy adult volunteers
<b>Inclusion Criteria</b>	<p>Eligible subjects must:</p> <ol style="list-style-type: none"> <li>1. Be informed of the nature of the study and provide written informed consent before any study-specific procedures are performed.</li> <li>2. Be 18 to 75 years of age, inclusive, at time of consent.</li> <li>3. Be in good health, in the opinion of the Investigator, based on medical history, physical examination, vital signs, electrocardiogram (ECG) and laboratory testing (ie, absence of any clinically relevant abnormality) during Screening.</li> <li>4. Have a body mass index 18 to 32 kg/m<sup>2</sup>, inclusive, at Screening.</li> <li>5. If female, be surgically sterile or post-menopausal (no menses for at least 12 months), or if of child-bearing potential, must be using an acceptable method of contraception (other than a combination estrogen/progestin hormonal contraceptive) for at least 1 month prior to Day 1, such as an intrauterine device (IUD), implant, or two forms of the following: diaphragm, cervical cap, patch, condom, spermicide, or sponge. In addition, females of child-bearing potential must agree to continue to use their method of birth control for the duration of the study and 12 weeks following discharge from the study.</li> <li>6. If male, be surgically sterile, or agree to use appropriate contraception (latex condom with spermicide) when engaging in sexual activity and agree to not donate sperm for the duration of the study and 12 weeks following discharge from the study</li> <li>7. Have suitable venous access for multiple venipunctures.</li> </ol>
<b>Exclusion Criteria</b>	<p>Eligible subjects must not:</p> <ol style="list-style-type: none"> <li>1. Have any of the following findings at Screening: <ol style="list-style-type: none"> <li>a. Hemoglobin or hematocrit value outside the normal range</li> <li>b. Platelet count outside the normal range</li> <li>c. Prothrombin time or activated partial thromboplastin time outside the normal range</li> <li>d. Plasma fibrinogen outside the normal range</li> <li>e. Serum triglycerides or total cholesterol outside the normal range</li> <li>f. Serum creatinine &gt;1.5 mg/dL (133 µmol/L) or known renal disease</li> <li>g. Aspartate aminotransferase or alanine aminotransferase &gt;2 x the upper limit of normal, or known liver disease</li> <li>h. Total bilirubin outside the normal range</li> <li>i. Positive viral screen for hepatitis B virus, hepatitis C virus, or human immunodeficiency virus</li> </ol> </li> </ol>

	<ul style="list-style-type: none"> <li>j. Positive pregnancy test (females)</li> <li>k. Positive drug, tobacco or alcohol screen</li> <li>l. Any clinically significant findings on 12-lead ECG or urinalysis</li> </ul> <ol style="list-style-type: none"> <li>2. Have a personal or family history of clotting disorder or hematologic abnormality, such as excessive bleeding, joint hematoma, thrombovascular disease, thrombocytopenia, or any chronic condition requiring treatment with transfusions.</li> <li>3. Have a history of unexplained syncope.</li> <li>4. Have a history within 6 months prior to Screening of major bleeding, trauma, surgical procedure of any type, or vaginal delivery.</li> <li>5. Have a history within 6 months prior to Screening of peptic ulcer or gastrointestinal bleeding (including hematemesis, melena, or rectal bleeding).</li> <li>6. Have received any blood product or anticoagulant within 3 months prior to Screening.</li> <li>7. Have donated blood or blood products within 3 months prior to Screening.</li> <li>8. Have a history of minor bleeding episodes (eg, epistaxis, bruising or gingival bleeding) within 1 month prior to Screening, or a long-standing history of such bleeding.</li> <li>9. If female, have a history of excessive or dysfunctional uterine bleeding (unless the subject had a subsequent hysterectomy).</li> <li>10. Have used any tobacco or nicotine-containing products within 3 months prior to Screening.</li> <li>11. Have used any systemic prescription or non-prescription drugs (including vitamins, supplements, and herbal products) within 14 days prior to Day 1 (except for permitted contraceptives). NOTE: subjects should be asked specifically about use of aspirin and other non-steroidal anti-inflammatory drugs.</li> <li>12. If female, be pregnant, breastfeeding, or planning to become pregnant during the study.</li> <li>13. Have received ciraparantag in any prior clinical study.</li> <li>14. Have received another investigational drug within 5 half-lives or 30 days, whichever is longer, prior to Day 1.</li> <li>15. Known allergy to edoxaban, apixaban or rivaroxaban.</li> <li>16. Have any other condition that, in the opinion of the Investigator, would interfere with a subject's ability to adhere to the protocol, interfere with assessment of the investigational product, or compromise the safety of the subject or the quality of the data.</li> </ol>
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<b>Study Product</b>	Ciraparantag: 6 mg/mL solution in single use vials
<b>Comparator</b>	Placebo (Sterile 0.9% Sodium Chloride Injection, USP)
<b>Dose, Route, Regimen, Duration of Administration</b>	<p><b>Edoxaban:</b> 60 mg PO once daily (qd) in the morning from Day 1 to Day 3 or Day 4.</p> <p><b>Apixaban:</b> 10 mg PO every 12 hours (q 12 h) from Day 1 to the morning of Day 3 or Day 4.</p> <p><b>Rivaroxaban:</b> 20 mg PO once daily (qd) in the morning from Day 1 to Day 3 or Day 4.</p> <p><b>Ciraparantag/PBO:</b> Single IV dose on Day 3 or Day 4</p> <p>Group 1 of each cohort: 180 mg</p> <p>Group 2 of each cohort: a dose from 120 to 360 mg (decision to enroll this cohort and dose to be determined by the data review team)</p>
<b>Efficacy Assessments</b>	Coagulation status will be determined by WBCT, which will be measured at the study site immediately after blood collection. WBCT Testing will be performed using the Perosphere Technologies' PoC Coagulometer at all planned WBCT timepoints: Day 1 prior to first dose of anticoagulant*; ciraparantag/PBO dosing day as follows: after anticoagulant but before ciraparantag/PBO*, and 0.25, 0.5, 1*, 3, 6, and 8 hours after ciraparantag/PBO; the following day at 24 hours after ciraparantag/PBO*, and on subsequent study days* as needed until protocol threshold criteria are met. At the selected timepoints designated with the asterisk (*), WBCT also will be tested simultaneously using the manual method.
<b>Pharmacokinetic Assessments</b>	Blood samples for PK assessments (for ciraparantag/metabolite[s] and anticoagulant) will be obtained starting on the ciraparantag/PBO dosing day as follows: prior to anticoagulant, prior to ciraparantag/PBO, and 0.25, 0.5, 0.75, 1, 1.5, 3, 6, and 24 hours after ciraparantag/PBO.
<b>Study Endpoints</b>	<p>For all efficacy endpoints listed below, analyses will be based on WBCT results obtained with the coagulometer unless otherwise specified.</p> <p><b>Primary Efficacy Endpoint:</b> Achieving a WBCT <math>\leq 120\%</math> 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.</p> <p><b>Secondary Efficacy Endpoints:</b></p> <p>The secondary efficacy endpoints are as follows:</p>

	<ol style="list-style-type: none"> <li>1. Achieving WBCT <math>\leq 115\%</math> 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.</li> <li>2. Achieving WBCT <math>\leq 110\%</math> 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.</li> <li>3. Achieving WBCT <math>\leq 120\%</math> 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.</li> <li>4. Achieving WBCT <math>\leq 115\%</math> 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.</li> <li>5. Achieving WBCT <math>\leq 110\%</math> 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.</li> <li>6. Achieving a WBCT <math>\leq 120\%</math> 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.</li> <li>7. Achieving a WBCT <math>\leq 115\%</math> 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.</li> <li>8. Achieving a WBCT <math>\leq 110\%</math> 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.</li> </ol> <p><b>Tertiary Efficacy Endpoints:</b></p> <p>The tertiary efficacy endpoints are as follows:</p> <ul style="list-style-type: none"> <li>• Achieving a WBCT <math>\leq 120\%</math> 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).</li> <li>• Achieving a WBCT <math>\leq 115\%</math> 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).</li> </ul>
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	<ul style="list-style-type: none"> <li>• Achieving a WBCT <math>\leq 110\%</math> 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).</li> <li>• Achieving a WBCT <math>\leq 120\%</math>, <math>\leq 115\%</math>, or <math>\leq 110\%</math> of BL at 1 hour after administration of ciraparantag/PBO by the manual method</li> <li>• 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).</li> <li>• Change from Day 3/Day 4 pre-ciraparantag/PBO 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).</li> </ul> <p><b>Safety Endpoints:</b></p> <ul style="list-style-type: none"> <li>• Treatment-emergent adverse events (TEAEs)</li> <li>• Treatment-emergent serious adverse events (SAEs)</li> <li>• Change from BL in vital signs</li> <li>• Change from BL in clinical laboratory evaluations</li> </ul>
<b>Statistical Methods</b>	<p>The analysis of both efficacy and safety parameters will be conducted for each cohort (i.e., for 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.</p> <p><b>Efficacy Analyses:</b> The primary efficacy parameter is the proportion of subjects that achieve a WBCT <math>\leq 120\%</math> of BL within 1 hour after the administration of the study drug which is subsequently sustained after 1 hour through at least 6 hours after the administration of the study drug. Summary statistics (n, %) will be provided for each treatment group, and 95% confidence interval (CI) will be constructed by the Clopper-Pearson method. Each active dose will be compared with the PBO group by Boschloo's test at 0.05 two-sided significance level. A 95% CI for the difference in percentages will be constructed by the Miettinen and Nurminen method. In addition, the Cochran-Mantel-Haenszel Test, with stratification by age group, will be used to compare each active dose with placebo as a sensitivity analysis.</p> <p><b>Safety Analyses:</b> The safety parameters include AEs, clinical laboratory parameters (including prothrombotic markers), vital sign measurements, and ECG parameters. All safety parameters will be analyzed descriptively. The number and percentage of subjects with at least one TEAE, at least one</p>

	<p>serious TEAE, at least one study drug related TEAE, and at least one TEAE leading to study withdrawal will be presented for each treatment group.</p> <p><b>Sample Size Justification:</b> Assuming true response rates for the primary efficacy endpoint of 78% and 5% in the first active dose group and the PBO group, respectively, 18 subjects with a 2:1 randomization ratio will have 91% power at 0.05 two-sided significance level based on Boschloo's test. Assuming a response rate of 66% and 5% in the second active dose group and the PBO group, respectively, 12 subjects in each group will have 94% power.</p>
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## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
AME	Absorption, metabolism, and excretion
ANCOVA	Analysis of covariance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BAP	1,4-bis (3- aminopropyl) piperazine
BL	baseline
CI	confidence interval
CL	Total plasma clearance (IV administration)
CL/F	Total plasma clearance uncorrected for bioavailability (F)
C <sub>max</sub>	Maximum plasma concentration
C <sub>24</sub>	Concentration 24 hours after dosing
CRF	Case Report Form
EC	Ethics Committee
ECG	electrocardiogram
F	Bioavailability
FDA	US Food and Drug Administration
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ICF	Informed Consent Form
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous
IWRS	Interactive Web Response System

Abbreviation	Definition
LMWH	low molecular weight heparin
MR <sub>Cmax</sub>	Metabolite to parent ratio of C <sub>max</sub>
MR <sub>AUC(0-last)</sub>	Metabolite to parent ratio of AUC <sub>(0-last)</sub>
MR <sub>AUC(0-inf)</sub>	Metabolite to parent ratio of AUC <sub>(0-inf)</sub>
$\lambda_z$	Elimination rate constant
NOACs	non-vitamin K oral anticoagulants
PD	pharmacodynamic
PK	pharmacokinetic
PO	Oral(ly)
PoC	Point-of-Care
PF 1.2	prothrombin fragment 1.2
PT	prothrombin time
q	every
qd	once a day (daily)
SAE	serious adverse event
SOC	System Organ Class
TAP	Test Article Preparer
TEAE	treatment-emergent adverse event
TFPI	tissue factor pathway inhibitor
UFH	unfractionated heparin
V <sub>z</sub>	Apparent volume of distribution
V <sub>z</sub> /F	Apparent volume of distribution uncorrected for bioavailability (F)
WBCT	whole blood clotting time

## 1. INTRODUCTION

### 1.1. Background

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-threatening bleeding, prior to urgent or emergency surgery, after major trauma, or in cases of anticoagulant overdose.

Various anticoagulant drugs and the respective reversal agents that are currently available are shown in Table 3, along with the limitations of the reversal agents.

