Clinical Trial Protocol: PER977-02-011

Study Title: Phase 2 Placebo-Controlled, Single-Site, Single-Blind Study of Apixaban Reversal by Ciraparantag as Measured by WBCT

Document Date: Version 4: 02May2019

NCT: NCT03288454

Clinical Trial Protocol: PER977-02-011

Study Title:	Phase 2 Placebo-Controlled, Single-Site, Single-Blind Study of Apixaban Reversal by Ciraparantag as Measured by WBCT
Study Number:	PER977-02-011
Study Phase:	2
Product Name:	Ciraparantag
IND Number:	117,224
Indication:	Reversal of edoxaban, rivaroxaban, apixaban, dabigatran, or enoxaparin-induced anticoagulation when medically indicated.
Investigators:	[redacted]
Sponsor:	Perosphere Inc., a wholly-owned subsidiary of AMAG Pharmaceutical
Sponsor Contact:	[redacted]
Medical Monitor:	[redacted]
Protocol Version:	4

	Date
Version 4:	02May2019

Summary of Main Changes Made in Version 3.0 to Generate Version 4.0

Item	Revision in Version 4.0
Section 6.10: Adverse Events Assessments	Add: "If in the opinion of the Investigator or the sponsor, an AE meets the criteria of an SAE it is to be reported. SAEs occurring up to 30 calendar days post treatment should be reported. Any AEs and SAEs that occur after the specified reporting period should also be reported if in the opinion of the investigator, there is a reasonable possibility for a causal association with the study product."
Section 6.10.5: AE Severity	Add: "Severity should be distinguished from seriousness. Severity is a measure of intensity whereas seriousness is classified by the criteria based on the regulatory definitions. An AE of severe intensity need not necessarily be classified as serious."
Section 6.10.10.1: Initial Reports	Change from: [redacted] Cell phone: [redacted] Facsimile: [redacted] Email: [redacted] To: AMAG Pharmacovigilance Email: [redacted] Fax: [redacted]
Section 6.10.10.2: Follow up Reports	Add: The Investigator will follow all SAEs until the SAE is: • Resolved, or • Stabilized (e.g., in the case of persistent impairment), or • Returned to baseline, if a Baseline value is available, or • Otherwise justified by the investigator in agreement with the Sponsor and • All relevant data are received

Item	Revision in Version 4.0
Section 6.10.12: Pregnancy	Change from: Any pregnancy diagnosed during the study, or that the Investigator becomes aware of within 30 days after stopping study medication, must be reported by the Investigator to the Sponsor using the [redacted] Initial Pregnancy Report Form. To: Any pregnancy diagnosed during the study, or that the Investigator becomes aware of within 30 days after stopping study medication, must be reported by the Investigator to the Sponsor using the [redacted] Initial Pregnancy Report Form within 24 hours of awareness.
Section 10.1.1: Sponsor	Change from: Perosphere Inc. [redacted] To: Perosphere Inc., a wholly-owned subsidiary of AMAG Pharmaceutical [redacted] **Perosphere Clinical Study Leader** Change From: [redacted] To: [redacted]
Section 10.1.2: Clinical Research Organization Project Manager Principal Investigator Sub-Investigator	Change from: **Clinical Project Manager** [redacted] **Principal Investigator** [redacted]

Item	Revision in Version 4.0
	Sub-Investigator [redacted] To: **Clinical Project Manager** [redacted] **Principal Investigator** [redacted] **Sub-Investigator** [redacted]
Appendix 1 Sponsor and Investigator's Signature	Change from: [redacted] To: [redacted] Investigator's Signature Change from: [redacted] Principal Investigator [redacted] To: [redacted] Principal Investigator [redacted]

Item	Revision in Version 4.0
Page 1, Investigator, Sponsor, Sponsor Contact, Medical Monitor, Protocol Version Number	Change from: Investigators: [redacted] Sponsor: Perosphere, Inc Sponsor Contact: [redacted] Medical Monitor: [redacted] Protocol Version: 3 To: Investigators: [redacted] Sponsor: Perosphere Inc., a wholly owned subsidiary of AMAG Pharmaceutical Sponsor Contact: [redacted] Medical Monitor: [redacted] Protocol Version: 4 Date of final document

Summary of Main Changes Made in Version 2.0 to Generate Version 3.0

Item	Revision in Version 3.0
Inclusion criteria #6 in Synopsis on page 15 and section 4.3 on page 46	To modify Pregnancy Screen procedures. Changed from "Female subjects must have a negative urine pregnancy test at screening AND: be surgically sterile (with documentation of hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal ligation/tubal occlusion) OR post-menopausal (no menstruation for a minimum of 12 months and confirmed by follicle stimulating hormone [FSH] of ≥ 40 mIU/ml) OR, if of child-bearing potential, must be using an acceptable method of contraception such as an IUD, implant or contraceptive injection, or two forms of the following (e.g., diaphragm, cervical cap, patch or vaginal hormonal contraceptive, condom, spermicide, or sponge) for the last three months, OR in a monogamous relation with a male partner who has undergone a documented vasectomy a minimum of 6 months prior to study commencement. All females must agree to continue to use their method of birth control for the duration of the study and for a minimum of one complete menstrual cycle or 28 days following discharge from the study" to "Female subjects must have negative pregnancy tests at screening and

<table>
<tr><th>Item</th><th>Revision in Version 3.0</th></tr>
<tr><td></td><td>check-in AND: be surgically sterile at least 6 months prior to the first dose (with documentation of hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal ligation/tubal occlusion); OR post-menopausal (no menstruation for a minimum of 12 months and confirmed by follicle stimulating hormone [FSH] of ≥ 40 mIU/ml and serum estradiol < 30 pg/ml at screening and check-in); OR if of child-bearing potential, must be using an acceptable method of contraception such as an IUD, implant or contraceptive injection, or two forms of the following (e.g., diaphragm, cervical cap, patch or vaginal hormonal contraceptive, condom, spermicide, or sponge) for the last three months. All females must agree to continue to use their method of birth control for the duration of the study and for a minimum of one complete menstrual cycle from the study".</td></tr>
<tr><td>Study Procedure on page 21 and 22</td><td>To modify the schedule for pregnancy tests in the Study Procedure Table

1. Added a row for serum pregnancy test
2. Added serum pregnancy test at check-in on Day -1
3. Removed urine pregnancy test on Day -1

Changed table from

<table>
<tr><th rowspan="2">Day→
Procedure ↓</th><th>Screening[a]</th><th colspan="6">Treatment Period</th><th>Follow-up</th></tr>
<tr><th>Day -36 to -1</th><th>Day -1 Check-in</th><th>Day 1</th><th>Day 2</th><th>Day 3</th><th>Day 4</th><th>Day 5</th><th>Day 7-10</th></tr>
<tr><td>Urine pregnancy</td><td>X</td><td>X</td><td></td><td></td><td></td><td></td><td>X</td><td></td></tr>
</table>
To

<table>
<tr><th rowspan="2">Day→
Procedure ↓</th><th>Screening[a]</th><th colspan="6">Treatment Period</th><th>Follow-up</th></tr>
<tr><th>Day -36 to -1</th><th>Day -1 Check-in</th><th>Day 1</th><th>Day 2</th><th>Day 3</th><th>Day 4</th><th>Day 5</th><th>Day 7-10</th></tr>
<tr><td>Urine pregnancy</td><td>X</td><td></td><td></td><td></td><td></td><td></td><td>X</td><td></td></tr>
<tr><td>Serum pregnancy test[i]</td><td></td><td>X</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table>
Changed from "i. Urine pregnancy testing will be performed for all women at screening, at check-in on Day -1, and at discharge.

To "i. Urine pregnancy testing will be performed for all women at screening and at discharge. Serum pregnancy test will be performed at check-in on Day -1."</td></tr>
</table>

<table>
<tr><th>Item</th><th>Revision in Version 3.0</th></tr>
<tr><td>Section 6.2 Medical History on page 53</td><td>To include that subjects will need to sign a medical release.

Added “To ensure subject safety, the Investigator may ask the subject to sign a medical release form allowing him to contact the subject's doctor for more information about subject's medical history.”</td></tr>
<tr><td>Section 6.6.2 Laboratory Parameters on page 55</td><td>To modify Pregnancy Screen portion of the table.

Changed from:

<table><tr><td>PREGNANCY SCREEN** (to be performed at screening, check-in, and discharge)</td></tr><tr><td>Urine pregnancy test (females only)
FSH will be done on post-menopausal females
**the pregnancy tests may be performed in-clinic using CLIA-waived marketed kits.</td></tr></table>
To

<table><tr><td>PREGNANCY SCREEN** (females only)</td></tr><tr><td>Urine pregnancy tests will be performed at screening and at discharge.
Serum pregnancy test will be done at check-in on Day -1.
FSH and estradiol tests will be done on post-menopausal females at screening and check-in on Day -1.
**the urine pregnancy tests may be performed in-clinic using CLIA-waived marketed kits.</td></tr></table></td></tr>
<tr><td>Section 7.1 Screening Visit (Day -36 to -1) on page 68</td><td>To modify pregnancy screen procedure at screening.

Added: “FSH and Estradiol test for post-menopausal female subjects”</td></tr>
<tr><td>Section 7.2.1 Check-in (Day -1) Procedures on page 69</td><td>To modify pregnancy screen procedure at check-in on Day -1.

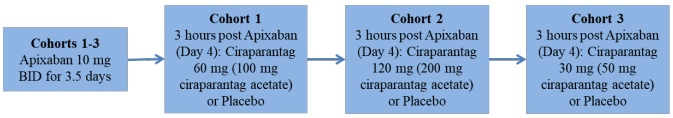
Changed from “Urine pregnancy for all female subjects” to “serum pregnancy tests in all female subjects”

Added: “FSH and Estradiol tests for post-menopausal female subjects”</td></tr>
<tr><td>9.7 Pharmacodynamic Analyses on page 81</td><td>To correct and clarify criteria for apixaban non-responder.

Changed from: “The anticoagulant effect of apixaban will be evaluated by comparing WBCT measured at pre-PER977 (four hours) versus baseline (pre-apixaban at four hours pre-dose on Day 3). For the purposes of the PD analyses, subjects with percent-of-baseline WBCT at pre-PER977 ≤125% (i.e., ≤25% increase) will be considered as apixaban non-responders and will be excluded from all PD summaries and assessments.”</td></tr>
</table>

Item	Revision in Version 3.0
	To "The anticoagulant effect of apixaban will be evaluated by comparing WBCT measured at pre-PER977 (three hours post-apixaban on the morning of Day 4) versus baseline (pre-apixaban on the morning of Day 1). For the purposes of the PD analyses, subjects with percent-of-baseline WBCT at pre-PER977<120% (i.e., <20% increase) will be considered as apixaban non-responders and will be excluded from all PD summaries and assessments."
Section 9.8 Statistical Analysis of the Primary PD End Point (WBCT) on page 82	To clarify statistical analysis and definition of reversal of anticoagulation Change section title from "9.8 Categorical Analysis of the Primary PD Endpoint (WBCT)" to "9.8 Analysis of the Primary PD Endpoint (WBCT)" Changed from "Complete reversal is defined as mean WBCT to ≤110% of baseline up to and including 1 hour following test article administration." To "Complete reversal is achieved for a treatment group or for a subject if the mean WBCT is ≤ 110% of baseline at any post-baseline time point up to and including 1 hour following test article administration. Complete reversal is achieved if WBCT is <=110% of baseline at any post-baseline time point up to and including 1 hour following test article administration." Changed from "Complete and sustained reversal of anti-coagulation is defined as a return of mean WBCT to ≤115% of baseline at all time points between 1 and 8 hours following test article administration." To "Complete and sustained reversal of anti-coagulation is achieved for a treatment group if the mean WBCT is ≤ 115% of baseline at all time points between 1 and 5 hours (inclusive) following test article administration. Complete and sustained reversal of anti-coagulation is achieved for a subject if WBCT is ≤ 115% of baseline at all time points between 1 and 5 hours (inclusive) following test article administration."

Summary of Main Changes Made in Version 1.0 to Generate Version 2.0

Item	Revision in Version 2.0
Dose Schema: In Synopsis and section 3.1	Dosing schema was revised. The version 2.0 dosing schema was replaced with following dosing schema. 

Item	Revision in Version 2.0
Apixaban Dosage: 1. In Synopsis 2. In Study Procedure 3. In section 2 4. In section 3.1 5. In section 5.2.3 6. In section 5.3 7. In section 7.2.2 8. In section 7.2.3 9. In section 7.2.4.1	Increase apixaban dosage Increased apixaban dosage from 5 mg BID (Q12) for 3.5 days as a single oral tablet to 10 mg BID (Q12) for 3.5 days as two oral tablets
Exclusion Criteria #3	Clarify exclusion criteria Changed from "History of major bleeding, trauma, or surgical procedure of any type" to "History of major bleeding, trauma, or surgical procedure of any type based on PI discretion"
Stroke Assessment: In Synopsis	Add stroke assessment Add in Safety Assessments: "Stroke assessment"
Stroke Assessment In Study Procedures	Add stroke assessment Add stroke assessment in Study Procedure Table on Day 1 to 4 Add in k: "Stroke assessments will be performed by PI or designee at approximately 3 hours post-apixaban dose on the morning (±1-hour window) on Day 1 to 4."
Stroke Assessment In section 6.5	Add section 6.5 Stroke Assessment Add: "Stroke assessments will be performed by PI or designee at approximately 3 hours post-apixaban dose on the morning (±1-hour window) on Day 1 to 4. PI or designee will check for stroke warning signs and physical symptoms: Stroke warning signs: • Sudden weakness or numbness of the face, arm or leg, especially on one side • Sudden confusion or difficulty understanding • Trouble speaking, walking or seeing • Dizziness or loss of balance • Sudden onset of severe headache Physical symptoms: • Facial smiling or showing of teeth on one side • One arm does not move or drifts compared to the other on extension

Item	Revision in Version 2.0
	• Abnormal slurred speech, improper choice of words, inability to speak or acute confusion and disorientation"
Stroke Assessment 1. In section 7.2.2. 2. In section 7.2.3. 3. In section 7.2.4.1	Add stroke assessment Add: "Stroke assessment at approximately 3 hours post-apixaban dose on the morning (±1-hour window)"

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SYNOPSIS

Sponsor:

Perosphere Inc., a wholly-owned subsidiary of AMAG Pharmaceutical

Name of Active Therapeutic Product:

Ciraparantag, PER977

Study Title:

Phase 2 Placebo-Controlled, Single-Site, Single-Blind Study of Apixaban Reversal by Ciraparantag as Measured by WBCT

Study Number:
PER977-02-011

Study Phase: 2

Study Design:

This study is a randomized, single-blind, placebo-controlled study to assess the efficacy and safety of ciraparantag administered to healthy volunteers anticoagulated with apixaban measuring clotting times using Whole Blood Clotting Time (WBCT). All subjects will undergo screening up to 36 days prior to enrollment. Randomization will take place on Day 4.

Subjects will be enrolled sequentially. If the Screening visit takes place within 3 weeks prior to check-in, the check-in procedures may be modified to exclude redundant procedures (safety laboratory tests, ECG, and physical examination) at the discretion of the Investigator. There will be a safety review after completion of treatment in one cohort and the initiation of treatment in the subsequent cohort.

Subjects (n=16 per cohort) will be randomized in a 3:1 ratio to receive ciraparantag or placebo (saline for injection). For the dosing schema, please refer to the figure below.

All subjects will receive 10 mg apixaban for 3.5 days (Twice daily Q12 on Days 1-3 and once on the morning of Day 4). On Day 4, approximately 3 hours after administering apixaban, study drug or placebo will be intravenously (IV) administered. Study drug or placebo will be administered only to those subjects who have a minimum increase in clotting time of 20% (as measured by WBCT) above Day 1 pre-apixaban baseline at the pre-study drug (i.e., 2.75 hours post-apixaban) time point on Day 4. Any subject who does not have a minimum increase in clotting time of 20% above the Day 1 pre-apixaban baseline at the pre-study drug time point on Day 4 will be discontinued from the study and replaced.

Individual subjects may participate in one dose cohort of this study. Any subject who discontinues prior to completion for reasons other than an adverse event (AE) will be replaced and the replacement subject will receive the same treatment as the original subject. Subjects who discontinue due to an AE that precedes administration of study

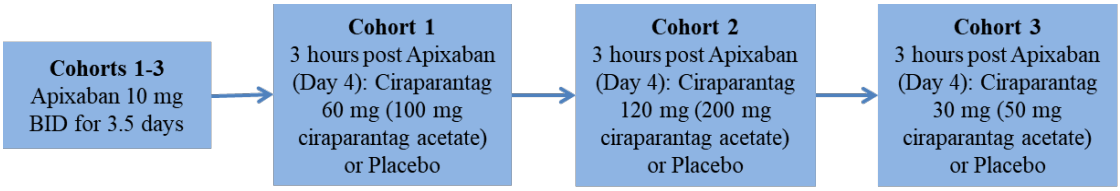
drug may be replaced at the discretion of the Sponsor. Subjects who discontinue due to AEs that follow administration of study drug will not be replaced.

A complete schedule of events for Cohort 1-3 is provided.

Throughout this protocol, the active study drug doses are expressed as active drug moiety (ciraparantag) (as opposed to previously used ciraparantag acetate salt). The administered dose is based on a concentration of 6 mg/mL ciraparantag (active moiety) and translates to the following dose conversions from previously used dose identifications:

Ciraparantag Acetate	Ciraparantag	Dose Volume
600 mg	**360 mg**	60 mL
300 mg	**180 mg**	30 mL
100 mg	**60 mg**	10 mL
50 mg	**30 mg**	5 mL
25 mg	**15 mg**	2.5 mL

Dose Schema



The goal of the study is to explore the dose range of ciraparantag that reverses the anticoagulation induced by therapeutic doses of apixaban at steady state. The study is intended to establish a dose of ciraparantag that fully reverses steady-state apixaban, to evaluate at least one dose above the reversal dose to establish a therapeutic index, and at least one partial or no effect dose.

Dose Rationale

A total of three dosing cohorts (Cohorts 1-3) are planned. The planned doses of ciraparantag or placebo (administered as a volume equivalent of ciraparantag) have been evaluated as single and repeat IV doses from 5 mg ciraparantag acetate (3 mg ciraparantag) up to 600 mg ciraparantag acetate (360 mg ciraparantag) in previous protocols (PER977-01-001, PER977-01-002, PER977-01-003, and PER977-02-001).

Primary Objective(s):

The primary objectives of this study are:

- To evaluate the efficacy of ciraparantag in the reversal of anticoagulation induced by apixaban 10 mg BID (Q12) at steady state as assessed by WBCT.
- To evaluate the safety and tolerability of ciraparantag 60 mg (100 mg), 120 mg (200 mg), and 30 mg (50 mg), and additional cohorts if necessary approximately

administered 3 hours after 10 mg apixaban administration at steady state.

- To assess the PK characteristics of apixaban and of ciraparantag and its primary metabolite, 1,4-Bis(3-aminopropyl) piperazine (BAP).

Eligibility

Inclusion Criteria

1. Adults age 50 to 75 years, inclusive
2. Laboratory tests (chemistry, hematology and coagulation assessments) and urinalysis performed during screening up to 36 days prior to administration of study treatment deemed not clinically significant by the principal investigator.
3. No clinically significant findings on 12-lead electrocardiogram (ECG) performed during screening
4. Body mass index (BMI) 18 to $\leq$ 32 kg/m^2, inclusive
5. Male subjects agree to use appropriate contraception (i.e., latex condom with spermicide) in addition to their partner using an acceptable form of contraception (e.g., diaphragm, cervical cap, intrauterine device, hormonal contraceptives, surgical sterilization or post-menopausal), when engaging in sexual activity during the course of the study. Moreover, male subjects should not donate sperm or attempt to impregnate a partner during the course of the study and for a period of 12 weeks following discharge from the study.
6. Female subjects must have negative pregnancy tests at screening and at check-in AND: be surgically sterile at least 6 months prior to first dose (with documentation of hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal ligation/tubal occlusion); OR post-menopausal (no menstruation for a minimum of 12 months and confirmed by follicle stimulating hormone [FSH] of $\geq$ 40 mIU/ml and serum estradiol < 30 pg/ml), OR if of child-bearing potential, must be using an acceptable method of contraception such as an IUD, implant or contraceptive injection, or **two** forms of the following (e.g., diaphragm, cervical cap, patch or vaginal hormonal contraceptive, condom, spermicide, or sponge) for the last three months. All females must agree to continue to use their method of birth control for the duration of the study and for a minimum of one complete menstrual cycle.
7. Subjects who have participated in a prior study of ciraparantag must have been discharged from the study a minimum of 3 months prior to the planned treatment.
8. Subjects must understand and agree to comply with the requirements of the study and they must be willing to sign the informed consent form indicating voluntary consent to participate in the study prior to initiation of screening or study-related activities