**Table 3: Selected Anticoagulants and Reversal Agents**

Anticoagulant			Reversal Agent <sup>a</sup>	
Name	Class	Initial Approval (US)	Name	Use and Limitations
UFH	Heparin	1939	Protamine	Dosing is based on timing and dose of last UFH/LMWH administration. Reversal potency is lower for LMWH vs UFH. Hypotension, bradycardia or allergic reactions can occur.
Warfarin	Vitamin K antagonist	1954	Vitamin K	Must decide upon IV or oral dosing based on INR and bleeding risk. Excessive dosing may lead to inability to re-anticoagulate with warfarin for several days.
Dabigatran	FIIa inhibitor	2010	Idarucizumab (Praxibind®), a monoclonal Fab that binds to dabigatran	Store refrigerated (beyond 48 hours). Adult regimen = two sequential IV doses. (Initial US approval 2015)
Rivaroxaban	FXa inhibitor	2011	Coagulation factor Xa (recombinant) (Andexxa®)	Store refrigerated. Requires reconstitution and IV preparation time. Adult regimen = 30 minute IV bolus then 2 hour infusion. Dosing is based on timing and dose of each FXa inhibitor. Activity requires continuous infusion and wanes quickly after end of infusion. Black box warning for thromboembolic risks. (Initial US approval 2018)
Apixaban	FXa inhibitor	2012		

Source: (Alquwaizani, 2013; Boehringer Ingelheim Pharmaceuticals, 2018b; Macdonald, 2018; Portola Pharmaceuticals, 2018).

Abbreviations: Fab=antibody fragment; FIIa=factor IIa (thrombin); FFP=fresh frozen plasma; FXa=factor Xa; INR=international normalized ratio; IV=intravenous; LMWH=low molecular weight heparin; PCC=prothrombin complex concentrate; UFH=unfractionated heparin.

<sup>a</sup> Shown are anticoagulant-specific reversal agents. Non-specific reversal therapies may include PCC, FFP, or recombinant factor VIIa; for oral anticoagulants, activated charcoal also may be used.

## 1.2. Ciraparantag

Ciraparantag (previously known as PER977, now known as AMAG-977) 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 edoxaban, apixaban, rivaroxaban, 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

### 1.2.1. Non-clinical Studies

*In vivo* (in rat models) and/or *ex vivo* (in human plasma), ciraparantag was shown to reverse the anticoagulant effect of edoxaban, apixaban, rivaroxaban, dabigatran, low molecular weight heparin (LMWH), and fondaparinux. Ciraparantag did not reverse the anticoagulant effect of warfarin *in vivo*. In a rat tail transection model, intravenous (IV) administration of ciraparantag reversed the anticoagulant effect of edoxaban, apixaban, rivaroxaban, dabigatran, unfractionated heparin (UFH), and enoxaparin, a LMWH.

In dynamic light scattering studies, ciraparantag was shown to physically associate with the anticoagulants that were tested (i.e., edoxaban, apixaban, rivaroxaban, LMWH, UFH and fondaparinux). Ciraparantag showed no self-association, or interaction with fXa, fIIa, antithrombin III, or commonly used cardiac drugs (aspirin, clopidogrel, digoxin, propafenone, hydrochlorothiazide, triamterene, lisinopril, diltiazem, propranolol), antiepileptic drugs (carbamazepine, gabapentin, lamotrigine, phenytoin sodium, valproate sodium), or other drugs (metformin, atorvastatin, azithromycin, streptokinase) by the same measure.

In human plasma containing all coagulation factors and albumin, ciraparantag displayed no plasma protein binding. In citrated human whole blood, ciraparantag had no effect on platelet aggregation.

Ciraparantag displayed no concentration-dependent inhibition of hepatic cytochromes and displayed no concentration-independent inhibition of hERG *in vitro*.

With respect to safety, in 14-day repeat IV dosing studies in Sprague Dawley rats and in beagle dogs, there were no signs of systemic toxicity at ciraparantag acetate doses up to 20 mg/kg/day (the highest dose tested). The NOAEL was determined to be 20 mg/kg/day ciraparantag acetate. Further, this dose had no consistent dose-related effects on heart rate, blood pressure, cardiac rhythm or electrocardiogram parameters including QTc in beagle dogs.

The primary metabolite of ciraparantag, 1,4-bis (3- aminopropyl) piperazine (BAP), was estimated to have 1/34th the potency of ciraparantag on a molar basis with respect to pre-clinical edoxaban reversal. *In vivo* testing of BAP in rats and dogs at IV doses up to 20 mg/kg/day ciraparantag acetate showed no treatment related findings.

### 1.2.2. Clinical Studies

Ciraparantag has been evaluated in more than 270 healthy adult volunteers across seven completed clinical trials ([Table 4](#)). To date, 6 completed clinical studies have evaluated single IV doses of ciraparantag following administration of edoxaban, UFH, enoxaparin, apixaban or rivaroxaban. A separate completed study evaluated the absorption, metabolism, and excretion (AME) of radiolabeled ciraparantag.

Early clinical studies originally presented doses expressed as the drug substance ciraparantag acetate. In accordance with new guidelines, dosing is now expressed as the active moiety (ciraparantag) ([Section 1.3](#)). In the presentation of data from previous clinical studies, dosing is expressed as the active moiety unless otherwise specified.

Monitoring of coagulation status in clinical studies initially was attempted using traditional assays such as prothrombin time (PT), activated partial thromboplastin time (aPTT) or thromboelastography reaction time. However, ciraparantag is cationic and binds to the anionic substances (citrate, ethylenediaminetetraacetic acid, and oxalate) in standard blood collection tubes used for coagulation testing. Ciraparantag also binds to the colloidal activators (eg, kaolin or Celite) used in some coagulation assays. Therefore, such assays are not appropriate markers for measuring ciraparantag effect because of reagent interference and assay insensitivity.

Despite the challenges with traditional assays, reversal of anticoagulant effect was visually observed by the study personnel who were handling blood samples in the first clinical study. Whole blood clotting time (WBCT) was performed manually on several blood samples in that study and was found to be a good measure of coagulation status (ie, showing an increase in clotting time following edoxaban administration, with agreement between independent observers). WBCT is a direct measure of the time required for blood clot formation *ex vivo* and uses blood drawn into reagent-free collection tubes; the test uses only glass as the activating agent. Therefore, WBCT became the key measure of coagulation status in clinical studies of ciraparantag.

WBCT testing in prior clinical studies was performed manually. In order to reduce the possibility of inter-operator differences in testing and technique, a handheld point-of-care coagulometer device was developed for automated WBCT testing. In this study, WBCT testing will be performed with the coagulometer device (Perosphere Technologies' PoC Coagulometer) and the manual testing method.

**Table 4: Clinical Studies of Ciraparantag**

Study #	Status	Study Type	Ciraparantag Treatment <sup>a</sup>		Key Pharmacodynamic Findings <sup>b</sup>
			N	IV Dose Range	
01-001	completed	PK/PD – reversal of edoxaban	66	3–180 mg	<p>Period 1: administered alone, ciraparantag displayed no pro-coagulant activity.</p> <p>Period 2: when administered 3 hours following edoxaban 60 mg PO, ciraparantag demonstrated dose-related reversal of anticoagulation (WBCT return to <math>\leq 120\%</math> of baseline), with significant effect compared to PBO at most or all timepoints within 1 hour post-dose for doses <math>\geq 60</math> mg. The effect typically started 10–30 minutes post-dose and was sustained through 24 hours.</p>
01-002	completed	PK/PD – reversal of UFH	48	60–360 mg	<p>UFH was given as a 5000 u IV bolus then 3 hours infusion. When administered within 30 minutes after the end of UFH infusion, ciraparantag did not demonstrate significant reversal of anticoagulation compared to PBO at the doses tested. Higher doses were considered but the study was closed early for business reasons (there were no safety concerns regarding higher dosing). The findings were not unexpected due to the much higher binding ability of UFH for ciraparantag compared to smaller enoxaparin molecules and NOACs. In addition, the anticoagulant effect of UFH naturally reverses quickly after the end of infusion given its short half-life.</p>
01-003	completed	PK/PD – reversal of enoxaparin	32	15–180 mg	<p>When administered 4 hours following enoxaparin 1.5 mg/kg SC, reversal of WBCT (to <math>\leq 120\%</math> of baseline within 1 hour post-dose and sustained in the 1 to 6-hour interval) was observed in 100% of subjects receiving ciraparantag doses <math>\geq 60</math> mg and no subject in the PBO group. The effect typically started within 20 minutes post-dose and was sustained through 24 hours (with notable difference from PBO through ~6-8 hours after dosing).</p> <p>Those in the 15 mg group received 15 mg IV every 30 minutes x 4 doses. In this group 71% had WBCT reversal to <math>\leq 120\%</math> of baseline at 1 hour post-dose and sustained in the 1 to 6-hour interval. However mean WBCT was notably slower to decline compared to the other active dose groups.</p>
01-004	completed	Mass balance, metabolic disposition	6	120 mg	<p>Subjects received a single IV dose of <math>^{14}\text{C}</math>-labeled ciraparantag. Ciraparantag is primarily cleared by hydrolysis; it is rapidly enzymatically hydrolyzed to MAP, which is converted to BAP; these are the major metabolites observed in serum.</p>

Study #	Status	Study Type	Ciraparantag Treatment <sup>a</sup>		Key Pharmacodynamic Findings <sup>b</sup>
			N	IV Dose Range	
					Full recovery of radioactivity was suboptimal because elimination continued longer than expected.
02-001	completed	PK/PD – reversal of edoxaban	41	15–360 mg	Day 3: when administered 3 hours following edoxaban 60 mg PO, reversal of WBCT (to $\leq 120\%$ of baseline within 1 hour post-dose and sustained in the 1 to 6-hour interval) was observed in 89-100% of subjects receiving ciraparantag doses $\geq 60$ mg vs 60% for PBO.  Day 4: administration of another dose of edoxaban 60 mg PO resulted in successful re-anticoagulation, with WBCT results similar to those observed pre-ciraparantag on Day 3. Administration of ciraparantag 3 hours following edoxaban on Day 4 demonstrated reversal of WBCT with results comparable to Day 3.  Ciraparantag at all doses administered in this study had no apparent impact on the PK of edoxaban.
02-011	completed	PK/PD – reversal of apixaban	36	30–120 mg	Day 4: when administered 3 hours following apixaban 10 mg PO, reversal of WBCT (to $\leq 110\%$ of baseline within 1 hour post-dose and sustained through 5 hours) was observed in 67%, 100% and 100% of subjects receiving ciraparantag 30, 60 and 120 mg, respectively, vs 17% for PBO.
02-012	completed	PK/PD – reversal of rivaroxaban	48	30–180 mg	Day 3: when administered 4 hours following rivaroxaban 20 mg PO, reversal of WBCT (to $\leq 110\%$ of baseline within 1 hour post-dose and sustained through 6 hours) was observed in 58%, 75%, 67% and 100% of subjects receiving ciraparantag 30, 60, 120 and 180 mg, respectively, vs 13% for PBO.

Abbreviations: BAP=1,4-bis (3-aminopropyl) piperazine; IV=intravenous; NOAC=non-vitamin K oral anticoagulant; MAP=mono-arginine piperazine; PBO=placebo; PD=pharmacodynamics, PK=pharmacokinetics; SC=subcutaneously; UFH=unfractionated heparin; WBCT=whole blood clotting time.

<sup>a</sup> N shown for subjects who received ciraparantag. Doses are expressed as the active moiety (ciraparantag); unless otherwise specified, these were single IV doses administered over ~10 minutes.

<sup>b</sup> Unless otherwise specified, findings are based on manual WBCT results.

Ciraparantag exhibits linear pharmacokinetics. Across the range of doses that have been evaluated, the mean half-life of ciraparantag ranged from 12 to 19 minutes.

Ciraparantag was well tolerated across the range of doses that were evaluated. The most common adverse events (AEs) related to ciraparantag were mild, transient sensations of warmth (typically reported as hot flashes or flushing), paresthesia, and alterations in taste. There were no clinically significant adverse trends in laboratory values, vital signs, or electrocardiogram (ECG) parameters.

Additional details of the results of prior studies of ciraparantag are available in the Investigator's Brochure.

### 1.3. Dosing Nomenclature

It should be noted that in previously completed non-clinical and clinical studies, the doses of study drug (mg) referred to the salt form (ciraparantag acetate). These ciraparantag acetate doses have been used in various publications and presentations for these studies; however, regulatory preference is now to quantify dosing using the active drug moiety (ciraparantag). The conversion factor is as follows:

$$\text{ciraparantag (mg)} = \text{ciraparantag acetate (mg)} \times 0.6$$

For reference, the equivalent amounts of each drug form are given in Table 5.

**Table 5: Ciraparantag Dosing Conversion**

Ciraparantag Acetate	Ciraparantag
25 mg	15 mg
50 mg	30 mg
100 mg	60 mg
200 mg	120 mg
300 mg	180 mg
600 mg	360 mg

Throughout this protocol, active study drug doses are expressed as ciraparantag moiety alone, without the associated acetate counter-ion.