Exclusion Criteria

1. History or current evidence of clinically significant cardiac, hepatic, renal, pulmonary, endocrine, neurologic, infectious, gastrointestinal (including gallbladder disease or surgery), hematologic, or oncologic disease as determined by screening history, physical examination, laboratory test results or 12-lead ECG assessment. History or current evidence of liver function tests greater than 50% of the upper limit of normal (ULN) or renal function tests (serum creatinine) greater than 1.5 mg/dl and based on PI discretion. History or current evidence of QTc (QTcF) greater than normal (450 msec for males or 470 msec for females).
2. History of unexplained syncope
3. History of major bleeding, trauma, or surgical procedure of any type based on PI discretion
4. Vaginal delivery within six months prior to screening
5. History of peptic ulcer, gastrointestinal bleeding (including hematemesis, melena, rectal bleeding) within one year prior to screening
6. Long standing history of bleeding episodes such as epistaxis, bruising or gingival bleeding or if not long standing, within 1 month prior to screening
7. Personal or family history of clotting disorder or abnormality, excessive bleeding, joint hematoma, thrombovascular disease or any hematologic disorder involving platelets or clotting abnormalities or any condition requiring treatment with transfusions, or history of thrombocytopenia
8. Females with a history of dysfunctional uterine bleeding who have not undergone hysterectomy, including history of menorrhagia (heavy menstrual bleeding), menometrorrhagia or polymenorrhea
9. Smokers or use of tobacco and/or nicotine containing products within 3 months prior to dosing as determined by the subject's verbal history
10. Pregnant or breast-feeding
11. Males with a history of hormone therapy within 3 months prior to screening
12. Administration of any blood product or anticoagulant within 3 months prior to study entry or any non-steroidal anti-inflammatory drug or cyclooxygenase inhibitor within 2 weeks prior to dosing
13. Taking any type of chronic medication (including vitamin, nutritional and herbal supplements) for more than 14 consecutive days within the 4 weeks prior to study entry (use of hormonal contraceptives is acceptable except for oral contraceptives)
14. Positive serologic test for human immunodeficiency virus (HIV), Hepatitis C virus antibody (HCV-Ab), or Hepatitis B surface antigen (HBsAg)

15. Donation of blood or blood products within 56 days prior to screening
16. Participation in any study with an investigational compound or device within 30 days prior to signing informed consent
17. Active drug or alcohol dependence within the prior 12 months or any condition that, in the opinion of the Investigator, would interfere with adherence to study protocol
18. Allergic to apixaban

Study Population:

No formal sample size calculations were performed for this study; sixteen (16) subjects enrolled in each cohort (3:1; active: placebo) is considered adequate to achieve the objectives of the study.

Estimated number of subjects screened:	120
Planned number of subjects randomized:	48
Planned number of evaluable subjects:	48

Test Product, Dose, and Mode of Administration:

The following dosage forms will be provided for this study:

- Ciraparantag for IV injection
- Placebo saline for IV injection
- Apixaban 5 mg tablets (ELIQUIS® Pfizer/BMS) for oral administration

All doses of study drug (ciraparantag or placebo) will be administered by IV injection (over a minimum of 10 minutes) into an indwelling catheter. The indwelling catheter will be flushed with 5.0 mL of sterile 0.9% Sodium Chloride Injection, USP before and after administration of study drug. All doses of study drug will be administered in a single-blinded-fashion.

Duration of Treatment:

Expectation of the total duration of the study is up to approximately 3 months. Individual subject participation is approximately 50 days inclusive of screening and follow-up. Subjects enrolled will spend up to 5 nights admitted to an in-patient facility.

Concomitant Medications:

Use of concomitant medications (including vitamin, nutritional and herbal supplements) is prohibited as per Exclusion criteria, during screening and for the course of the study. Acetaminophen up to 1 gram/24 hours may be administered as needed for treatment at the discretion of the Investigator. As needed use of over-the-counter antihistamines during screening, prior to admission on Day -1, and following discharge from the clinic site on Day 5 is permitted. Use of hormonal contraceptives is acceptable except for oral contraceptives.

Pharmacokinetic Assessment:

Apixaban PK time points:

Day 1: pre-apixaban (within 1 hr. prior to dosing)

Day 4: post-apixaban at 2.75 hr and post-study drug at 15, 30, 45 minutes, and 1, 3, 5, 24 hrs.

Ciraparantag and BAP PK time points:

Day 4: pre-study drug (within 1 hr. prior to dosing of ciraparantag or placebo) and post-study drug at 15, 30, 45 minutes, and 1, 3, 5, 24 hrs.

Pharmacodynamic Assessments:

WBCT time points:

Day 1: pre-apixaban baseline (within 1 hr. prior to dosing)

Day 4: post-apixaban at 2.75 hr and post-study drug at 15, 30, 45 minutes, and 1, 3, 5, 24 hrs. (only subjects with at least 20% increase of clotting time from the Day 1 pre-apixaban baseline will be randomized).

Safety Assessments:

The following parameters will be assessed:

- Physical examination
- Vital signs
- Electrocardiograms (ECGs)
- Stroke assessment
- Blood and urine safety laboratories
- Fecal occult blood
- Experimental safety biomarker assessment

Citrated plasma for experimental safety biomarker assessment will be collected at pre-apixaban (within 1 hr. prior to dosing) on Day 1, and at 2.75 and 8 hrs. (i.e, 5 hrs post-study drug) post-apixaban on Day 4. Experimental safety biomarker assessment will be done at the PI's discretion.

Subjects will be observed for a minimum of 24 hours following the final study drug administration. If, in the opinion of the Investigator, all potentially occurring AEs have resolved, coagulation parameters (WBCT) are not clinically significant, and no further observation is necessary, the subject will be discharged from the facility on Day 5.

On Day 7-10, subjects will be followed-up by telephone call. Subjects will be discharged

from the study after the telephone call if all AEs have resolved to the satisfaction of the Investigator.

Over the course of the study, the total estimated volume of blood to be sampled for the combined PK, PD and safety evaluations is approximately 225 mL per subject.

Statistical Methods:

All data collected will be presented in data listings. Data from subjects excluded from an analysis set will be presented in the data listings, but not included in the calculation of summary statistics. For categorical variables, frequencies, and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum). Data will be tabulated by treatment, across active treatment groups when applicable, with all placebo subjects pooled into a single group.

All evaluable data from subjects in the analysis sets will be included in the analyses. No adjustment or imputation will be utilized for missing values or for subjects who withdraw prior to completing the study.

Baseline values will be defined as the last assessment prior to investigational product administration and per period if applicable.

Definition of Reversal of Anticoagulation – Clotting Time by WBCT

- Complete reversal is defined as a return of mean WBCT to ≤110% of baseline up to and including 1 hour following test article administration.
- Complete and sustained reversal of anti-coagulation is defined as a return of mean WBCT to ≤115% of baseline at all time points between 1 and 5 hours following test article administration. Dose escalation or de-escalation will be determined by this criterion.

Details of all statistical analyses will be specified in a separate statistical analysis plan (SAP) that will be finalized prior to data base lock.

Date of Original Protocol: 9 August 2017

Prepared in: Microsoft Word 2013

STUDY PROCEDURES

Day→ Procedure ↓	Screening[a]	Treatment Period						Follow-up
	Day -36 to -1	Day -1 Check-in	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7-10
Written informed consent	X							
Inclusion/exclusion criteria	X[b]	X						
Demographic data	X							
Height	X							
Weight	X	X						
Medical/ surgical history	X							
Medication history	X							
Physical exam[c, d]	X	X					X	
Vital signs (BP and HR), RR and temp [c,e]	X	X	X	X	X	X	X	
Safety laboratories [c, f]	X	X					X	
Fecal occult blood[f]		X						
Drug and alcohol screen[g]	X	X						
Viral hepatitis/HIV serology[g]	X							
12-lead ECG[c, h]	X	X	X	X	X	X	X	
Urine pregnancy test[i]	X						X	
Serum Pregnancy test[i]		X						
Admission to CRU[j]		X						
Randomization						X		
Apixaban administration[k]			X	X	X	X		
Study drug administration[k]						X		
Stroke assessment[k]			X	X	X	X		
Experimental safety biomarker[f]			X			X		
PD measurements[c, l]			X			X	X	
PK sample collections[m]			X			X	X	
Adverse event monitoring	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X
Discharge from clinical site							X	
End of the study participation[n]								X

a. Screening procedures are to be conducted -36 to -1 day before check-in on Day -1. All subjects will be provided lifestyle and dietary guidelines appropriate for an anticoagulant study and for fecal occult blood testing. If the screening visit takes place within 3 weeks prior to check-in, the check-in procedures may be modified to exclude redundant procedures at the discretion of the Investigator.
b. Subjects should conform to the inclusion/exclusion criteria for the duration of the study. If a subject violates an inclusion or exclusion criterion at any point during the study, he/she may be removed from the study and replaced.
c. When timing for assessments coincide, PD assessments will be performed first followed by PK assessment(s) and then safety assessments.
d. A complete physical examination will be performed at screening. An abbreviated physical examination will be performed at check-in and prior to discharge from the clinical site.
e. Vital signs (blood pressure, heart rate, respiration rate, and temperature) will be measured at screening and check-in. Vital signs will be measured within 60 minutes prior to administration of apixaban on the morning of Days 1-4, within 30 minutes prior to study drug dosing, and at 1.5, 4, 8 and 24 hrs. post-study drug dosing.
f. Safety laboratory tests (hematology, coagulation, blood chemistry and urinalysis) will be performed at screening, at check-in (if the screening lab are not conducted within 3 weeks prior to check in), and prior to discharge. Blood samples for experimental

safety biomarker assessments will be collected at pre-apixaban on Day 1 and post-apixaban 2.75 and 8 hours on Day 4 Fecal occult blood tests will be performed at check-in. Occult blood kits will be given to subjects at screening and should be returned at check-in. Occult fecal blood tests must be negative at check-in to continue study participation. In the event an occult blood kit is not returned, a rectal exam for stool sample may be performed at the discretion of the Investigator. Following the treatment period, coagulation parameters (WBCT result) must be not clinically significant prior to discharge.

g. Urine drug and saliva alcohol tests will be performed at screening and at check-in. A blood sample will be taken to assess the presence of HbsAg, HCV-Ab and HIV at screening.
h. Electrocardiograms (12-lead) will be performed at screening, check-in, after receiving apixaban on the morning of day 1-4, and prior to discharge. Additional ECG may be performed at PI discretion.
i. Urine pregnancy testing will be performed for all women at screeningand at discharge. Serum pregnancy test will be performed at check-in on Day -1.
j. Subjects will be admitted to the clinical site on Day -1 for baseline assessments and will remain confined until 24 hours after the study drug administration provided that, in the opinion of the Investigator, it is safe to be discharged.
k. Apixaban oral tablet will be administered as 10 mg BID (Q12) after meal on Days 1-3. On Day 4, a single dose 10 mg apixaban will be administered after breakfast on the morning and the study drug injection will follow approximately 3 hours later. Stroke assessment will be performed at approximately 3 hours post-apixaban dosing on the morning (±1-hour window) on Day 1 to 4.
l. Blood samples for WBCT will be collected on Day 1 pre-apixaban (as baseline), Day 4 post-apixaban at 2.75 hrs. and post-study drug at 15, 30, 45, minutes, and at 1, 3, 5, and 24 hrs. Only subjects with at least 20% increase of clotting time from Day 1 pre-apixaban baseline will be randomized for study drug treatment.
m. Blood samples for PK assessment of apixaban and ciraparantag and its metabolite will be collected on Day 4 post-apixaban at 2.75 hr and post-study drug at 15, 30, 45 minutes, and at 1, 3, 5, and 24 hrs. For apixaban PK, a pre-apixaban blood sample on Day 1 will also be collected.
n. Follow-up will be performed by telephone on Day 7-10. Subjects may be discharged from the study after the telephone call if all AEs have resolved to the satisfaction of the Investigator.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION	DEFINITION
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AV	atrioventricular
BAP	1,4-Bis(3-aminopropyl)piperazine
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximal concentration
C_{24}	Observed quantifiable analyte concentration in the sampled matrix at the 24-hour time point
C_{last}	Last observed quantifiable analyte concentration in the sampled matrix
CRF	case report form
CRO	contract research organization
ECG	electrocardiogram
EDC	electronic data capture
EDTA	ethylenediaminetetraacetic acid
E_{max}	maximum effect
E_{min}	minimum effect
FIIa	factor IIa

ABBREVIATION	DEFINITION
FXa	factor Xa
F1.2	prothrombin fragments F1 and 2
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	good clinical practice (refers to ICH and CFR)
HBsAg	hepatitis B surface antigen
HCV-Ab	hepatitis C virus antibody
HDPE	high density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IMPD	Investigational Medicinal Product Dossier
IND	Investigational New Drug
IRB	institutional review board
IV	intravenous
LMWH	low molecular weight heparin
LLOQ	lower limit of quantification
LOQ	limit of quantification
NOAC	new oral anticoagulants
NS	normal saline
MedDRA	Medical Dictionary for Regulatory Activities
PD	pharmacodynamic
PK	pharmacokinetic

ABBREVIATION	DEFINITION
PoC	point-of-care
PT	prothrombin Time
QTcF	QTc Fridericia
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SOC	System Organ Class
SOP	standard operating procedures
SUSAR	serious unexpected serious adverse reaction
$t_{1/2}$	half-life
t_{last}	time of C_{last}, obtained directly from the observed concentration versus time data
TEAE	treatment-emergent adverse event
TEG-R	thromboelastography reaction time
Temp	temperature
TFPI	tissue factor pathway inhibitor
T_{max}	time of the maximum observed activity value
TMF	trial master file
UFH	unfractionated heparin
ULN	upper limit of normal
WBCT	whole blood clotting time
WHO	World Health Organization

1 INTRODUCTION

Ciraparantag (PER977) is a small, synthetic water-soluble new molecular entity that physically associates with heparins and related anticoagulant drugs (i.e., direct factor Xa [FXa] and factor IIa [FIIa] inhibitors) allowing rapid re-establishment of a normal blood coagulation state. This reversal effect is due to direct non-covalent binding to the anticoagulant molecule with no binding to blood coagulation factors or proteins in the blood.

1.1 Clinical Problem

In the United States, the number of patients requiring anticoagulation annually numbers in the millions; upwards of 600,000 patients with thromboembolic events or pulmonary embolism, (CDC Fast Stats 2012) and over 1 million joint replacement procedures (knee and hip), (CDC Statistics 2010) necessitate prophylactic post-operative anticoagulation, and most of the 2.66 million patients with atrial fibrillation will also be prophylactically anticoagulated. (CDC Atrial Fibrillation Fact Sheet)

Anticoagulation is time consuming and problematic for both physicians and patients. The traditional anticoagulants (heparin and warfarin) have a long history of successful clinical use, with an accepted risk of substantial bleeding. (Palareti G 2011, FDA Safety Alert 2012) Due to the incidence of major bleeding associated with the traditional anticoagulants, demand for new therapeutic anticoagulants has been met with the introduction of low molecular weight heparin (LMWH) products and selective oral inhibitors of clotting factor IIa and Xa. Although the new oral anticoagulants (NOACs) have several advantages including rapid therapeutic effectiveness, ease of dosing, and lack of monitoring requirements, each is associated with risk of major bleeding. (ISMP 2012)

A significant obstacle to adoption of the new FXa and FIIa inhibitors is clinical concern regarding the lack of an effective reversal agent (e.g., vitamin K for warfarin, protamine for heparin and LMWH [partial reversal]). This is germane in cases of overdose, trauma, need for emergency or urgent surgery, and in patients undergoing elective procedures (cardiac ablations, endoscopies with biopsies, extensive dental surgery) that may require discontinuation, changing, or bridging of anticoagulation. Current recommendations call for termination of anticoagulants between 2 – 4 days prior to the elective procedures and cautiously keeping a patient off anticoagulation for some period of time after the procedure, especially if a biopsy or invasive procedure has been used. (McLean 2012) In emergency surgeries, where it is desirable to wait until at least 3 half-lives have passed before surgical intervention, if possible, patients are at risk of significant bleeding.

An efficacious reversal agent for the LMWHs and oral FXa and FIIa inhibitors would permit rapid reversal of anticoagulation for emergency purposes, minimize the time

patients are off their anticoagulant pre-procedure, and provide a level of confidence regarding restarting the anticoagulant therapy post-procedure.

Equally germane is the issue of identification of biomarkers for both efficacy and safety monitoring for pro-coagulation signals for drugs under development for reversal of anticoagulants. Many of the commonly used biomarkers (prothrombin time [PT], activated partial thromboplastin time [aPTT], anti-factor Xa [anti-FXa], etc.) show significant disparity between the biomarker's indication of a reversal and the lack of bleeding cessation, if there is reagent interference. The primary goal of reversing an anticoagulant is simply to return the ability of the blood to clot; historical biomarkers have been used for this purpose but they remain surrogate biomarkers. This problem is addressed by WBCT, which measures clotting time in fresh whole blood samples.

1.2 Clinical Development of Ciraparantag

As of August 15, 2016, ciraparantag (PER977; previously, aripazine) has been evaluated in four clinical studies of single escalating doses of ciraparantag following administration edoxaban (PER977-01-001; NCT01826266), unfractionated heparin (PER977-01-002; NCT02206087), and enoxaparin (PER977-01-003; NCT02206100), and following anticoagulation and re-anticoagulation with edoxaban (PER977-02-001; NCT02207257). In this protocol, all doses are listed as the ciraparantag base equivalent. Both dosing formats are utilized in the presentation of clinical data from previous studies.

In each of the protocols the dosing of active study drug was described based on the drug substance ciraparantag acetate (salt). In accordance with new guidelines, the drug substance content is now labeled as active moiety (ciraparantag). Throughout this document, the active study drug doses are expressed according to the new convention.

Completed safety and efficacy data from PER977-01-001, PER977-01-003, and PER977-02-001 are presented.

1.2.1 PER977-01-001

PER977-01-001 was a phase 1, first in human, double-blind, placebo-controlled, sequential group, two-period, ascending ciraparantag dose study administered alone and in combination with edoxaban in healthy volunteers. The study consisted of two periods: a single intravenous IV injection of 3 mg, 9 mg, 15 mg, 30 mg, 60 mg, 120 mg or 180 mg ciraparantag, respectively (ciraparantag acetate 5, mg, 15, mg, 25 mg, 50 mg, 100 mg, 200 mg, or 300 mg) alone or placebo with serial PK, pharmacodynamic (PD), and safety monitoring. After a one-week washout, a single dose of edoxaban 60 mg was administered followed 3 hours later by a single dose of ciraparantag or placebo at the same dosage as was administered in the first period, and with serial PK, PD, and safety monitoring.

The highest incidence of treatment emergent adverse events (TEAEs) in Period 1 (ciraparantag monotherapy) were in the system organ class (SOC) of general disorders and administration-site conditions (feeling hot; n=14, 24.1%), and in nervous system disorders (dysgeusia; n=8, 13.8%). Adverse events in placebo subjects comprised feeling cold, headache, infusion related reaction and peripheral coldness reported in one subject each.

The highest incidence of TEAEs in Period 2 was in the SOC of general disorders and administration-site conditions (feeling hot n=11, 17.2%), nervous system disorders (dysgeusia n=8, 12.5%), and in injury, poisonings, and procedural complications (contusion n=7, 10.9%). Adverse events in placebo subjects comprised feeling cold chest discomfort, infusion site coldness, vessel puncture site pain, dysgeusia, headache, contusion, infusion related reaction, peripheral coldness, and hematoma reported in one subject each.

No serious AEs were reported during the conduct of the study, no laboratory results were reported as AEs and there were no clinically significant changes in vital signs. There were no clinically significant AEs and no dose-related findings occurred with regard to interval prolongations in median of triplicate ECG tracings with regard to HR, P-R, QRS, QTcF or R-R intervals.

The protocol initially designated prothrombin time (PT) and thromboelastography reaction time (TEG-R) as the primary PD efficacy variables based on their use in *in vitro* studies. One of the objectives of the protocol was to assess which biomarkers were the best endpoints for future clinical trials. In seeking a biomarker for ciraparantag reversal effect on anticoagulants, the fact that cationic ciraparantag exhibits strong binding to anionic citrate, ethylene diaminetetra acetic acid (EDTA), and oxalate due to charge interaction became problematic. Plasma tubes contain a large molar excess of anions that overwhelm and disrupt the ciraparantag-anticoagulant complex rendering the results of plasma-based assays non-representative of physiologic conditions. Findings in Cohorts 1-4 of the study indicated that PT and TEG-R would not be acceptable biomarkers in clinical trials due to their insensitivity and high variability. Whole blood collected in tubes and transported to the laboratory for TEG-R testing were observed to be clotting clinically faster as study drug dose increased, and yet the PT values showed no change and TEG-R showed a high degree of variability between time points and between subjects. Mean PT and TEG-R showed no change over time within cohorts and across escalating dose cohorts.