## 2. STUDY OBJECTIVES

### 2.1. Primary Objective

- To demonstrate that a single IV administration of ciraparantag is superior to PBO in the reversal of anticoagulation induced by each of the evaluated anticoagulant drugs (edoxaban, apixaban, or rivaroxaban) in healthy adults, as assessed by WBCT measured with Perosphere Technologies' POC Coagulometer.

### 2.2. Secondary Objectives

- 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

#### 3.1. Overview

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 (Section 6.6.2).

The study will 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. The selection of the ciraparantag dose(s) to be evaluated is discussed in Section 5.2.2.

During the Screening period, which is the same for all cohorts, subjects will be assessed for eligibility, and as part of informed consent, they will receive activity and dietary guidelines appropriate for a study involving an anticoagulant. Eligible subjects will be admitted to the clinical study unit on Day -1. Fecal occult blood test results must be negative for a subject to participate (Section 6.6.1). The next day (Day 1), baseline (BL) WBCT will be determined prior to receiving the anticoagulant based on the cohort to which they were enrolled (Table 6).

**Table 6: Anticoagulation Regimen by Cohort**

Cohort	Anticoagulant	Regimen
1	Edoxaban	60 mg PO once daily in the morning from Day 1 to Day 3 or Day 4
2	Apixaban	10 mg PO every 12 hours from Day 1 to the morning of Day 3 or Day 4
3	Rivaroxaban	20 mg PO once daily in the morning from Day 1 to Day 3 or Day 4

PO=orally

Within each cohort, subjects will be assessed for sufficient anticoagulation on Day 3 or Day 4 before proceeding further in the study. The Day 3/Day 4 option is provided to allow for flexibility in scheduling the day of the week on which this visit will occur. WBCT will be determined following the morning dose of anticoagulant at the approximate timepoint specified (Table 7) for purposes of determining sufficient anticoagulation. If this WBCT result is  $\geq 130\%$  of BL (based on the coagulometer), the subject will proceed in the study. If testing occurs 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. If testing occurs on Day 4 and does not meet WBCT criteria for sufficient anticoagulation, the subject will be discontinued from the study (Section 6.11.3).

Subjects who proceed in the study will be randomized to a single IV dose of ciraparantag or PBO in a 2:1 ratio. Randomization will be stratified by age (18 to <50 years vs.  $\geq 50$  to 75 years). Within each cohort, between 50% and 70% of randomized subjects will be  $\geq 50$  to 75 years of age, and there will be approximately equal numbers of male and female subjects.

The ciraparantag/PBO dose will be administered starting at the approximate timepoint specified in Table 7, followed by multiple WBCT and PK measurements.

**Table 7: Timepoints for Assessing Sufficient Anticoagulation and for Ciraparantag/Placebo Dosing (Day 3 or Day 4)**

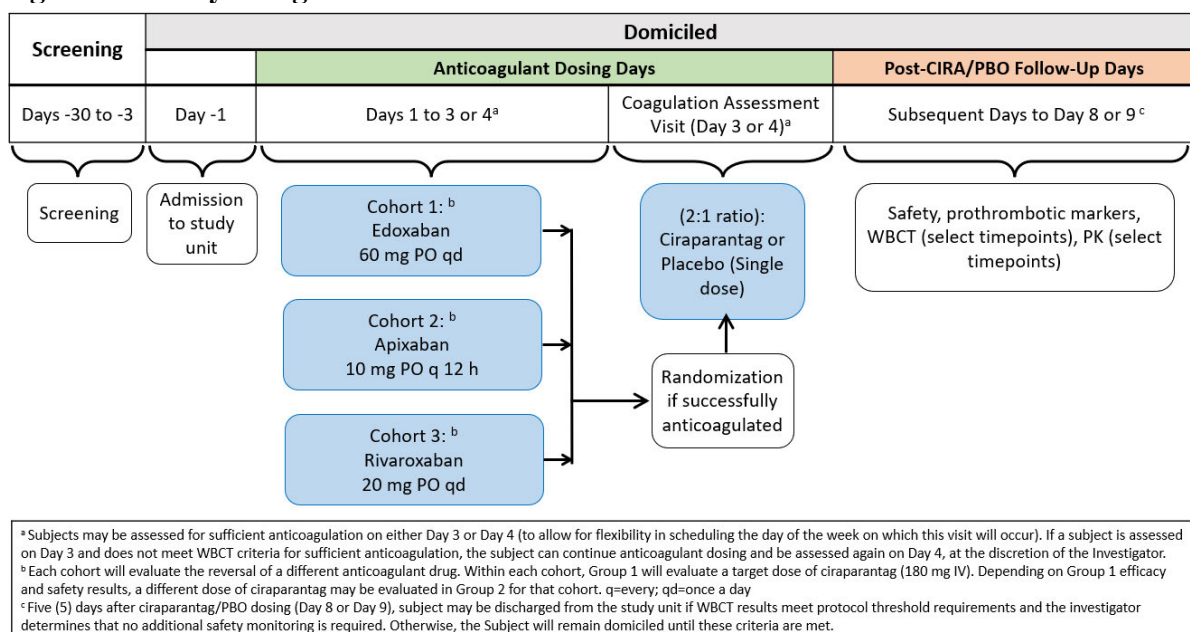
Cohort	Anticoagulant	Timepoint for assessing sufficient anticoagulation	For sufficiently anticoagulated subjects, timepoint for ciraparantag/placebo dose
1	Edoxaban	2.75 hours after Day 3 or Day 4 edoxaban dose	3 hours after the last edoxaban dose
2	Apixaban	3.75 hours after Day 3 or Day 4 apixaban dose	4 hours after the last apixaban dose
3	Rivaroxaban	3.75 hours after Day 3 or Day 4 rivaroxaban dose	4 hours after the last rivaroxaban dose

Subjects in all cohorts who receive ciraparantag/PBO will remain domiciled in the clinical study unit for 5 days after dosing (i.e., through Day 8 or Day 9). Evaluations on the day following ciraparantag/PBO dosing will include WBCT, PK, and safety assessments (including testing for prothrombotic markers). On subsequent days, follow-up safety assessments (including testing for prothrombotic markers) will continue. Any subject with WBCT on the day following ciraparantag/PBO dosing that is  $>120\%$  of BL (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 is  $\leq 120\%$  of BL (based on the coagulometer) and  $\leq 110\%$  of BL (based on the manual method). Note that the differences in these thresholds is based on the differences in assay sensitivity between the two testing methods (Section 3.2.2). Once both WBCT thresholds have been met, no further WBCT testing is required.

Five days after ciraparantag/PBO dosing (Day 8 or Day 9), subjects may be discharged from the study unit, provided that the last (final) WBCT results are  $\leq 120\%$  of BL (based on the coagulometer) and  $\leq 110\%$  of BL (based on manual WBCT), and the Investigator determines that no additional safety monitoring is required. Otherwise the subject will remain domiciled until these criteria are met. The detailed schedule of study assessments is provided in [Appendix A](#).

An overview of the study design is provided in [Figure 1](#).

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



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 (eg, 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 enrolled in only one group at a time. Individual subjects may only be randomized 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 as described in Section 10.2.2. Criteria for stopping dosing in a cohort are described in Section 10.2.3.

Subjects who remain eligible after the Day -1 assessments and who are admitted to the study unit will be considered enrolled in the study. As described above, 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.

## 3.2. Rationale for Key Study Design Elements

### 3.2.1. General Design Elements

This study will be conducted in double-blind fashion in conjunction with a PBO control in an effort to remove evaluation biased by the expected effects of study drug. A PBO control group is considered appropriate because it will provide the comparative data on the “natural” time course of return to normal coagulation status following anticoagulant dosing based on WBCT.

Adult subjects will be stratified into two groups (18 to <50 years vs.  $\geq 50$  to 75 years), and between 50% and 70% of randomized subjects will be  $\geq 50$  to 75 years of age, in order to evaluate ciraparantag across a range of ages that reflect its potential use in clinical practice. For example, reversal of anticoagulation is likely to be needed in relatively younger patients in cases of severe bleeding from trauma, and in relatively older patients in cases of spontaneous internal bleeding.

Evaluation of reversal of anticoagulation will be performed on Day 3 or Day 4 of anticoagulant dosing to ensure that subjects are at clinically relevant concentrations of the anticoagulant when they receive ciraparantag/PBO. Per prescribing information and literature, steady state concentrations for each of the anticoagulants are achieved within 3 days or less with the regimens administered in this study ([Daiichi Sankyo, 2017](#); [Frost, 2014](#); [Sanofi-Aventis U.S., 2018](#)).

Ciraparantag/PBO will be administered 3 or 4 hours after the anticoagulant dose on Day 3 or Day 4, in order to evaluate study drug treatment administered near the time of maximum concentration and effect of the anticoagulant.

### 3.2.2. Use of WBCT Testing

WBCT is the key clinical efficacy measurement because ciraparantag is cationic and binds to the anionic substances in standard blood collection tubes used for coagulation testing, and also binds to anionic, colloidal activators used in the traditional coagulation assays such as PT or aPTT (Section 1.2.2). Therefore, such assays are not appropriate markers for measuring ciraparantag effect because of reagent interference and assay insensitivity. WBCT is a direct measure of the time required for blood clot formation *ex vivo* and uses blood drawn into reagent-free collection equipment; the test uses only glass as the activating agent.

WBCT testing can be performed with different methods. In this study, WBCT will be tested with both the Perosphere Technologies' PoC Coagulometer and with a manual testing method. The Perosphere Technologies' PoC Coagulometer uses near infrared (IR) spectroscopy to detect fibrin assembly; it was developed specifically to provide an objective, sensitive and consistent method to measure anticoagulant effects with high precision. Manual WBCT testing is simply a visual determination of time to gross clot formation in a test tube; it is an old method that is more prone to variability and depends on operator consistency in technique and interpretation. While impractical for larger studies across many sites, manual WBCT can be performed acceptably under the controlled conditions of a small number of dedicated study units.

Extensive validation studies have shown that coagulometer results showed a high degree of linear correlation with blood concentrations of anticoagulants over a broad range of concentrations, as well as a high degree of linear correlation with manual WBCT results. However, it is important to note that the results of the coagulometer and manual WBCT are not interchangeable. The coagulometer yields clotting times that are approximately half as long as manual WBCT results. For example, a typical “normal” blood sample from a healthy individual may show a manual WBCT result of approximately 500 seconds, while this same sample may show a coagulometer WBCT result of approximately 250 seconds. Similarly, the sensitivity of the assay to the effect of anticoagulation is greater with the coagulometer – ie, the proportionate increase in clotting time relative to the baseline in response to a given anticoagulant concentration is approximately double in comparison to manual WBCT.

In this study, the coagulometer will provide the primary WBCT assessments for efficacy analyses and will be performed at all planned WBCT timepoints. Manual WBCT testing also will be performed at selected timepoints in order to further describe the correlation between results obtained with the two methods, and to ensure certainty that a subject’s WBCT has returned to near baseline after the study drug treatment period and before discharge from the study unit.

### **3.2.3. Determination of Sufficient Anticoagulation and Efficacy Endpoints**

The thresholds for relevant changes from baseline in WBCT as measured by the coagulometer are based on multiple factors including:

- known ranges for plasma concentrations of anticoagulants at therapeutic doses, and their associated bleeding risk
- results of manual WBCT testing following anticoagulant dosing in ciraparantag clinical studies conducted to date
- correlation between anticoagulant concentrations, manual WBCT testing, and coagulometer WBCT testing in a methods comparison study conducted as part of coagulometer validation

#### Rationale for sufficient anticoagulation

Subjects will be considered sufficiently anticoagulated if the WBCT measurement obtained just prior to the planned ciraparantag/PBO dose shows an increase in WBCT to  $\geq 130\%$  of BL (based on the coagulometer).

This threshold was selected for the following reasons:

- In most prior clinical studies of ciraparantag using manual WBCT testing, the threshold for sufficient anticoagulation was WBCT  $\geq 120\%$  of baseline, and in those studies the proportion of subjects who reached this threshold following therapeutic doses of anticoagulants was high (eg, 85% with apixaban and 100% with rivaroxaban [unpublished data on file from Studies 977-02-011 and 977-02-012]).
- In a methods comparison study, manual WBCT changes to 120% of baseline corresponded to NOAC concentrations of approximately 150 ng/mL. In that

study, NOAC concentrations of 150 ng/mL corresponded to WBCT changes of approximately 130% of baseline as measured by the coagulometer [unpublished data from validation studies for Perosphere Technologies' POC Coagulometer].