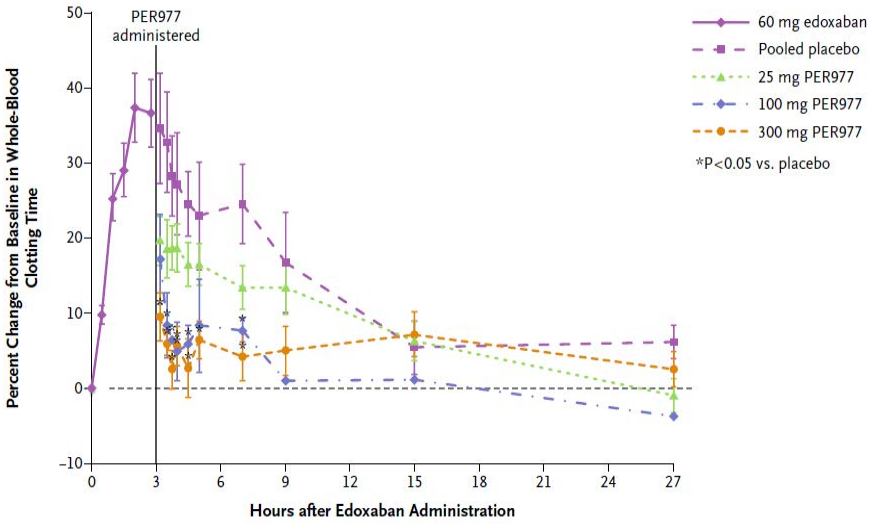
Enhanced clotting of anticoagulated blood was observed beginning in Cohort 2 (30 mg ciraparantag [ciraparantag acetate 50 mg]). Whole blood clotting time (WBCT; referred to as ‘venous clotting time’ or ‘VCT’ in the protocol or Lee-White clotting time where-in glass is the only activating agent) was performed on discarded blood samples from a few patients. This was done in order to assess whether blood was clotting slower than baseline with edoxaban administration (e.g., anticoagulation) and possibly returning to

baseline after administration of study drug (i.e., reversal of anticoagulation by ciraparantag). Data from the pilot subjects showed a significant increase in clotting time with edoxaban and agreement between independent observers. As a result of these observations, measurement of clotting, glass bead activated clotting time and WBCT were added to the study as additional exploratory biomarkers for Cohorts 6-7 (120 mg ciraparantag [ciraparantag acetate 200 mg] and 180 mg ciraparantag [300 mg ciraparantag acetate], respectively).

Ciraparantag acetate displayed no pro-coagulant activity as demonstrated by lack of effect on WBCT, D-dimer, prothrombin fragments 1 and 2 (F1.2), or tissue factor pathway inhibitor (TFPI) when administered alone in doses ranging from 3 to 180 mg ciraparantag (5 to 300 mg ciraparantag acetate).

When administered following edoxaban, a single IV dose of ciraparantag acetate 30 mg, 60 mg, 120 mg, and 180 mg ciraparantag (50 mg, 100 mg, 200 mg and 300 mg ciraparantag acetate) demonstrated reversal of edoxaban-induced anticoagulation versus placebo for the full testing period of 24 hours following study drug administration. Evidence of reversal of anticoagulation was noted 10 - 30 minutes post-study drug administration in subjects administered 30 mg to 180 mg ciraparantag (50 to 300 mg ciraparantag acetate). Initial signs of reversal were noted in Cohort 4 (30 mg ciraparantag [50 mg ciraparantag acetate]) and full reversal was confirmed with subsequent increasing dose in Cohorts 5 to 7 (60 to 180 mg ciraparantag [100 mg to 300 mg ciraparantag acetate]). There was no evidence of significant reversal of WBCT in subjects who received 15 mg ciraparantag (25 mg ciraparantag acetate) in a repeat cohort of new subjects.

Figure 1: WBCT Following a Single IV Dose of Ciraparantag Acetate (PER977) Versus Pooled Placebo Data in Subjects Administered a Single Oral Dose of Edoxaban 60 mg



(Ansell NEJM 2014)

Ciraparantag Dose	Ciraparantag Acetate Dose	Onset of Reversal (min)	Duration of Reversal (hr)
15 mg	(25 mg)	NOED	NOED
30 mg	(50 mg)	30	24
60 mg	(100 mg)	30	24
120 mg	(200 mg)	10	24
180 mg	(300 mg)	10	24

NOED- no observed effect dose

A dose of 15 mg ciraparantag (equivalent to 25 mg ciraparantag acetate; see conversion table above) administered after a single dose of edoxaban 60 mg did not yield a statistically significantly improvement in change in WBCT (percent change from baseline). The administration of 30 mg ciraparantag (50 mg ciraparantag acetate) (4 subjects) resulted in numerical and statistically significant differences from placebo at 10 minutes and 60 minutes. The 60 mg ciraparantag (100 mg ciraparantag acetate) dose group showed statistically significant percentage change from baseline compared to placebo at all time points but the 10-minute group. Average WBCT in subjects who received 120 mg and 180 mg ciraparantag (200 mg and 300 mg ciraparantag acetate) showed significantly different percentage changes from baseline compared to placebo at all time points. Based on these results, 60 mg ciraparantag (100 mg ciraparantag acetate) was selected as the effective reversal dose.

Table 1: Number of Subjects with Return to Within 20% of Baseline WBCT by Dose Cohort and Time Point

	Number of Ciraparantag Treated Subjects with WBCT within 20% of Baseline				
Time after Ciraparantag	15 mg (25 mg)	30 mg (50 mg)	60 mg (100 mg)	120 mg (200 mg)	180 mg (300 mg)
10 min	6/10	3/4*	4/6	7/8*	7/8*
30 min	8/10	4/4	6/7*	7/8*	8/8*
45 min	6/10	ND	7/7*	8/8*	8/8*
60 min	4/10	4/4*	7/7*	8/8*	8/8*

*$p<0.05$ between ciraparantag and placebo groups.
ND = No data for time point.

The designated biomarkers in the protocol (PT and TEG-R) were found to be insensitive and too variable for clinical study use. Whole blood clotting time was identified as the most sensitive and clinically relevant biomarker in a subset of the cohorts and was targeted for use as the primary efficacy variable in all subsequent studies.

1.2.2 PER977-01-002

This was a single-blind, placebo-controlled, sequential group, ascending ciraparantag dose study in healthy volunteers. Ten subjects were enrolled in each dose cohort and randomized in an 8:2 ratio to ciraparantag: placebo. All subjects in all cohorts received UFH 5000u by IV bolus injection followed immediately by 5000u administered by IV infusion over 3 hours (~1667u/hour).

Six cohorts of 10 subjects had been enrolled and had received 60 mg, 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg ciraparantag, respectively. Cohort 4 (240 mg) only was performed as a two-period treatment where each subject received a single dose of ciraparantag alone during Period 1 and during Period 2, each subject received UFH followed by a single dose of ciraparantag.

Perosphere had planned to advance dosing to 480 mg ciraparantag, but the study was closed early for business reasons. Current clinical study plans involve a return to a protocol investigating the reversal of unfractionated heparin by ciraparantag following completion of studies with edoxaban and enoxaparin. There were no safety concerns that lead to the early termination. No dose limiting toxicities or TEAEs of concern were observed.

Following ciraparantag dosing, over the 60 mg to 360 mg dose levels administered in the study, there were no apparent differences in WBCT for the active treatments compared to placebo.
Complete, partial, and no reversal for WBCT were observed at the same rate for all PER977 doses combined and placebo group. There were no apparent dose-related relationships for any of the reversal categories. There were no statistically significant differences between geometric least-squares means in ciraparantag treatments compared to placebo group for percent of baseline WBCT at most time points and for PD parameters. The WBCT return to baseline was achieved at similar times, two-hour or four-hour time points, across active treatments and placebo group.

For the secondary endpoints, there were no statistically significant differences for active ciraparantag treatments versus placebo in most comparisons for PoC-aPTT and the procoagulant biomarkers TEG-R, D-dimer, F1.2, and TFPI.

Across the 60 mg to 360 mg ciraparantag dose levels, assessments of relationship between dosage and reversal of anticoagulation (complete reversal versus partial or reversal) and exposure response showed no statistically significant correlations.

The lack of reversal of unfractionated heparin at the ciraparantag doses utilized in the protocol was not unexpected due to the much higher binding ability of unfractionated heparin for ciraparantag compared to the newer oral anticoagulants and the smaller enoxaparin molecules.

No deaths, serious adverse events (SAEs), or discontinuations due to AEs were reported.

At least one TEAE was reported for 35 (72.9%) of the subjects who received ciraparantag following UFH: three subjects (37.5%) who received 60 mg ciraparantag, six subjects (75.0%) who received 120 mg ciraparantag, six subjects (75.0%) who received 180 mg ciraparantag, six subjects (75.0%) who received 240 mg ciraparantag following UFH, six subjects (75.0%) who received 300 mg ciraparantag, all eight subjects (100.0%) who received 360 mg ciraparantag and these were all considered related to the study drug by the investigator; and seven subjects (87.5%) who received 240 mg ciraparantag without UFH. At least one TEAE was reported for two subjects (16.7%) who received placebo following UFH – one of them was considered related to the study drug, and one subject (50.0%) who received placebo without UFH (not related).

The most common TEAE, feeling hot, was reported for a total of 20 subjects (41.7%) who received ciraparantag following UFH and for two subjects (25.0%) who received 240 mg ciraparantag without UFH. All of these events were transient and considered to be mild and related to ciraparantag by the Investigator. No event of feeling hot was reported for subjects who received placebo.

All TEAEs were considered to be mild in severity by the Investigator.

No safety concerns or notable differences were observed in safety laboratory, vital signs, pulse oximetry, ECG, telemetry, and fecal occult blood assessments, when comparing active treated cohorts or comparing active treated cohorts and placebo.

1.2.3 PER977-01-003

PER977-01-003 was a single-blind, placebo-controlled, sequential group, ascending ciraparantag repeating-dose study in healthy volunteers who received a single subcutaneous (sc) injection of enoxaparin 1.5 mg/kg. Four dose cohorts of ciraparantag (60 mg, 120 mg, 180 mg, and 4 x 15 mg ciraparantag, respectively [100 mg, 200 mg, 300 mg and 4 x 25 mg ciraparantag acetate, respectively]) were tested. In Cohort 1 to 3, additional doses of study drug were allowed in subjects randomized to ciraparantag if PD assessments (WBCT and aPTT) were >120% of baseline value following evaluation of the 60 minute post study drug WBCT assessment. For the purposes of analysis, subjects with percent of baseline WBCT at the pre-study drug time point ≤120% (i.e.≤20% increase following enoxaparin) were considered enoxaparin non-responders and were excluded from PD assessments.

A total of 40 subjects were enrolled (32 to ciraparantag and 8 to placebo) and completed the study. In Cohorts 1-3 (ciraparantag 60 mg, 120 mg, and 180 mg [ciraparantag acetate 100 mg, 200 mg, and 300 mg]) the most commonly AE was flushing, reported in 10 subjects: 2 subjects (25%) who received 60 mg ciraparantag (100 mg ciraparantag acetate), 3 subjects (37.5%) who received 120 mg ciraparantag (200 mg ciraparantag acetate), and 5 subjects (50%) who received 180 mg ciraparantag (300 mg ciraparantag acetate). Flushing was considered study drug-related in 1 subject (12.5%) who received 60 mg ciraparantag (100 mg ciraparantag acetate) and in all of the subjects who received 120 mg and 180 mg ciraparantag (200 mg and 300 mg ciraparantag acetate) who reported

flushing. Other TEAEs reported by the investigator as study drug related were feeling hot and throat tightness (ciraparantag 60 mg [ciraparantag acetate 100 mg]), chills and facial pain (ciraparantag 120 mg [ciraparantag acetate 200 mg]), and chills and dysgeusia (ciraparantag 180 mg [ciraparantag acetate 300 mg]).

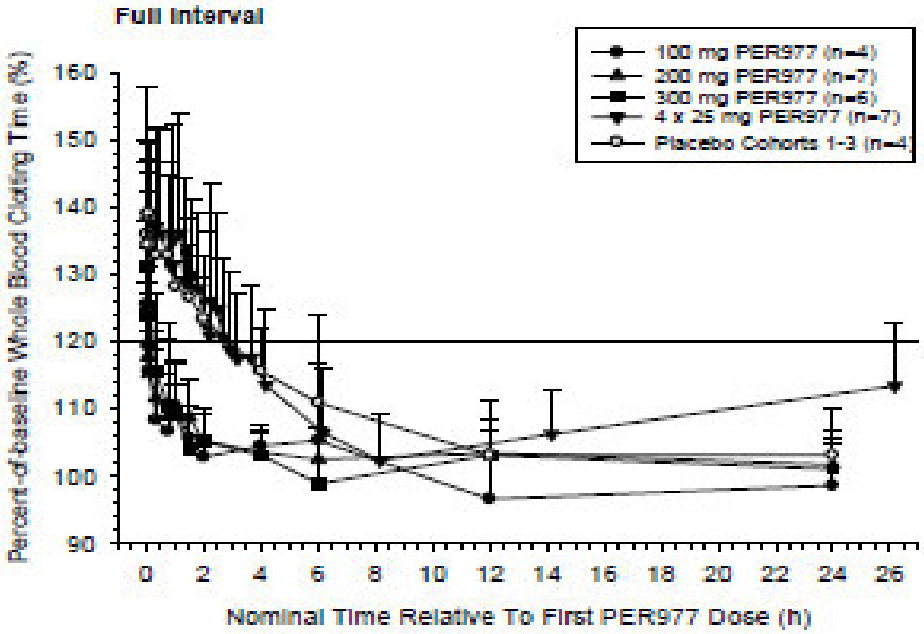
Table 2: Summary of TEAEs by SOC and Preferred Term for Each Treatment

	Ciraparantag					
	60 mg (100 mg) n=8	**120 mg (200 mg) n=8**	**180 mg (300 mg) n=8**	**15 mg (25 mg) x 4 n=8**	**All Doses n=32**	**Placebo n=8**
All related TEAEs, n (%)	2 (25)	4 (50)	7 (87.5)	0	13 (40.6)	0
General disorders and Administration Site Conditions	1 (12.5)	2(25)	1 (12.5)	0	4 (12.5)	0
Chills	0	1 (12.5)	1 (12.5)	0	2 (6.3)	0
Facial Pain	0	1 (12.5)	0	0	1 93.1)	0
Feeling Hot	1 (12.5)	0	0	0	1 (3.1)	0
Nervous System Disorders	0	0	1 (12.5)	0	1 (3.1)	0
Dysgeusia	0	0	1 (12.5)	0	1 (3.1)	0
Respiratory, Thoracic, and Mediastinal Disorders	1 (12.5)	0	0	0	1 (3.1)	0
Epistaxis	0	0	0	0	0	0
Throat Tightness	1 (12.5)	0	0	0	1 (3.1)	0
Vascular Disorders	1 (12.5)	3 (37.5)	5 (62.5)	0	9 (28.1)	0
Flushing	1 (12.5)	3 (37.5)	5 (62.5)	0	9 (28.1)	0

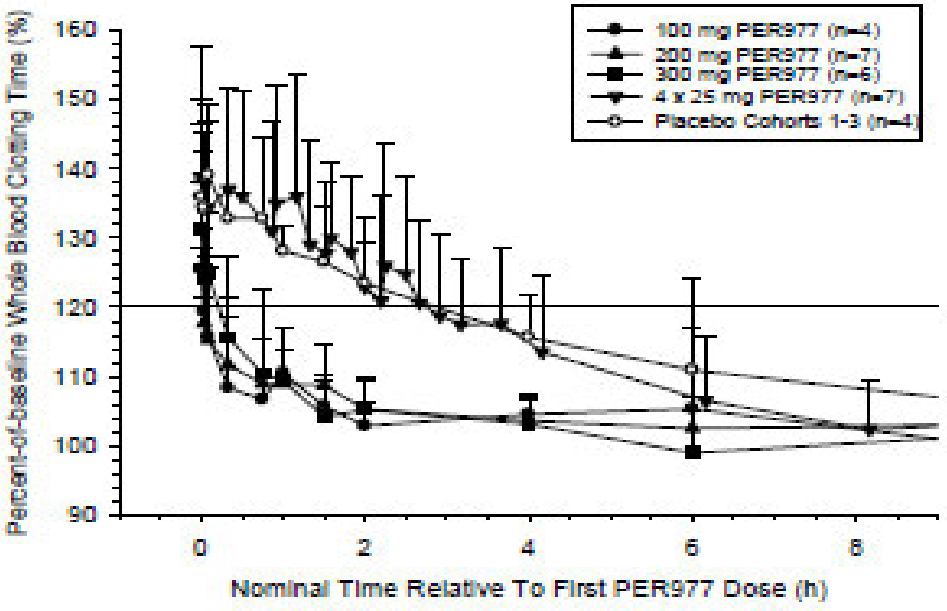
A total of 30 subjects (75%) were included in the PD population. Across the three active treatments (ciraparantag 60 mg, 120 mg, and 180 mg [ciraparantag 100 mg, 200 mg, and 300 mg] in Cohorts 1-3), the mean percent-of-baseline WBCT dropped to ≤120% by 20 minutes after the end of the ciraparantag injection and remained below 120% for the remainder of the 24-hour period. The maximum effect (E_{max}) was consistently observed at 2 minutes after the completion of the 10-minute injection. The mean percent-of-baseline WBCT maximum effect (E_{max}) were comparable across the active ciraparantag 60 mg, 120 mg and 180 mg (ciraparantag acetate 100 mg, 200 mg, and 300 mg) treatments (120.77%, 119.57%, and 127.08%, respectively) versus 144.02% in the ciraparantag 15 mg (ciraparantag acetate 25 mg) x 4 dose cohort and 140.63% in the placebo group.

Figure 2: Percent of Baseline (A-B) WBCT for All Treatments

A. Percent of Baseline Full Interval



B. Percent of Baseline Partial Interval (pre-study drug to 6 hour post final dose)



*All doses expressed as ciraparantag acetate

Complete reversal (WBCT ≤120% at the 1-hour post study drug administration and remaining ≤120% for the 1 to 6-hour interval) was observed in 100% of subjects in Cohorts 1, 2, and 3 (60 mg, 120 mg, and 180 mg ciraparantag [100 mg, 200 mg, 300 mg ciraparantag acetate], respectively), 71.4% in Cohort 4 (ciraparantag 4 x 15 mg [25 mg ciraparantag acetate]) and no subject in the placebo group. Partial reversal (120% to ≤190% at the 1-hour post-study drug administration and for the 1 to 6-hour interval) was observed in 28.6% in Cohort 4 (ciraparantag 4 x 15 mg [25 mg ciraparantag acetate]) and 100% in the placebo group.

Statistical assessments comparing ciraparantag treatment versus placebo from all cohorts showed no significant differences in F1.2 percent of baseline maximal effect (E_{max}), minimum effect (E_{min}) or E_{min} from 0 to 6 hours. Decreases compared to placebo in TFPI percent of baseline E_{min} (0-6h) were observed with single dose ciraparantag 160 mg to 180 mg (ciraparantag acetate 100 mg to 300 mg). There were no significant differences between doses in the time to reach minimum effect. There were no significant changes compared to placebo in any of the secondary pharmacodynamic endpoints following ciraparantag 15 mg (ciraparantag acetate 25 mg) x 4 treatments.

Complete reversal of enoxaparin anticoagulation, measured as WBCT response, was achieved at a single-dose level of 60 mg ciraparantag (100 mg ciraparantag acetate) or higher. Administration of a single-dose of 60 mg ciraparantag (100 mg ciraparantag acetate) or above had better reversal of enoxaparin anticoagulation effect than the 15 mg ciraparantag (25 mg ciraparantag acetate) x 4 treatments.

1.2.4 PER977-02-001

PER977-02-001 was a randomized single-blind sequential group ascending ciraparantag reversal dose study in healthy volunteers who received a single dose of 60 mg edoxaban in the morning on Days 1-4 followed on Day 3 and Day 4 by a single IV dose of study drug. Five dose cohorts of 15 mg, 30 mg, 60 mg, 180 mg, and 360 mg ciraparantag (25 mg, 50 mg, 100 mg, 300 mg, and 600 mg ciraparantag acetate), respectively were planned and completed. Any subject who did not have a minimum increase in WBCT of 25% above baseline at the pre-study drug time point on Day 3 was discontinued from the study and replaced.

The pharmacokinetic results show that following 10-minute IV injection of ciraparantag on Day 3 and Day 4, serum PER977 C_{max} were typically observed at 0.25 hour (i.e., at the first postdose time point measured five minutes after the end of the 10-minute injection). Ciraparantag was then rapidly eliminated, with mean half-life ($t_{1/2}$) ranging from 0.207 to 0.336 hour (12.4 to 20.2 minutes). Clearance and volumes of distribution remained relatively constant across most doses and on both Days 3 and 4. Over the 24-fold dose range from 15 mg to 360 mg, ciraparantag C_{max} and total exposures ($AUC_{(0\text{-inf})}$ and $AUC_{(0\text{-last})}$) increased approximately proportionally to the dose increase. However, the 90% confidence interval (CI) of the slope for Day 4 $AUC_{(0\text{-last})}$ were completely above the predefined (0.9298, 1.0702) critical region; and the upper bounds of the 90% CI of the

slopes for other exposure parameters on Day 3 and Day 4 were just above the upper limit of the critical region. Dose-proportionality thus could not be statistically concluded.

Quantifiable concentrations of BAP were measured in serum as early as at the first time point, five minutes after the end of ciraparantag 10-minute injection, and C_{max} was reached between 0.42 hour to 0.92 hour after the start of injection. Elimination of BAP was slower than that of ciraparantag and, the mean $t_{1/2}$ of BAP ranged from 0.527 to 1.76 hours. Available data on Day 3 suggested an increase in $t_{1/2}$ at the 360 mg dose level compared to lower ciraparantag doses. Molar ratios of BAP/ciraparantag exposures ranged from 0.279 to 0.414 for C_{max} and from 0.538 to 2.49 for total exposures. With ciraparantag administration over the 24-fold dose range, more than proportional increases in serum BAP C_{max} and total exposures were observed. The slope estimates for C_{max} and total exposures over the 24-fold dose range were 12% to 48.3% higher than unity and the corresponding 90% CIs were completely above the predefined critical region for dose proportionality.