- Therefore, the WBCT threshold of  $\geq 130\%$  of BL (based on the coagulometer, which is the primary WBCT assessment method for study) represents a degree of anticoagulation that is expected to be achievable for the therapeutic anticoagulant dosing regimens to be administered and provides a sufficient level from which a meaningful improvement can be measured after administration of ciraparantag/placebo.

#### Rationale for efficacy endpoint

In this study, the coagulometer will provide the primary WBCT assessments for efficacy analyses, because the coagulometer is expected to provide greater sensitivity and precision compared to the manual method (Section 3.2.2). The primary efficacy endpoint is based on achieving a WBCT  $\leq 120\%$  of baseline based on the coagulometer. This threshold was selected for the following reasons:

- Available published guidance and clinical study precedent indicates that the threshold for clinically relevant anticoagulation with NOACs lies within the range of 30 to 75 ng/mL (Connolly, 2019; Levy, 2016; Pernod, 2013).
- In a methods comparison study, NOAC concentrations of 75 ng/mL corresponded to manual WBCT changes of approximately 110% of baseline [unpublished data from validation studies for Perosphere Technologies' POC Coagulometer]. Accordingly, among subjects who have been anticoagulated, achievement of manual WBCT  $\leq 110\%$  of baseline within a given time period (eg, within 1 hour after administration of study drug) has been utilized as an efficacy endpoint in some prior clinical studies of ciraparantag, and those studies have shown significant differences between ciraparantag and placebo (Section 1.2.2).
- When tested with the coagulometer (in the methods comparison study), NOAC concentrations of 75 ng/mL correspond to WBCT changes of approximately 120% of baseline.
- Therefore, the coagulometer WBCT threshold of  $\leq 120\%$  of baseline was selected as the primary target for demonstration of reversal of anticoagulation.
- As described in Section 9.2.1, other WBCT thresholds for reversal of anticoagulation will also be examined.

### **3.3. Duration of Subject Participation**

Subjects will participate in the study for up to approximately 6 weeks. This will consist of a Screening period (up to 30 days) and a domiciled period in the study unit (up to 10 days).

## **4. STUDY POPULATION**

### **4.1. Inclusion Criteria**

Eligible subjects must:

1. Be informed of the nature of the study and provide written informed consent before any study-specific procedures are performed.
2. Be 18 to 75 years of age, inclusive, at time of consent.
3. Be in good health, in the opinion of the Investigator, based on medical history, physical examination, vital signs, ECG and laboratory testing (ie, absence of any clinically relevant abnormality) during Screening.
4. Have a body mass index 18 to 32 kg/m<sup>2</sup>, inclusive, at Screening.
5. If female, be surgically sterile or post-menopausal (no menses for at least 12 months), or if of child-bearing potential, must be using an acceptable method of contraception (other than a combination estrogen/progestin hormonal contraceptive) for at least 1 month prior to Day 1, such as an intrauterine device (IUD), implant, or two forms of the following: diaphragm, cervical cap, patch, condom, spermicide, or sponge. In addition, females of child-bearing potential must agree to continue to use their method of birth control for the duration of the study and 12 weeks following discharge from the study.
6. If male, be surgically sterile, or agree to use appropriate contraception (latex condom with spermicide) when engaging in sexual activity and agree to not donate sperm for the duration of the study and 12 weeks following discharge from the study.
7. Have suitable venous access for multiple venipunctures.

### **4.2. Exclusion Criteria**

Eligible subjects must not:

1. Have any of the following findings at Screening:
  - a. Hemoglobin or hematocrit value outside the normal range
  - b. Platelet count outside the normal range
  - c. PT or aPTT outside the normal range
  - d. Plasma fibrinogen outside the normal range
  - e. Serum triglycerides or total cholesterol outside the normal range
  - f. Serum creatinine >1.5 mg/dL (133 µmol/L) or known renal disease
  - g. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2 x the upper limit of normal, or known liver disease
  - h. Total bilirubin outside the normal range
  - i. Positive viral screen for hepatitis B virus, hepatitis C virus (HCV), or human immunodeficiency virus (HIV)
  - j. Positive pregnancy test (females)
  - k. Positive drug, tobacco or alcohol screen
  - l. Any clinically significant findings on 12-lead ECG or urinalysis

2. Have a personal or family history of clotting disorder or hematologic abnormality, such as excessive bleeding, joint hematoma, thrombovascular disease, thrombocytopenia, or any chronic condition requiring treatment with transfusions.
3. Have a history of unexplained syncope.
4. Have a history within 6 months prior to Screening of major bleeding, trauma, surgical procedure of any type, or vaginal delivery.
5. Have a history within 6 months prior to Screening of peptic ulcer or gastrointestinal bleeding (including hematemesis, melena, or rectal bleeding).
6. Have received any blood product or anticoagulant within 3 months prior to Screening.
7. Have donated blood or blood products within 3 months prior to Screening.
8. Have a history of minor bleeding episodes (eg, epistaxis, bruising or gingival bleeding) within 1 month prior to Screening, or a long-standing history of such bleeding.
9. If female, have a history of excessive or dysfunctional uterine bleeding (unless the subject had a subsequent hysterectomy).
10. Have used any tobacco or nicotine-containing products within 3 months prior to Screening.
11. Have used any systemic prescription or non-prescription drugs (including vitamins, supplements, and herbal products) within 14 days prior to Day 1 (except for permitted contraceptives). NOTE: subjects should be asked specifically about use of aspirin and other non-steroidal anti-inflammatory drugs.
12. If female, be pregnant, breastfeeding, or planning to become pregnant during the study.
13. Have received ciraparantag in any prior clinical study.
14. Have received another investigational drug within 5 half-lives or 30 days, whichever is longer, prior to Day 1.
15. Known allergy to edoxaban, apixaban or rivaroxaban.
16. Have any other condition that, in the opinion of the Investigator, would interfere with a subject's ability to adhere to the protocol, interfere with assessment of the investigational product, or compromise the safety of the subject or the quality of the data.

## **5. STUDY DRUG ADMINISTRATION**

### **5.1. 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 (18 to <50 years vs.  $\geq 50$  to 75 years) within each dose group of each cohort.

## **5.2. Selection of Doses**

### **5.2.1. Anticoagulants**

For each of the anticoagulants (edoxaban, apixaban, or rivaroxaban), the dosing regimens administered in this study ([Table 6](#)) represent a recommended dose for subjects with normal renal function, as per prescribing information.

### **5.2.2. Ciraparantag**

#### **5.2.2.1. Group 1**

For each cohort, the Group 1 target dose of ciraparantag is 180 mg. This dose was selected based on the following considerations:

- Prior clinical studies have evaluated single IV doses of ciraparantag ranging between 3 and 360 mg. In general, ciraparantag exhibited dose-related reversal of anticoagulation, with the most notable effects at doses  $\geq 60$  mg based on manual WBCT ([Table 4](#)).
- The most recent clinical studies (Studies 02-011 and 02-012) provide data for subjects anticoagulated with apixaban or rivaroxaban ([Table 4](#)). Following apixaban administration, reversal of manual WBCT (to  $\leq 110\%$  of baseline within 1 hour post-dose and sustained through 5-6 hours) was observed in 100% of subjects receiving ciraparantag 60 or 120 mg. Following rivaroxaban administration, such reversal was observed in 75%, 67% and 100% of subjects receiving ciraparantag 60, 120 and 180 mg, respectively. Thus, reversal of anticoagulation was achieved in high proportions of subjects with doses of 120-180 mg. To maximize the chances that a single ciraparantag dose can be identified for reversal of all anticoagulants of interest, the high end of this dose range (i.e., 180 mg) was favored.
- In prior clinical studies, ciraparantag was well tolerated across the range of doses that were evaluated (i.e., up to 360 mg). In the completed clinical studies, there were no serious adverse events (SAEs) related to study drug. Adverse events that appeared to be dose-related were sensations of warmth (e.g., hot flashes or flushing) and paresthesia; however, to date these events have been mild and did not lead to study discontinuation.
- Therefore, the data from prior clinical studies indicate that a ciraparantag dose of 180 mg should be well tolerated and has a high likelihood of reversing anticoagulation in a high proportion of subjects, for multiple different anticoagulant medications.

#### **5.2.2.2. Group 2**

If it is determined that a second ciraparantag dose group will be evaluated in a given cohort, that dose for Group 2 will be within the range of 120 to 360 mg. Based on prior clinical studies, ciraparantag doses below 120 mg are not expected to provide high success rates in

reversal of all anticoagulants of interest, and doses up to 360 mg (the highest dose tested to date) were well tolerated with no dose-limiting toxicity.

### **5.3. 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], Section 8.3) 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 (Section 10.2.2).

At the conclusion of each dose group in each cohort (i.e., after study treatments and assessments 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 (Section 5.2.2.2).
- Subjects and study site personnel (except the TAP) will remain blinded to individual subject treatment assignment throughout the study.

#### **5.3.1. Unblinding of Therapy Assignments**

The blind is to be strictly maintained as described in this protocol. However, in the event of a medical emergency for which the treatment assignment needs to be known in order to manage a subject, the study blind may be broken by the Investigator or designee through the IWRS system. Whenever possible, the Investigator should contact the Medical Monitor prior to unblinding a subject, unless the emergent nature of the situation precludes this communication. In the latter situation, the Investigator must notify the Medical Monitor as soon as possible if the blind is broken for any reason. The IWRS will record the date of any unblinding of individual therapy assignments. The Investigator will document the details of the circumstances surrounding the unblinding.

If expedited regulatory reporting is required, the report will identify the individual subject's treatment assignment. When applicable, a copy of the regulatory report will be sent to Investigators, IRBs and Ethics Committees (ECs) in accordance with relevant regulations. Clinical study personnel will not be unblinded to treatment assignment when they are involved with these reporting responsibilities.

### **5.4. Timing of Doses and Dose Administration**

#### **5.4.1. Anticoagulants**

For use in the respective cohorts, the anticoagulant drugs will be administered as specified in Table 8. Each morning dose after Day 1 will be administered at a time of day  $\pm 1$  hour of the time of administration of the morning dose on Day 1. Oral anticoagulant drugs will be

administered under the supervision of clinical site personnel. Additional information regarding dietary guidelines during the study is provided in Section 6.10.1.

The date and time of administration of each dose of anticoagulant will be recorded in the Case Report Form (CRF).

**Table 8: Administration Specifications for Anticoagulant Dosing**

Cohort	Anticoagulant	Administration	
		Amount per dose	Dosing Specifications
1	Edoxaban	60 mg (1 x 60 mg tablet) PO per dose	Administer with 240 mL of water in the morning within 15 minutes after completion of breakfast
2	Apixaban	10 mg (2 x 5 mg tablets) PO per dose	Administer each dose with 240 mL of water. Morning doses will be administered within 15 minutes after completion of breakfast. Evening doses will follow a q 12 hour schedule, with no restrictions relative to food.
3	Rivaroxaban	20 mg (1 x 20 mg tablet) PO per dose	Administer with 240 mL of water in the morning within 15 minutes after completion of breakfast.

#### 5.4.2. Ciraparantag

For subjects who are successfully anticoagulated (as per Section 3.1), a single IV dose of ciraparantag/PBO will be administered starting at the timepoint specified in Table 7 ( $\pm 5$  minutes). Each dose of ciraparantag/PBO will be administered over 10 minutes ( $\pm 1$  minute).

Ciraparantag/PBO will be infused into an indwelling catheter that is not attached to any other IV solution and will not result in dilution of the study drug. The indwelling catheter will be flushed with 5 mL of sterile 0.9% Sodium Chloride Injection, USP before *and* after administration of study drug.

The date and the exact start time and stop time of the ciraparantag/PBO infusion will be recorded in the CRF.

#### 5.5. Duration of Dosing

Subjects will receive doses of anticoagulant for 3 or 4 days. Each randomized subject will receive only a single IV dose of ciraparantag/PBO on Day 3 or Day 4.

#### 5.6. Adherence

All study treatments (i.e., anticoagulant and ciraparantag/PBO) will be administered in the study unit by clinical site personnel.

The ingestion of oral anticoagulant doses will be witnessed and verified by clinical site personnel.

## **6. STUDY PROCEDURES**

### **6.1. Screening**

The Investigator or designee will obtain written informed consent from all subjects prior to initiation of any study-related procedures. Screening procedures will be performed as specified in the Schedule of Events ([Appendix A](#)).

As part of informed consent subjects will receive activity and dietary guidelines appropriate for a study involving an anticoagulant (Section 6.10). Fecal occult blood kits will be given to subjects at Screening (Section 6.6.1).

For subjects who are screen failures and do not receive any doses of anticoagulant or ciraparantag/PBO, demographics and the reason for Screening failure will be recorded. The same is true for those who pass Screening, but for any reason do not subsequently receive any doses of anticoagulant or ciraparantag/PBO.

Subjects who are Screen failures may be rescreened with Sponsor approval.

Per Section 3.1, 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).

### **6.2. Medical History**

A medical history will be taken during the Screening period and updated on Day -1 as specified in the Schedule of Events ([Appendix A](#)). All medical history findings that have been present/active within the 5 years prior to enrollment will be recorded regardless of clinical relevance or presence at study start. Medical history findings that have not been present/active within the 5 years prior to enrollment will be recorded if deemed clinically relevant by the Investigator to the conduct of the study. The medical history should include any history of allergic reactions to drugs.

### **6.3. Physical Examination**

The Investigator or qualified designee will perform physical examinations and measure body weight and height at the time points specified in the Schedule of Events ([Appendix A](#)).

The complete physical examination will consist of the following:

- General appearance, skin, eyes, ears, nose, throat, neck, heart, lungs, abdomen, extremities, vascular, and brief neurological examination (including testing of cranial nerves, sensation strength, deep tendon reflexes, coordination and gait).
- If indicated based on medical history or symptoms, additional examination (eg, breast, external genitalia, etc.) may be performed.

The abbreviated physical examination will consist of the following:

- General appearance, skin, heart, lungs, and abdomen.

Additional symptom-oriented physical examinations may be conducted at any time during the study if clinically indicated. Clinically relevant abnormalities prior to the first dose of

anticoagulant will be recorded as medical history; new or worsened clinically relevant abnormalities after the first dose of anticoagulant will be recorded as AEs.

## 6.4. Vital Signs

Subjects will have vital signs measured at the timepoints specified in the Schedule of Events ([Appendix A](#)). Whenever possible, vital signs will be taken using a standard procedure that maintains consistency in the position of each subject and method of measurement during the study. Subjects should be in a seated or supine position a minimum of 5 minutes prior to obtaining vital signs. Additional vital sign measurements may be performed at any time during the study if clinically indicated.

Clinically relevant abnormalities prior to the first dose of anticoagulant will be recorded as medical history. New or worsened clinically relevant findings after the first dose of anticoagulant will be recorded as AEs.

## 6.5. Electrocardiograms

A 12-lead ECG will be performed at the timepoints specified in the Schedule of Events ([Appendix A](#)). Subjects should be in a supine or semi-reclining position a minimum of 5 minutes prior to obtaining ECGs. Additional ECGs may be performed 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.

Clinically relevant abnormalities prior to the first dose of anticoagulant will be recorded as medical history. New or worsened clinically relevant findings after the first dose of anticoagulant will be recorded as AEs.

## 6.6. Clinical Laboratory Tests

Samples for clinical laboratory testing will be obtained at the timepoints specified in the Schedule of Events ([Appendix A](#)). Additional safety laboratory tests may be performed at any time during the study if clinically indicated.

Laboratory parameters to be evaluated are listed below. Testing will be performed at the local laboratory unless otherwise specified.

- **Hematology:** hematocrit, hemoglobin, platelet count, red blood cells, white blood cells with differential,
- **PT/international normalized ratio (INR) and aPTT.**
- **Fibrinogen activity**
- **Anti-fXa activity** [local or central laboratory]
- **Prothrombotic markers** [central laboratory]: D-dimer, prothrombin fragment 1.2 (PF 1.2), and tissue factor pathway inhibitor (TFPI).

- **Chemistry:** ALT, albumin, AST, bilirubin (total, indirect and direct), blood urea nitrogen, calcium, chloride, carbon dioxide, creatinine, glucose, magnesium, potassium, sodium, and total protein.
- **Triglycerides and Total cholesterol** (fasting will be required for collection of these blood samples)
- **Pregnancy Testing:** serum pregnancy test; (urine pregnancy test also permitted on Day -1).
- **Urinalysis:** dipstick (blood, glucose, ketones, protein) and microscopic examination if dipstick positive.
- **Viral Screen:** hepatitis B surface antigen, HCV antibody test, and HIV antibody test.
- **Drug/Tobacco/Alcohol Screen:** urine drug screen (minimum screening: opiates, amphetamines, methamphetamines, cocaine, cannabinoids, barbiturates, and nicotine/cotinine); breath or saliva test for alcohol.

#### 6.6.1. Fecal Occult Blood Testing

Fecal occult blood kits will be given to subjects at Screening with instructions on their use (also see dietary guidance in Section 6.10.1). The subject should obtain a stool sample within 2 days prior to Day -1 (preferably at a time as close as possible prior to the Day -1 visit) and return the kit 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.

Additional fecal occult blood testing may be performed at any time during the study if clinically indicated.

#### 6.6.2. Whole Blood Clotting Time Assessments

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 9), and also in the Schedule of Events ([Appendix A](#)).

**Table 9: Blood Sample Collection Timepoints for WBCT**

WBCT Method	Day 1 <sup>c</sup>	Day of CIRA/PBO dose (time relative to CIRA/PBO dose) <sup>a</sup>							Day after CIRA/PBO dose	Subsequent days until criteria met
		Pre-dose <sup>d</sup>	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 <sup>b</sup>
Manual	X	X			X				X	X <sup>b</sup>

<sup>a</sup> 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.

<sup>b</sup> WBCT testing to continue daily as needed until protocol threshold criteria are met (Section 3.1).

<sup>c</sup> WBCT testing on Day 1 to occur prior to first dose of anticoagulant.

<sup>d</sup> 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.

Phlebotomy is an important consideration in this study because for each timepoint, blood samples for WBCT will be collected from a “fresh” venipuncture. These samples are *not* to be collected from any indwelling vascular catheter, because fibrin and other blood proteins can adsorb to and deposit on catheter walls, which may alter WBCT results. Further, each venipuncture should be performed at a site separate from recent venipunctures, so that the blood being drawn does not pass through a thrombus or recently damaged blood vessel wall.

WBCT testing will be performed at the study site immediately after blood sample collection. The individual(s) performing WBCT testing at a study site must be blinded to treatment assignment and will not be involved in the assessment or recording of safety data. In addition, whenever possible the same person should perform a given WBCT test method for all timepoints for a given subject.

#### 6.6.2.1. WBCT Testing – Perosphere Technologies’ PoC Coagulometer

The coagulometer is a handheld device that requires only one drop of blood and will provide an automated measurement of WBCT. Additional information about the coagulometer is provided in Section 8.5. Full details for collection of blood and the process for WBCT testing at the study site will be provided in a separate Procedures Manual.

#### 6.6.2.2. WBCT Testing – Manual Method

The manual WBCT testing method involves placing a small quantity of blood in the bottom of reagent-free glass test tubes, which are then placed in a 37°C water bath. The evaluator then gently tilts the tubes at 30 second intervals until blood does not flow freely in the tube and a clot has visibly established. Full details for collection of blood and the process for WBCT testing at the study site will be provided in a separate Procedures Manual.

### 6.7. Pharmacokinetic Assessments

Blood samples for PK testing will be collected at the timepoints specified in the Schedule of Events (Appendix A). Unlike samples for WBCT testing, PK blood samples can be collected from an indwelling vascular catheter. Thus, in this study, the IV catheter that is used for

infusion of ciraparantag/PBO will be maintained whenever possible to allow for subsequent PK sampling through 1.5 hours after the end of ciraparantag/PBO infusion. If for any reason the IV catheter cannot be maintained in this time period, blood samples for PK testing can be taken from the venipunctures performed for WBCT testing. For the timepoints at which only PK blood samples are planned (i.e., 45 minutes and 1.5 hours after the end of ciraparantag/PBO infusion), if the IV catheter cannot be maintained, those particular PK samples can be omitted for that subject, in order to preserve venipuncture sites.

PK blood samples will be sent to a central laboratory and tested for concentrations of ciraparantag, ciraparantag metabolite(s), and the anticoagulant being evaluated in a given cohort.

Details for collection and processing, and shipping of PK samples will be provided in a separate Procedures Manual.

## **6.8. Blood Volume Collected**

Over the course of the study, the total estimated volume of blood to be collected from each subject who completes all scheduled assessments (i.e., safety, WBCT and PK) is approximately 390 mL.

## **6.9. Prior and Concomitant Medications and Therapies**

### **6.9.1. Prior Medications**

The Investigator or qualified designee will review prior medication use with the subject and record the use of any prescription or non-prescription drugs taken by the subject within 14 days before Day 1.

**Note:** Except for permitted contraceptives, systemic medications are prohibited within 14 days prior to Day 1 (Section 4). Subjects should be asked specifically about use of aspirin and other non-steroidal anti-inflammatory drugs that could create a safety issue if used in conjunction with an anticoagulant.

### **6.9.2. Concomitant Medications and Therapies**

Concomitant medication usage for a subject will be recorded for the period starting on Day 1 and continuing throughout the study, including medications administered for management of any AEs.

Concomitant medications to be recorded include prescription and non-prescription drugs, including vaccines, vitamins, herbal supplements, and recreational drugs.

Non-pharmacologic therapies should be recorded if relevant to a reported AE.

### **6.9.3. Prohibited Medications**

Non-study systemic prescription and non-prescription drugs, including vaccines, vitamins, herbal supplements, recreational drugs, and other investigational drugs, are prohibited from Day -1 through discharge (Day 8 or 9), with the following exceptions:

- Contraceptive therapy, other than a combination estrogen/progestin, is permitted.

- **Note:** Combination estrogen/progestin hormonal contraceptives are prohibited because they can increase the risk of thrombotic vascular events.
- Acetaminophen up to 1 g every 24 hours may be administered if needed for management of AEs, at the discretion of the Investigator.

If there is a clinical indication for any prohibited therapy, such as management of an AE/SAE, the Investigator should contact the Medical Monitor to discuss the situation and determine if the subject should be discontinued from study treatment and/or the study. The final decision on any supportive therapy rests with the Investigator and/or the subject's primary physician. However, the decision to continue the subject in the study requires the mutual agreement of the Investigator, the Sponsor, and the subject.

## 6.10. Restrictions

### 6.10.1. Dietary Guidelines

**Prior to Check-in on Day -1:** The following instructions will be provided to subjects at Screening regarding their diet prior to admission to the study unit. The purpose of the required diet is to prevent a false positive reading for the fecal blood test.

- Beginning Day -3 (i.e., two days before Day -1), the following foods and beverages should *not* be consumed: red or rare meat, horseradish, cantaloupe, raw turnips, broccoli, cauliflower, red radishes, parsnips, or alcohol (beer, wine, or liquor).
- The following foods and beverages are suggested for consumption during the two days prior to Day -1: pasta, rice, potatoes, dairy, vegetables, and non-alcoholic beverages (e.g., non-alcoholic sparkling cider, ginger-ale, Sprite, Crystal-light with no caffeine, and whole milk [cow, goat, or soy]).

**During the Study:** Meals and snacks will be provided by the study site during the domiciled period. Among the anticoagulant drugs (edoxaban, apixaban, or rivaroxaban), only rivaroxaban has a requirement to be administered with food as per prescribing information ([Janssen Pharmaceuticals, 2016](#)). Apixaban and edoxaban do not have dosing restrictions with respect to food. However, for consistency across cohorts and to minimize the chance for interruption of the strict schedule of blood draws, the doses of anticoagulants in all cohorts will follow the following schedule:

- All morning doses of anticoagulant (edoxaban, apixaban, or rivaroxaban) will be administered within 15 minutes after completion of breakfast.
- On study days other than the ciraparantag/PBO dosing day, meals after breakfast will follow a standardized schedule for the study unit. For the apixaban cohort, the evening doses of apixaban will be administered according to the q 12 hour schedule, with no restrictions relative to food.
- On the ciraparantag/PBO dosing day following the anticoagulant dose, subjects will fast (except for water *ad libitum*) until completion of the blood draw at 1 hour post-ciraparantag/PBO (an estimated fasting period of no more than 6 hours). Otherwise, meals will follow a standardized schedule for the study unit.

- The calories from fat for each day during the domiciled period will not exceed 30% per day.
- No alcohol may be consumed for the duration of the domiciled period.

#### **6.10.2. Activity Guidelines**

While domiciled, subjects will be encouraged to engage in regular, low level exercise (such as walking laps within the study unit). During this time, subjects will be advised against using manual razors and dental flosses; electric razors and soft toothbrushes will be allowed.

Throughout the study (from Screening through study completion) subjects will be advised against performing any activities that are strenuous or outside of their normal living activities. No tobacco or nicotine products may be used for the duration of the study.