Urine recovery of ciraparantag dose as unchanged ciraparantag was negligible. Over the 12-hour collection interval, the mean overall fraction of dose excreted in urine for analyte over a 12-hour collection ($f_{e(0-12)}$) was 0.0377% or less of administered dose.

The metabolite BAP was excreted in the urine within the first zero to four hour collection interval in most subjects; and overall, mean $f_{e(0-12)}$ ranged from 0.886% to 17.7%. More than dose proportional amount of BAP was recovered in the urine. The mean renal clearance (CL_r) increased with escalating doses, and ranged from 1.38 L/h at the 15 mg dose level to 9.02 L/h at the 360 mg dose level. The mean CL_r at the 360 mg dose level (9.41 L/h) was comparable to the 180 mg dose level.

Administration of ciraparantag at doses from 15 mg to 360 mg 3 hours after edoxaban dosing had no apparent impact on the PK of edoxaban and D21-2393. Serum profiles and exposures of edoxaban and D21-2393 and recovery of edoxaban in the urine across all PER977 treatments were similar to the placebo group.

The pharmacodynamics results show that at pre-study drug on Day 3, mean observed WBCT after edoxaban dosing increased to similar levels in the placebo group and ciraparantag treatments. Over the one to six hours postdose interval (inclusive) after the first ciraparantag dose, complete reversal for WBCT was achieved in a higher percentage of subjects in the active treatments (82.9% for all doses) compared to the placebo group (60.0%). Across the 30 mg ciraparantag to 360 mg PER977 treatments, the rate of complete reversal at 30 mg was slightly lower (62.5%) while the rate was similar for 60 mg or higher dose levels (88.9% to 100%). Both evaluable subjects (100%) in the 15 mg PER977 treatment had partial reversal. None of the subjects in any of the placebo or active treatments had percent-of-baseline WBCT >190% at any time point (i.e., no reversal).

Results of statistical comparisons showed ciraparantag had no impact on re-anticoagulation with edoxaban as measured by WBCT at pre-study drug on Day 4 versus pre-study drug on Day 3. Over the 1 to 6 hour postdose interval (inclusive) after the second ciraparantag dose on Day 4, the rates of complete reversal were comparable to Day 3. Overall, 88.6% of the subjects in the active ciraparantag treatments and 53.3% of subjects in the placebo group had complete reversal. Across the 30 mg to 360 mg active treatments, the rate of complete reversal was slightly lower (66.7%) for 180 mg while the rate was similar for all other dose levels (87.5% to 100%). None of the subjects in any of the placebo or active treatments had percent-of-baseline WBCT >190% at any time point (i.e., no reversal).

Treatment comparisons of percent-of-baseline WBCT showed lower values compared to placebo following 60 mg to 360 mg ciraparantag on Day 3 that were statistically significant at most time points between five minutes to three hours after the end of injection (geometric least-squares [LS] ratios ranged from 86.52% to 93.70%); and following 30 mg to 360 mg ciraparantag on Day 4 at most time points between five minutes to six hours after the end of injection (geometric LS ratios ranged from 84.91% to 95.71%). On both study days, WBCT at different dose levels in the active ciraparantag treatments returned to baseline within the 0.083-hour to 0.75-hour time points. Post-baseline WBCT in placebo-treated subjects did not decrease to baseline level until the 1-hour (Day 4) to 1.5-hour (Day 3) post-study drug time point.

Secondary evaluations of ciraparantag effects on whole blood PoC-PT compared to placebo were performed for both Day 3 and Day 4. On both days, none of the subjects in the placebo or ciraparantag treatments had complete reversal. The rates of partial reversal across all ciraparantag treatments were lower than placebo on Day 3 (25.7% versus 40.0%), and higher than placebo on Day 4 (45.7% versus 26.7%). There were no statistically significant differences between ciraparantag treatments and placebo for maximum and minimum percent-of-baseline PoC-PT (maximum value [E_{max}], minimum value [E_{min}], and E_{min} over the partial six-hour interval post study drug [ciraparantag or placebo] [$E_{min(0\text{-}6h)}$]), except for E_{max} of 100 mg ciraparantag on Day 4 (LS ratio of 85.19%). A trend for time to reach minimum value achieved earlier in the ciraparantag treatments compared to placebo was observed; in which the differences were statistically significant for the time of the minimum value (tE_{min}) at 360 mg ciraparantag dose level on Day 3 (LS difference of -0.7500 h) and tE_{min} at 30 mg PER977 dose level on Day 4 (LS difference of -3.705 hours).

For other secondary endpoints, there were no statistically significant differences versus placebo in most comparisons for observed and percent-of-baseline values D-dimer, F1.2, and TFPI.

Results of exposure-response assessments showed statistically significant differences for tE_{min} achieved earlier with increasing ciraparantag C_{max} (i.e., negative slopes) on Day 3.

There were no statistically significant correlations on Day 4. Similar results were seen for BAP.

Safety analyses showed no deaths or serious AEs were reported during the study. One subject with an AE leading to study discontinuation (due to migraine) was reported

There was an increase in the number of subjects who reported at least one treatment emergent AE with an increase in the dose of ciraparantag administered

No relevant trends were observed over time in the mean and median laboratory values between active-treated cohorts and between active-treated cohorts and placebo

No notable differences were noted in pulse oximetry, ECGs, telemetry, or fecal occult blood assessments, when comparing active treatment groups or comparing active treatment groups and placebo.

In summary, PER977-02-001 concluded the following:

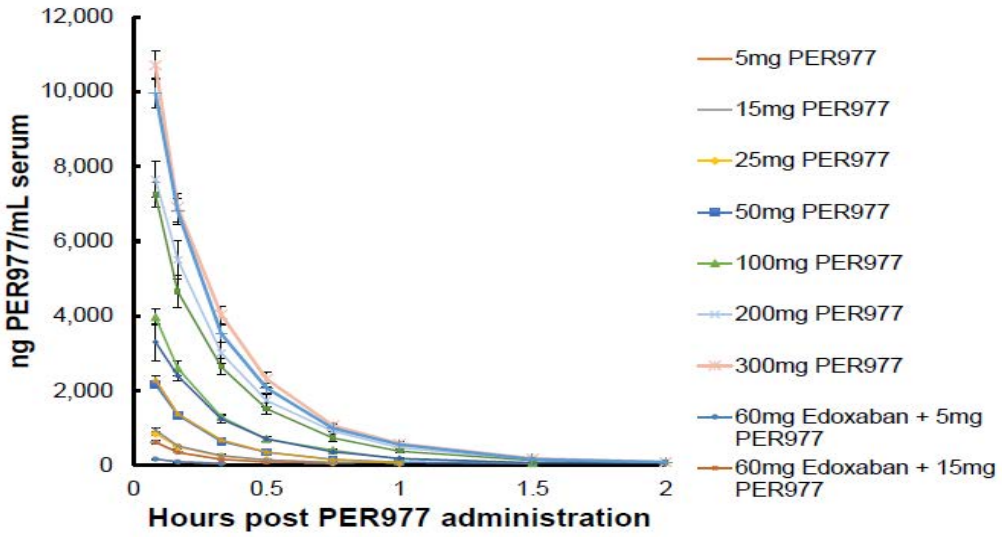
- Serum ciraparantag C_{max} and total exposures increased in an approximately proportional manner for escalating doses from 15 mg to 360 mg; with no dose dependent changes in systemic clearance and volume of distribution.
- BAP is a major metabolite of ciraparantag that exhibits elimination rate limited kinetics.
- Serum BAP C_{max} and total exposures increased more than proportionally to ciraparantag doses over the 15 mg to 360 mg range.
- Fractions of the ciraparantag dose recovered in the urine as BAP and CL_r increased with escalating doses.
- Administration of ciraparantag three hours after edoxaban dosing had no apparent impact on the PK of edoxaban and D21-2393.
- The integrated PD results suggest an anticoagulation reversal effect, as measured by WBCT, at 60 mg ciraparantag dose or above.
- Single-dose administration of ciraparantag had no impact on re-anticoagulation with edoxaban.
- There were no statistically significant differences versus placebo for any of the analytes (D-dimer, F1.2, and TFPI) measured to detect procoagulation signal.
- Escalating IV doses of ciraparantag (15 mg, 30 mg, 60 mg, 180 mg, and 360 mg) administered three hours after a 60 mg edoxaban administration were considered well tolerated in the study population.

1.2.5 Pharmacokinetics

In PER977-01-001, ciraparantag and its primary metabolite, 1,4-Bis(3-aminopropyl) piperazine (BAP), demonstrate dose-proportional response both with respect to maximal

concentration (C_{max}) and half-life ($t_{½}$). When administered alone, at the lowest dose of ciraparantag administered, 3 mg (5 mg ciraparantag acetate), the average C_{max} was approximately 172 ng/mL ciraparantag in serum and the average $t_{½}$ was approximately 12 minutes. At the highest ciraparantag dose analyzed, 180 mg (300 mg ciraparantag acetate), the average C_{max} was approximately 10704 ng/mL in serum and the average $t_{½}$ was approximately 17 minutes (Figure 3).

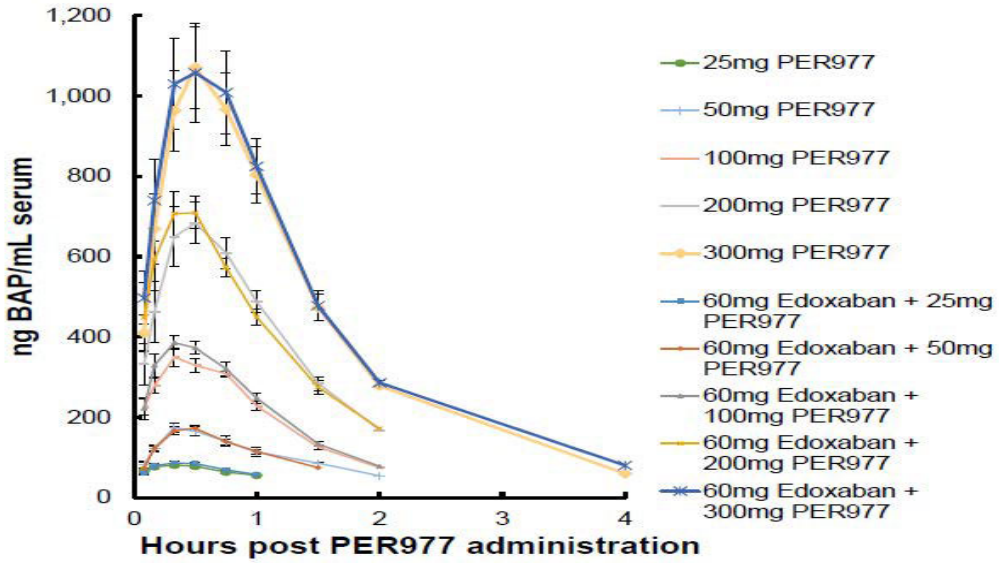
Figure 3: Ciraparantag* Serum Concentration Profile



* All doses expressed as ciraparantag acetate

BAP reaches T_{max} 20-30 minutes after ciraparantag administration, and C_{max} ranged from ~ 90 ng BAP/mL serum at a 15 mg ciraparantag (25 mg ciraparantag acetate) dose to 700 ng BAP/mL serum at a 180 mg ciraparantag (300 mg ciraparantag acetate) dose. Ciraparantag was found almost exclusively as BAP in 24-hour pooled urine samples indicating full metabolism prior to urinary excretion in keeping with the findings from the rat ^{14}C-PER977 study (Figure 4).