### **6.11. Discontinuation from Treatment or Study**

A subject may choose to discontinue study treatment and/or withdraw from the study at any time. Subjects who become pregnant or develop a condition which contraindicates the use of anticoagulant during the course of the study are to be withdrawn from study treatment. In the absence of a medical contraindication, every effort should be made by the Investigator to encourage subjects who prematurely discontinue treatment to remain in the study as appropriate and, at a minimum, follow the subject for safety data collection.

#### **6.11.1. Discontinuation from Study Drug Treatment**

A subject may be discontinued prematurely from study drug treatment (either anticoagulant or ciraparantag/PBO) for the following reasons:

- AE
- Withdrawal by subject (specify reason in the Case Report Form [CRF])
- Lost to Follow-up
- Pregnancy
- Physician decision (i.e., Investigator decision – specify reason in the CRF)
- Sponsor decision (specify reason in the CRF)
- Other (specify reason in the CRF)

#### **6.11.2. Discontinuation from Study**

A subject may be discontinued prematurely from the study (in its entirety) for the following reasons:

- Insufficient anticoagulation (Section [3.1](#))
- AE
- Withdrawal by subject (specify reason in the CRF)
- Lost to Follow-up

- Death
- Physician decision (i.e., Investigator decision – specify reason in the CRF)
- Sponsor decision (specify reason in the CRF)
- Other (specify reason in the CRF)

### **6.11.3. Data Collection and Follow-up for Withdrawn Subjects**

If a subject is discontinued prematurely from treatment or from the study, the reason for discontinuation will be collected in the CRF.

For subjects who discontinue from the study on Day 3 or Day 4 because of insufficient anticoagulation, subjects should have a physical examination performed and the Investigator should review results of local safety laboratory results for that day. These subjects may be discharged from the study unit later that day provided that WBCT results are  $\leq 120\%$  of BL (based on the coagulometer) and  $\leq 110\%$  of BL (based on manual WBCT), and the Investigator determines that no additional safety monitoring is required. Otherwise, the subject will remain domiciled and on subsequent days will have procedures performed for the follow-up days as specified in the Schedule of Events ([Appendix A](#)) until these criteria are met.

For subjects who discontinue from the study for reasons other than insufficient anticoagulation, withdrawal of consent, lost to Follow-up, or death, a reasonable effort should be made to complete certain study procedures at or near the time of discontinuation, as follows:

- Complete any remaining procedures (not already performed on that day) as specified for the final follow-up day (i.e., Day “FU-5”) in the Schedule of Events ([Appendix A](#)).

Any AEs that are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements.

If a subject is lost to Follow-up, every reasonable effort must be made by the study site personnel to contact the subject and determine the reason for discontinuation/withdrawal.

### **6.11.4. Subject Replacement**

Given the study objectives of characterizing the efficacy and safety of ciraparantag in generally healthy subjects in a tightly controlled setting, additional subjects will be enrolled as described below in order to achieve a full target dataset for each cohort.

For the following situations (i.e., subjects who are not randomized), an additional subject will be enrolled as needed to reach target randomization numbers, and each will receive a new subject identification number:

- Any subject who discontinues prior to completion of anticoagulant dosing
- Any subject who completes anticoagulant dosing, but does not achieve a sufficient level of anticoagulation prior to ciraparantag/PBO dosing ([Section 3.1](#))

For any subject who is randomized, but does not receive ciraparantag/PBO, an additional subject will be enrolled. This subject will receive a new subject identification number and, if eligibility requirements are met, will be randomized.

## **7. ADVERSE EVENTS**

The Investigator is responsible for monitoring of subjects for AEs/SAEs over the assessment period as specified in the Schedule of Events ([Appendix A](#)). Each AE/SAE will be evaluated as described in Section [7.2](#). Treatment of any AE/SAE will be managed by a physician. If any aspect of evaluation or treatment of an AE/SAE is performed by a physician who is not part of the study team (e.g., either at the study site or an external medical facility) the Investigator will ensure that the appropriate party is contacted as promptly as possible to collect the relevant information and documentation to complete the protocol-required assessment of each AE/SAE.

### **7.1. Definitions**

#### **7.1.1. Adverse Event**

As per GCP guidelines, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs will include (1) any new medical condition (sign/symptom/disease) that occurs during the AE reporting period, or (2) any preexisting condition that worsens in severity or frequency or changes in character during the AE reporting period.

#### **7.1.2. Serious Adverse Event**

An SAE is defined as an AE that, in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is a life-threatening AE
  - A life-threatening AE is defined as an AE that in the view of either the Investigator or Sponsor, places the patient or subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization (except hospitalization for elective procedures for a pre-existing condition that has not worsened, admission to a nursing home or rehabilitation facility, or social admissions)
- Results in persistent or significant disability or incapacity (substantial disruption of the ability to conduct normal life functions; it does not include experiences of

relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma [e.g., sprained ankle] that may interfere or prevent everyday life functions but do not constitute a substantial disruption)

- Is a congenital anomaly or birth defect (i.e., an adverse outcome in a child or fetus of a female subject exposed to the study product)
- Important medical events that do not meet any of the above criteria may be considered serious when, based upon appropriate medical judgment, they jeopardize the subject and may require intervention to prevent one of the other outcomes listed in this definition

## 7.2. Adverse Event Evaluation and Classification

All AEs will be assessed by the Investigator. Information to be recorded in the CRF will include a description of the event, date and time of onset, date and time of resolution, and classification of AEs by intensity (severity), causality (relationship to the study drug[s]), seriousness, outcome, and action taken. Subjects with AEs will be followed until the event(s) are either resolved or assessed as stable, or until it is determined that no further information will become available, or the subject is lost to follow-up.

### 7.2.1. Intensity (Severity)

The intensity (severity) of each AE will be assessed using the guidelines below:

- **Mild:** Does not interfere with usual activities, easily tolerated, requires no treatment.
- **Moderate:** Somewhat interferes with usual activities, may cause discomfort, may require treatment.
- **Severe:** Significantly interferes with usual daily activities, may be incapacitating, may require treatment.

Severity of an event is not the same as seriousness. Regardless of severity rating, an AE is considered serious if it meets the criteria for an SAE (Section 7.1.2).

### 7.2.2. Causality

The relationship between the AE and study drugs (i.e., separate assessments for relationship to ciraparantag/PBO and to anticoagulant) will be determined as one of the following:

- Related
- Possibly Related
- Unlikely Related
- Not Related

For analysis purposes, AEs assessed as Related or Possibly Related by the Investigator will be considered as "Related" events, while those assessed as Unlikely Related or Not Related will be considered as "Not related" events.

Causality will be determined based on clinical judgment and the following guidelines:

**Related:**

There is a reasonable possibility that the study product caused or contributed to the AE (e.g., the AE follows a reasonable temporal sequence from the study product administration, and cannot be reasonably explained by other factors such as the disease under study, concurrent diseases, or concomitant medications) or the AE follows a reasonable temporal sequence from the study product administration and represents a known reaction to the product, others products in its class, or is predicted by the known pharmacological properties of the product. Further, the AE resolves with discontinuation of the study product and/or recurs with rechallenge, if applicable.

**Possibly Related:**

There is a reasonable possibility that the study product caused or contributed to the AE (i.e. there is some evidence to suggest a causal relationship, such as the AE occurred within a reasonable time after study product administration). However, the influence of other factors may have contributed to the event (e.g., the disease under study, concurrent diseases, or concomitant medications).

**Unlikely Related:**

The AE's temporal relationship to study product administration makes a causal relationship improbable (e.g., the AE did not occur within a reasonable time after study product administration), and/or other factors (e.g., the disease under study, concurrent diseases, or concomitant medications) provide a plausible explanation.

**Not Related:**

There is no reasonable possibility that the study product caused or contributed to the AE (e.g., the AE does not follow a reasonable temporal sequence from study product administration), or can be reasonably explained by other factors (e.g., the disease under study, concurrent diseases, or concomitant medications).

### **7.2.3. Adverse Event Recording Guidelines**

To improve the quality and consistency of safety data, recording of AEs/SAEs in the CRF should follow these general guidelines:

- Standard English medical terminology should be used rather than colloquial expressions or abbreviations.
- Whenever possible, the AE should be evaluated and reported as a diagnosis rather than as individual signs or symptoms. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded.
- If an AE requires a surgical or diagnostic procedure, the illness leading to the procedure should be recorded as the AE, not the procedure itself.
- For deaths, whenever possible, the underlying or immediate cause of death should be reported as an SAE. Death should be recorded as an outcome of an SAE, not an SAE in itself.

### **7.3. Serious Adverse Event Reporting**

The Investigator and Sponsor are responsible for determining whether an event should be classified as serious. If in the opinion of the Investigator, the AE meets the criteria of an SAE, the SAE is to be reported to the Sponsor or Sponsor's designee. All SAEs, regardless of causality, must be reported. SAEs must be reported from the time the Informed Consent Form (ICF) is signed until 30 days after the last dose of study drug. SAEs considered related to study drug that occur after the specified Follow-up period should also be reported.

For expedited reporting purposes, SAEs assessed as Related or Possibly Related by the Investigator will be considered as "Related" events, while those assessed as Unlikely Related or Not Related will be considered as "Not related" events.

#### **7.3.1. Study Sponsor Notification by Investigator**

Any SAEs, regardless of causality, must be reported to the Sponsor or Sponsor's designee within 24 hours of the Investigator or any site staff's knowledge of the event.

Within 24 hours after receipt of additional relevant information, the Investigator must provide Follow-up information on the SAE along with any additional relevant documentation (e.g., test results, physician narrative, discharge summary, autopsy findings) that will assist in the understanding of the event.

#### **7.3.2. Institutional Review Board/Ethics Committee Notification**

The Investigator must report all SAEs (including Follow-up information) to the IRB/EC in accordance with IRB/EC requirements. Copies of each report and documentation of IRB/EC notification and receipt will be kept in the site's Regulatory Binder.

#### **7.3.3. Serious Adverse Event Follow-up**

The Investigator must respond to all queries received from the Sponsor and must submit Follow-up reports for all SAEs to the Sponsor or Sponsor's designee regarding the subject's subsequent course. All SAEs must be followed until:

- The SAE is Resolved, or
- Stabilized (e.g., in the case of persistent impairment), or
- Subject death, or
- Subject is lost to follow-up

SAE Follow-up information should be recorded in the source documents and SAE/CRF forms as applicable.

### **7.4. Pregnancy Reporting**

Should a female subject or female partner of a male subject become pregnant at any time during the study, the Investigator must notify the Sponsor within 24 hours after learning about the pregnancy. The Sponsor will request Follow-up information regarding the course of the pregnancy and its outcome. Voluntary consent must be obtained from a female subject or female partner of a male subject (and/or legally authorized representative if the subject is

mentally incompetent or physically incapacitated) before any pregnancy-related Follow-up is obtained.

Pregnancy, in and of itself, is not considered an AE, unless there is suspicion that the study product may have interfered with the effectiveness of a contraceptive medication or method. However, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE and will be followed accordingly. A spontaneous abortion is considered to be an SAE.

## 8. CLINICAL TRIAL MATERIALS

### 8.1. Study Drug Supplies

#### 8.1.1. Ciraparantag and Placebo

Supplies of IV ciraparantag and the PBO comparator are described in Table 10.

**Table 10: Identity of Investigational Product**

Study Drug	Formulation
Ciraparantag for IV injection (supplied by the sponsor)	Each single-use clear vial contains 30.5 mL of sterile, isotonic, pH neutral solution for injection containing 6 mg/mL ciraparantag (10 mg/mL ciraparantag acetate) + 6.8 mg/mL sodium chloride.
Placebo for IV injection (supplied by the study site)	Sterile 0.9% Sodium Chloride Injection, USP.

#### 8.1.2. Anticoagulants

All anticoagulant drugs will be supplied by the sponsor. For use in the respective cohorts, the anticoagulant drugs will be provided as follows:

- Savaysa® (edoxaban; Daiichi Sankyo, Inc.): 60 mg tablets for oral administration
- Eliquis® (apixaban; Bristol-Myers Squibb): 5 mg tablets for oral administration
- Xarelto® (rivaroxaban; Janssen Pharmaceuticals, Inc): 20 mg tablets for oral administration

### 8.2. Packaging and Labeling

#### 8.2.1. Ciraparantag

Vials will be labeled for clinical study use with identifying information such as the lot number, storage conditions, and other details as appropriate.

### **8.2.2. Placebo**

The PBO in this study is sterile 0.9% Sodium Chloride Injection, USP, which will be provided by the study site in amounts needed to match the administered volume of ciraparantag at any given dose level.

### **8.2.3. Anticoagulants**

Each of the commercially available anticoagulant drugs (edoxaban, apixaban, or rivaroxaban) will be provided by the Sponsor for the respective cohort.

## **8.3. Storage and Accountability**

Study drugs provided to participating clinical sites will be stored, dispensed, and recorded in accordance with this protocol and the Pharmacy Manual. Only subjects enrolled in the study may receive study drug.

### **8.3.1. Storage**

Ciraparantag will be stored refrigerated at 2 to 8°C (36 to 46°F) and shipped on cold packs to the clinical test site. Temperature will be monitored during shipping for excursions. After arrival at the clinical study site, it will be refrigerated at 2 to 8°C (36 to 46°F) until prior to administration.

PBO (sterile 0.9% Sodium Chloride Injection, USP) will be provided by the study site and stored at room temperature prior to administration.

Anticoagulant drugs should be stored according to their prescribing information (i.e., product labels).

Drug supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. Refer to the Pharmacy Manual for additional guidance on study drug storage.

### **8.3.2. Study Drug Accountability**

The Investigator or his/her designee will maintain accurate records of the receipt of all study drugs. In addition, accurate records will be kept regarding when and how much of each study drug is dispensed, used and unused by each study subject. Study center personnel should not dispose of any used or unused study drug until drug accountability is performed by the Sponsor or its designee. At the conclusion of the study, any unused study drug will be returned to the Sponsor or destroyed by the site pursuant to written authorization by the Sponsor and applicable federal and state regulations.

## **8.4. Preparation of Study Drug**

The study drugs must be prepared by qualified individuals, assigned by the Investigator.

The anticoagulant drugs will be administered in open-label fashion. Anticoagulant drug supplies can be handled by members of the study team who are qualified to store and dispense study drug.

An unblinded TAP will prepare the IV ciraparantag/PBO for each subject. The TAP must not be involved in the enrollment of subjects or in the performance or recording of any safety or efficacy assessments (including performance of any WBCT testing). Qualifications of the TAP and detailed instructions for the storage, handling, and preparation of study drugs will be provided in the Pharmacy Manual.

## **8.5. Point-of-Care Coagulometer**

The coagulometers to be used in this study are handheld devices supplied by Perosphere Technologies, Inc. that will provide an automated measurement of WBCT (Section 6.6.2). Each device uses single-use glass cuvettes onto which a small drop of blood is placed before insertion into the device. WBCT (based on fibrin clot formation) is measured using an infrared light beam; results are displayed on the device.

Instructions for use and maintenance of coagulometers are provided in a separate Procedures Manual. Study coagulometers will be returned to the Sponsor at the completion of the study. Specific instructions regarding return of coagulometers will be provided separately.

## **9. STATISTICAL PLAN**

### **9.1. Analysis Populations**

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

The Safety Population will include all randomized 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.

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

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.

## **9.2. Study Endpoints**

### **9.2.1. Efficacy Endpoints**

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

#### **9.2.1.1. Primary Efficacy Endpoint**

The primary efficacy endpoint is achieving a WBCT  $\leq 120\%$  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.

#### **9.2.1.2. Secondary Efficacy Endpoints**

The secondary efficacy endpoints are as follows:

1. Achieving WBCT  $\leq 115\%$  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 WBCT  $\leq 110\%$  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 WBCT  $\leq 120\%$  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  $\leq 115\%$  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 WBCT  $\leq 110\%$  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  $\leq 120\%$  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  $\leq 115\%$  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  $\leq 110\%$  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.

#### **9.2.1.3. Tertiary Efficacy Endpoints**

The tertiary efficacy endpoints are as follows:

- Achieving a WBCT  $\leq 120\%$  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).
- Achieving a WBCT  $\leq 115\%$  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).
- Achieving a WBCT  $\leq 110\%$  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).
- Achieving a WBCT  $\leq 120\%$ ,  $\leq 115\%$ , or  $\leq 110\%$  of BL at 1 hour after administration of ciraparantag/PBO by the manual method.
- 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).
- Change from Day 3/Day 4 pre-ciraparantag/PBO 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).

#### **9.2.2. Safety Endpoints**

- Treatment-emergent AEs (TEAEs)
- Treatment-emergent SAEs
- 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.

#### **9.2.3. Pharmacokinetic Parameters**

Individual subject plasma concentrations of ciraparantag and its primary metabolite (BAP) and each anticoagulant (edoxaban, apixaban, or rivaroxaban) will be listed and summarized using descriptive statistics (N, arithmetic mean, standard deviation, coefficient of variation, geometric mean, and geometric coefficient of variation) for each time point. The PK parameters ([Table 11](#)) will be computed using non-compartmental analysis using appropriate software and summarized using descriptive statistics (N, arithmetic mean, standard deviation, coefficient of variation, minimum, median, maximum, geometric mean, and geometric coefficient of variation). The relationships between PK parameters and dose will be evaluated and summarized.

**Table 11: PK Parameters**

Parameter	Units	Description	Ciraparantag/ BAP	Anticoagulant
$C_{\max}$	ng/mL	Maximum concentration in sampled matrix, obtained directly from observed concentration vs time data	X	X
$C_{24}$	ng/mL	Observed quantifiable analyte concentration in the sampled matrix at 24-hour time point		X
$t_{\max}$	H	Time of $C_{\max}$ , obtained directly from the observed concentration vs time data	X	X
$AUC_{(0-\text{last})}$	ng·h/mL	Area under the concentration-time curve, from time zero to the last quantifiable concentration ( $C_{\text{last}}$ )	X	
$AUC_{(0-\text{inf})}$	ng·h/mL	Area under the concentration-time curve in sampled matrix from time zero (predose) extrapolated to infinite time by addition of the last quantifiable concentration divided by the elimination rate constant: $AUC_{(0-\text{last})} + C_{\text{last}}/\lambda_z$	X	
$AUC_{(0-24)}$	ng·h/mL	Area under the concentration-time curve in sampled matrix over a 24-hour dosing interval		X
$AUC_{(0-12)}$	ng·h/mL	Area under the concentration-time curve in sampled matrix over a 12-hour dosing interval		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	
$MR_{C_{\max}}$		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	

## **9.3. Statistical Methods**

### **9.3.1. General Considerations**

A detailed statistical analysis plan will be developed separately and finalized prior to randomization of the first subject. Deviations from the protocol-planned analyses will be noted.

The statistical analysis of the data obtained from this study will be performed using SAS<sup>®</sup> Version 9.4 or higher. All statistical tests will be performed at the 0.05 (two-sided) significance level, unless otherwise noted.

The data collected in this study will be documented using summary tables and subject data listings. Continuous variables will be summarized using descriptive statistics, specifically the number of observations, mean, median, standard deviation, minimum and maximum. PK parameters will be summarized using these same statistics, plus the coefficient of variation, the geometric mean, and the geometric coefficient of variation. Categorical variables will be summarized by frequencies and percentages. 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 placebo group including all subjects randomized to placebo. Each active dose will be compared against placebo.

Baseline characteristics will be summarized using descriptive statistics or frequencies and percentages, as appropriate. No statistical hypothesis tests will be performed on these characteristics.

### **9.3.2. Efficacy Analyses**

#### **9.3.2.1. Primary Efficacy Endpoint Analyses**

The primary efficacy endpoint is achieving WBCT  $\leq 120\%$  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 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:

$$H_0: \pi_1 = \pi_2$$

and

$$H_1: \pi_1 \neq \pi_2,$$

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 the

Boschloo's test ([Boschloo, 1970](#)). A 95% CI for the difference in percentages will be constructed by the Miettinen and Nurminen method ([Newcombe, 1998](#)).

In addition, the Cochran-Mantel-Haenszel Test, with stratification by age group, will be used to compare each active dose with placebo as a sensitivity analysis.

#### **9.3.2.2. Secondary Efficacy Endpoint Analyses**

The secondary efficacy endpoints are as stated in Section [9.2.1.2](#). These endpoints will be analyzed in the same manner as the primary efficacy endpoint.

#### **9.3.2.3. Tertiary Efficacy Endpoint Analyses**

The tertiary efficacy endpoints are as stated in Section [9.2.1.3](#). 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  $\leq 120\%$ ,  $\leq 115\%$  or  $\leq 110\%$  of BL at each of the planned post-BL WBCT assessment timepoints by coagulometer or the manual method will be analyzed in the same manner as the primary efficacy endpoint.

The fifth and the sixth sets of tertiary efficacy endpoints will be summarized by cohort and treatment using descriptive statistics. In addition, the differences between ciraparantag doses and PBO will be evaluated using an Analysis of Covariance (ANCOVA) model. The ANCOVA model will include treatment as fixed effects, and baseline value and the stratification factor as covariates. A summary of the results of the ANCOVA, and pairwise differences in means and the corresponding 95% CI will be presented.

#### **9.3.2.4. Correlation 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. In addition, the agreement between these two methods with respect to the efficacy endpoints at 1 hour after administration of ciraparantag/PBO will be assessed.

### **9.3.3. Safety Analyses**

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

#### **9.3.3.1. Adverse Events**

All AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or later. TEAEs will be defined as those AEs that begin or worsen on or after the start of double-blind study drug administration (ciraparantag or PBO).

The number and percentage of subjects with at least one TEAE, at least one serious TEAE, at least one study drug related TEAE, and at least one TEAE leading to study withdrawal 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.

The numbers and percentages of subjects having a non-treatment-emergent AE and a non-treatment-emergent SAE in each System Organ Class (SOC) and having each individual type of non-treatment-emergent AE and SAE (Preferred Term) will be presented by cohort and treatment group.

The number and percentage of subjects having a TEAE in each System Organ Class (SOC) and having each individual type of TEAE (Preferred Term) will be presented by cohort and treatment group. TEAEs will also be summarized at the event level by SOC/Preferred Term and severity and by SOC/Preferred Term and relationship.

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

In addition, the number and percentage of subjects having an AE in each SOC and having each individual type of AE (Preferred Term) will be presented for the Anticoagulant Population prior to the treatment of ciraparantag/PBO.

#### **9.3.3.2. Vital Signs**

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 also will be summarized.

#### **9.3.4. Laboratory Tests**

All quantitative laboratory test results, including serum chemistry, hematology, prothrombotic markers, and urinalysis, will be summarized by cohort, treatment, test and time point using descriptive statistics for subjects in the Safety Population. Changes from BL to post-BL timepoints also will be summarized.

#### **9.3.5. Definition of Baseline Measurements**

Unless otherwise specified, BL values will be defined as the last assessment prior to administration of ciraparantag/PBO. However, BL WBCT will be defined as the Day 1 value (obtained prior to the first dose of anticoagulant).

#### **9.3.6. Handling of Missing Data**

For the binary efficacy endpoints, missing outcome will be imputed as non-responder.

#### **9.3.7. Sensitivity Analyses**

For the binary efficacy endpoints, the Cochran-Mantel-Haenszel Test, with stratification by age group, will be used to compare each active dose with placebo as a sensitivity analysis.

#### **9.3.8. Adjustment for Multiple Comparisons**

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 12. 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 12: Hypothesis Testing Paradigm of The Secondary Efficacy Endpoints For Each Dose Group Within Each Cohort**

<b>≤120% Reversal Target Cluster</b>	<b>≤115% Reversal Target Cluster</b>	<b>≤110% Reversal Target Cluster</b>
Achieved within 30 minutes 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

### 9.3.9. 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 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.

## 10. QUALITY ASSURANCE

To assure quality and consistent study data, procedures will only be carried out by the Principal Investigator or trained staff under the direction of the Principal Investigator. Study related procedures will be exercised in accordance with written materials (e.g., Procedures

Manual, Laboratory Manual, Pharmacy [study drug preparation] Manual, and CRF completion guidelines).

## **10.1. Data Handling, Record Keeping, and Direct Access to Data**

The Investigator is responsible for maintaining the following:

- Site Staff Responsibility Log showing the signatures and handwritten initials of authorized study staff and responsibilities.
- A Screening Log with all subjects who were screened for the study.
- A Subject Identification Log with subject identification numbers, names, and dates of birth to positively identify each subject enrolled in the study.
- Accurate, complete, and up-to-date source documentation related to the study, including any hospital records, films, tracings, computer or electronic source data or documents. Source data includes all information, original records of clinical findings, or other activities in a clinical study necessary for the reconstruction and evaluation of the study and are contained in source documents.
- Accurate, complete, and up-to-date CRFs.

### **10.1.1. Case Report Forms**

All CRFs will be completed according to CRF completion guidelines. The Principal Investigator must electronically sign and date a declaration on the CRF attesting to his/her responsibility for the quality of all data recorded and that the data represent a complete and accurate record of each subject's participation in the study. An electronic copy of the completed CRF will then be sent to the Investigator to be retained for their records.

## **10.2. Monitoring, Auditing, and Inspecting**

### **10.2.1. Study Monitoring**

Study Monitors representing the Sponsor will visit study sites during the study. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the Study Monitor, or other compliance or quality assurance reviewer, is given access to all study-related documents and study related facilities (e.g., pharmacy, diagnostic laboratory, medical records, etc.), and has adequate space to conduct the monitoring visit.

The Study Monitor will review ICFs and CRFs and compare them with source documents to verify adherence to the protocol, and to ensure complete, accurate, consistent, and timely collection of data. The Investigator will be asked to provide any missing information or to clarify any discrepancies found by the Study Monitor.

In addition to source document verification of CRFs and ICFs, the Study Monitor will review the Clinical Site Regulatory Binder that is to be maintained by the Principal Investigator.

### **10.2.2. Data Review Team**

At the conclusion of each dose group in each cohort (i.e., after study treatments and assessment are completed for subjects in that group), available efficacy data (i.e., WBCT results) and safety data for that group will be analyzed by a data review team, which will consist of the Principal Investigator (or a co-investigator designee) from each study site for that cohort, and Sponsor team members including but not limited to the Medical Monitor and the study statistician. As discussed in Section 5.3, Investigators will receive results that are unblinded at group level (not individual subject level) as part of these data reviews.

Specifically following analyses of Group 1 data for a given cohort, the data review team will determine:

1. whether or not a second ciraparantag dose will be evaluated for that cohort
2. if so, the ciraparantag dose to be evaluated in Group 2 for that cohort (within the dose range described in Section 5.2.2).

A summary and the conclusions of each data review team meeting will be documented with minutes. The data review team conclusions will be forwarded in writing to the participating study sites before proceeding to the next group in a given cohort. Study sites may forward this information to their respective IRB/EC in accordance with local policies.

### **10.2.3. Criteria for Stopping Enrollment**

Enrollment will be stopped for a cohort if any of the following occur:

- Any subject experiences bleeding that is reported as severe or requires intervention with medications, blood products or a non-bedside procedure
- Any subject experiences a serious AE (SAE)
- Two or more subjects develop either of the following laboratory abnormalities:
  - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $>3$  x the upper limit of normal
  - Total bilirubin  $>2$  x the upper limit of normal

If enrollment in a cohort is stopped based on findings as noted above (or any other safety concern identified by the Sponsor), subjects who are in the study at that time should discontinue study treatment (if still ongoing), but should complete other required study procedures including safety follow-up. The Sponsor will review all available safety data. If further dosing in that cohort is proposed, the findings will be presented to the Investigators and US FDA regulators; all must agree on the proposed dosing regimen if further dosing is to proceed.

### **10.2.4. Auditing and Inspecting**

The study may be evaluated by representatives of the US FDA, and where applicable, other government agencies, national health agencies, and national health authorities, who also will be allowed access to study documents. The Investigator should promptly notify the Sponsor

when any inspections are scheduled, as well as providing the results of any unscheduled investigations performed by any regulatory authorities.

The Investigator will permit study related monitoring, audits, and inspections by the IRB/EC, the Sponsor, government regulatory bodies, and compliance and quality assurance groups of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.). All authorized personnel, including health authority inspector(s), Sponsor and designees, Study/Medical Monitor(s), and auditor(s) will be given direct access to source data and documentation (e.g., medical records, laboratory results, etc.) for source data verification, provided that subject confidentiality is maintained in accordance with local requirements.

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance and quality assurance offices.

#### **10.2.5. Records Retention**

The Principal Investigator shall retain all study related documentation, including source data, source documents, CRFs, protocol and amendments, regulatory documentation and correspondence, ICFs, subject identification lists, and correspondence.

It is the Investigator's responsibility to retain essential study documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country, or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the Sponsor. In such a case, it is the responsibility of the Sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

If the Investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for record retention. Written notice of transfer of documentation shall be provided to the Sponsor.

## **11. ETHICAL CONSIDERATIONS**

### **11.1. Ethics**

This study will be conducted according to the Declaration of Helsinki, international standards of GCP, US FDA regulations, International Council for Harmonisation guidelines, and other applicable government regulations, and institutional research policies and procedures. Perosphere Pharmaceuticals, Inc. will also continue to support the principles of the Declaration of Helsinki.

### **11.2. Review**

This protocol and any amendments will be submitted to an appropriate IRB/EC, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB/EC concerning the conduct of the study will be made in writing to the Investigator, and

a copy of this decision will be provided to the Sponsor before commencement of this study. The Investigator should provide a list of IRB/EC members and their affiliates to the Sponsor. The IRB/EC must also approve all protocol amendments prior to implementation, as well as changes in study status (i.e., completion or termination of a study).

### **11.3. Investigator Responsibilities**

#### **11.3.1. General Responsibilities**

All Investigators are responsible for performing the study in accordance with the protocol and the above guidelines and regulations, and for collecting, documenting, and reporting the data accurately.

All Investigators must be familiar with the background and requirements of the study and with the properties of the study products as described in the current version of the Investigator's Brochure or Package Insert.

The Principal Investigator is responsible for distributing study information and documentation to all appropriate staff members prior to and during the course of the study as updated information becomes available.

The Principal Investigator is responsible for ensuring the privacy, health, and welfare of the subjects during and after the clinical study and must ensure that fully functional resuscitation equipment and personnel trained in its use are immediately available in the event of an emergency.

The Principal Investigator has the overall responsibility for the conduct and administration of the study at the clinical site and for contacts with the Sponsor, the IRB/EC, and local authorities.

#### **11.3.2. Protocol Compliance**

Except for a change intended to eliminate an immediate hazard to a study subject, the protocol shall be conducted as described without any changes or deviations. Any change must be reported immediately to the Sponsor and to the IRB/EC and/or regulatory authority as required by guidelines or regulation. Sites that fail to comply may be terminated.

#### **11.3.3. Protocol Amendments**

Protocol amendments will be prepared and approved by the Sponsor or designee and sent to the appropriate IRB/EC for review and approval. For each amendment to the protocol, the Investigator Protocol Agreement page will be signed by the Principal Investigator. Documentation of IRB/EC approval must be forwarded to the Sponsor or designee.

If an amendment significantly alters the study design, increases potential risk to the subject, or otherwise affects statements in the ICF, the ICF must be revised accordingly and submitted to the IRB/EC for review and approval. The approved ICF must be used to obtain informed consent from new subjects prior to registration (unless there is a significant safety risk) and must be used to re-obtain informed consent from subjects already registered if they are affected by the amendment.

#### **11.3.4. Subject Informed Consent**

Each subject will be provided a written ICF, describing this study and providing sufficient information to make an informed decision about participation in this study.

A copy of the proposed ICF must be submitted to the Sponsor and/or designee for review prior to submission to the reviewing IRB/EC. The ICF must be approved by the IRB/EC and must contain all elements required by federal, state, local, and institutional regulations or requirements. Institutions in the US must be in compliance with Health Insurance Portability and Accountability Act of 1996 with regard to obtaining authorizations for use and disclosure of Protected Health Information. In countries outside the US, local privacy regulations must be followed.

The study, including its goals, methods, expected benefits, and potential hazards will be completely explained to each prospective study subject. It will also be explained to subjects that they are free to refuse entry or to withdraw from the study at any time without prejudice to future treatment. Voluntary informed consent must be obtained from each eligible subject (and/or legally authorized representative if the subject is mentally incompetent or physically incapacitated) before any protocol-defined procedures are performed.

The subject's willingness to participate in this study will be documented on the IRB/EC approved ICF which must be signed and dated by the subject or legally acceptable surrogate, and the physician Investigator (Principal or sub-Investigator). The Investigator will keep the original ICF and a copy will be given to the subject. The process for obtaining informed consent should also be noted in the subject's source documentation.

#### **11.3.5. Confidentiality Regarding Study Subjects**

The Investigator must assure that the privacy of the subjects, including their identity and all personal medical information, will be maintained at all times. In the CRFs and other documents (e.g., laboratory reports, etc.) submitted to the Sponsor, subjects will not be identified by name, but by an identification code (e.g., subject identification numbers).

Personal medical information may be reviewed for the purpose of verifying data recorded in the CRF by the Study/Medical Monitor, Sponsor or designee, or regulatory authorities. Personal medical information will always be treated as confidential.

#### **11.3.6. Laboratory Accreditation**

Analyses of blood tests will be performed by the local site laboratory as appropriate. The laboratory facilities used for analysis of clinical laboratory samples obtained under this protocol will have adequate licensure and accreditation.

#### **11.3.7. Discontinuation of Study**

The Sponsor reserves the right to discontinue or terminate the study for any reason at any time. In addition, the study may be stopped at any time if, in the opinion of the Sponsor or Medical Monitor, the medical safety of subjects is being compromised. In the event of a discontinuation or termination, all investigative sites will immediately be notified, and in turn, sites must immediately notify their subjects and respective IRB/EC.

## **12. PUBLICATION POLICY**

The publication policy, including authorship, is in accordance with that described in the Clinical Trial Agreement.

### 13. REFERENCE LIST

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## APPENDIX A SCHEDULE OF EVENTS

Table 13: Schedule of Events

Study Procedure	Screening Period <sup>a</sup>	Domiciled Period							
		Day -1 <sup>b</sup>	Anticoagulant Dosing Days				Post-CIRA/PBO Follow-up Days		
			Day 1	Day 2	Day 3 <sup>u</sup>	Coagulation Assessment Visit <sup>v</sup> (Day 3 and/or 4)	FU-1	FU-2, FU-3, FU-4	FU-5 <sup>c</sup>
						Pre-Randomization	Post-Randomization		
Informed consent	X								
Medical/medication history	X	X							
Physical examination <sup>d,e</sup>	X	X						X	X
Height	X								
Weight	X	X							
Vital signs <sup>d,f</sup>	X	X	X	X	X	X	X	X	X
12-lead ECG <sup>d,g</sup>	X	X							
Blood Chemistry/Urinalysis <sup>d</sup>	X	X				X <sup>h</sup>		X	X
Triglycerides & Cholesterol <sup>d,i</sup>	X	X							
Hematology <sup>d</sup>	X	X				X <sup>h</sup>		X	X
PT/INR & aPTT	X	X				X <sup>h</sup>		X	X
Fibrinogen	X	X				X <sup>h</sup>		X	X
Anti-fXa activity			X <sup>t</sup>			X <sup>h</sup>		X	X
Prothrombotic markers <sup>j</sup>		X				X	X	X	X
Pregnancy test <sup>k</sup>	X	X							X
Viral hepatitis/HIV serology	X								
Drug/tobacco/alcohol screen <sup>l</sup>	X	X							
Fecal occult blood <sup>m</sup>		X							
Randomization							X		
Anticoagulant administration <sup>n</sup>			X	X	X	X			
Ciraparantag/PBO administration <sup>o</sup>							X		
WBCT measurements <sup>d,p</sup>			X			X	X	X <sup>q</sup>	X <sup>q</sup>
PK sample collections <sup>d,r</sup>						X	X	X	
Adverse event monitoring <sup>s</sup>	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X
Discharge from study unit <sup>c</sup>									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 ( $\pm 10$  minutes), 4 hours ( $\pm 10$  minutes), and 8 hours ( $\pm 10$  minutes) after the end of ciraparantag/PBO infusion; Day FU-1 at 24 hours ( $\pm 1$  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 ( $\pm 10$  minutes) after anticoagulant, and for Cohorts 2 and 3 these blood samples will be collected at 3.75 hours ( $\pm 10$  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 ( $\pm 10$  minutes) after anticoagulant for Cohort 1 and 3.75 hours ( $\pm 10$  minutes) after anticoagulant for Cohorts 2 and 3, ciraparantag/PBO dosing day at 6 hours ( $\pm 10$  minutes) after the end of ciraparantag/PBO infusion, Day FU-1 at 24 hours ( $\pm 30$  minutes) after the end of ciraparantag/PBO infusion, and on Days FU-2 through FU-5 (blood draws at a time of day  $\pm 2$  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  $\pm 1$  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 ( $\pm 5$  minutes) after the anticoagulant dose for Cohort 1 and 4 hours ( $\pm 5$  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 ( $\pm 10$  minutes) after anticoagulant for Cohort 1\* and 3.75 hours ( $\pm 10$  minutes) after anticoagulant for Cohorts 2 and 3\*. For sufficiently anticoagulated subjects, blood samples for WBCT will be collected at 15 minutes ( $\pm 5$  minutes), 30 minutes ( $\pm 5$  minutes), 1 hour ( $\pm 5$  minutes)\*, 3 hours ( $\pm 10$  minutes), 6 hours ( $\pm 10$  minutes) and 8 hours ( $\pm 10$  minutes) after the end of ciraparantag/PBO infusion; Day FU-1 at 24 hours ( $\pm 30$  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 ( $\pm 5$  minutes) and 1.5 hours ( $\pm 5$  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.