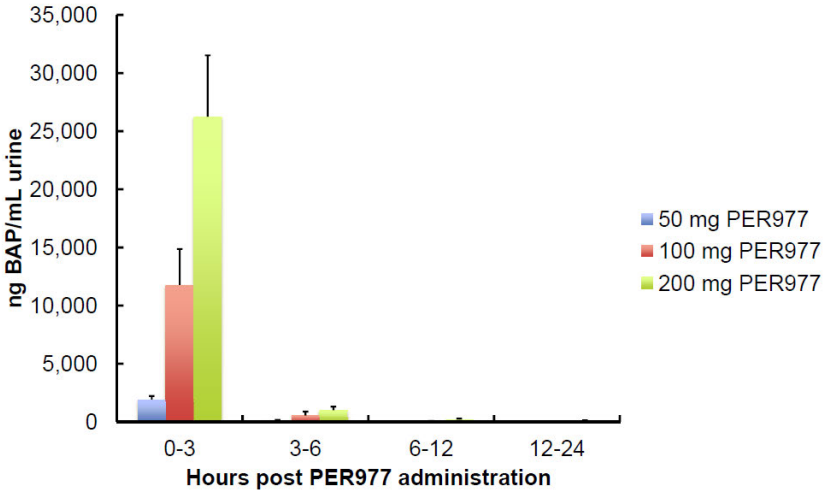
Figure 4: BAP Serum Concentration Profile*



* All doses expressed as ciraparantag acetate

Ciraparantag was found almost exclusively as BAP in pooled urine samples (Figure 5) indicating full metabolism prior to excretion as was observed in the nonclinical study.

Figure 5: Ciraparantag* Urinary Excretion Profile as BAP



* All doses expressed as ciraparantag acetate

In PER977-01-003, the full 24-hour mean profiles of WBCT generally mirrored enoxaparin mean concentration-time profiles, suggesting enoxaparin anticoagulation was well reflected by WBCT. The PK of ciraparantag and its metabolite, BAP, in serum and urinary excretion of plasma enoxaparin following administration of 15 mg ciraparantag (25 mg ciraparantag acetate) x 4 or single doses ranging from 20 mg to 180 mg

ciraparantag (100 mg to 300 mg ciraparantag acetate), or placebo (enoxaparin only; placebo group) were well characterized. Administration of ciraparantag four hours after enoxaparin did not appear to alter the PK profile of enoxaparin in plasma.

2 STUDY OBJECTIVES

The objectives of this Phase 2 study are:

- To evaluate the efficacy of ciraparantag in the reversal of anticoagulation induced by apixaban 10 mg BID (Q12) at steady state as assessed by WBCT
- To evaluate the safety and tolerability of ciraparantag 60 mg (100 mg), 120 mg (200 mg), and 30 mg (50 mg), and additional cohorts if necessary approximately administered 3 hours after 10 mg apixaban administration at steady state.
- To assess the PK characteristics of apixaban and ciraparantag and its primary metabolite

3 INVESTIGATIONAL PLAN

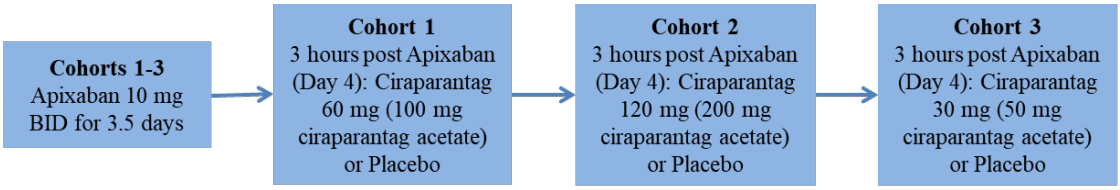
3.1 Overall Study Design and Plan

This is a randomized, single-blind, placebo-controlled assessment of the efficacy and safety of ciraparantag administered to healthy volunteers measuring clotting times using WBCT. All subjects will undergo screening up to 36 days prior to enrollment. Randomization will take place on Day 4 after administration of apixaban. Subjects will be enrolled sequentially into up to three cohorts.

If the Screening visit takes place within 3 weeks prior to check-in, the check-in procedures may be modified to exclude redundant procedures at the discretion of the Investigator. There will be a safety review after completion of treatment in one cohort and initiation of treatment in the subsequent cohort.

Subjects (n=16 per cohort) will be randomized in a 3:1 ratio to receive ciraparantag or placebo (saline for injection). Figure 6 depicts the experimental design.

Figure 6: Study Schema



Throughout the protocol, "study drug" will refer to randomized treatment with ciraparantag or placebo. The active study drug doses are expressed as active drug substance (ciraparantag).

The administered dose is based on a concentration of 6 mg/mL ciraparantag and translates to the following dose conversions:

Ciraparantag Acetate	Ciraparantag	Dose Volume
600 mg	**360 mg**	60 mL
300 mg	**180 mg**	30 mL
100 mg	**60 mg**	10 mL
50 mg	**30 mg**	5 mL
25 mg	**15 mg**	2.5 mL

All subjects will receive 10 mg apixaban for 3.5 days (twice daily Q12 on Days 1-3 and once on the morning of Day 4). On Day 4, approximately 3 hours after administering apixaban, study drug or placebo will be intravenously administered. Study drug will be administered only to those subjects who have a minimum increase in clotting time of 20% (as measured by WBCT) above Day 1 pre-apixaban baseline levels at the pre-study

drug time point on Day 4 (i.e., 2.75 hours post-apixaban). Any subject who does not have a minimum increase in clotting time of 20% above Day 1 pre-apixaban baseline levels at the pre-study drug time point on Day 4 will be discontinued from the study and replaced. At approximately 3 hours following apixaban a single IV dose of study drug (ciraparantag or placebo) will be administered.

Individual subjects may only participate in one dose cohort of this study. Any subject who discontinues prior to completion for reasons other than an AE will be replaced and the replacement subject will receive the same treatment as the original subject. Subjects who discontinue due to an AE that precedes administration of study drug may be replaced at the discretion of the Sponsor. Only those subjects who discontinue due to AEs that follow administration of study drug (ciraparantag or placebo) will not be replaced.

3.2 Dose Rationale

A total of three dosing cohorts (Cohorts 1-3) are planned. The planned doses of ciraparantag or placebo (administered as a volume equivalent of ciraparantag) have been evaluated as single and repeat IV doses from 5 mg ciraparantag acetate (3 mg ciraparantag) up to 600 mg ciraparantag acetate (360 mg ciraparantag) in previous protocols (PER977-01-001, PER977-01-002, PER977-01-003, and PER977-02-001). All doses of study drug will be administered by IV injection over a minimum of 10 minutes.

3.3 Study Duration and Dates

Expectation of the total duration of the study is approximately 3 months. Individual subject participation is approximately 51 days inclusive of screening and follow-up. Subjects enrolled will spend up to 5 nights admitted to an in-patient facility.

4 STUDY POPULATION

4.1 Screening and Enrollment

The Investigator will maintain a confidential screening log of all potential study candidates that includes limited information of the subjects (age, sex), date and outcome of screening process (e.g., enrolled in the study, reason for ineligibility, refused to participate).

The Investigator will be expected to maintain an Enrollment Log of all subjects enrolled in the study indicating their assigned study number.

The Investigator will maintain a confidential subject identification code list. This confidential list of names of all subjects allocated to study numbers upon enrolling in the study, allows the Investigator to reveal the identity of any subject when necessary.

Each subject will sign an Informed Consent Form (ICF) prior to any study assessments.

Subjects should conform to the inclusion/exclusion criteria for the duration of the study. If a subject violates an inclusion or exclusion criterion at any point during the study, he/she may be removed from the study and replaced.

4.2 Study Population

The study population will consist of healthy male and female adults, age 50-75 years (inclusive).

No formal sample size calculations were performed for this study; sixteen (16) subjects enrolled in each cohort (3:1; active:placebo) is considered an adequate number of subjects to achieve the objectives of the study.

Estimated number of subjects screened:	120
Planned number of subjects randomized/dosed:	48
Planned number of evaluable subjects:	48

4.3 Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

1. Adults age 50 to 75 years, inclusive
2. Laboratory tests (chemistry, hematology and coagulation assessments) and urinalysis performed during screening up to 36 days prior to administration of study treatment deemed not clinically significant by the principal investigator.

3. No clinically significant findings on 12-lead electrocardiogram (ECG) performed during screening
4. Body mass index (BMI) 18 to ≤ 32 kg/m^2, inclusive
5. Male subjects agree to use appropriate contraception (i.e., latex condom with spermicide) in addition to their partner using an acceptable form of contraception (e.g., diaphragm, cervical cap, intrauterine device, hormonal contraceptives, surgical sterilization or post-menopausal), when engaging in sexual activity during the course of the study. Moreover, male subjects should not donate sperm or attempt to impregnate a partner during the course of the study and for a period of 12 weeks following discharge from the study.
6. Female subjects must have negative pregnancy tests at screening and check-in AND: be surgically sterile at least 6 months prior to the first dose (with documentation of hysterectomy, bilateral oophorectomy, bilateral salpingectomy, bilateral tubal ligation/tubal occlusion); OR post-menopausal (no menstruation for a minimum of 12 months and confirmed by follicle stimulating hormone [FSH] of ≥ 40 mIU/ml and serum estradiol < 30 pg/ml); OR, if of child-bearing potential, must be using an acceptable method of contraception such as an IUD, implant or contraceptive injection, or **two** forms of the following (e.g., diaphragm, cervical cap, patch or vaginal hormonal contraceptive, condom, spermicide, or sponge) for the last three months. All females must agree to continue to use their method of birth control for the duration of the study and for a minimum of one complete menstrual cycle following discharge from the study
7. Subjects who have participated in a prior study of ciraparantag must have been discharged from the study a minimum of 1 months prior to the planned treatment.
8. Subjects must understand and agree to comply with the requirements of the study and they must be willing to sign the informed consent form indicating voluntary consent to participate in the study prior to initiation of screening or study-related activities

4.4 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study.

1. History or current evidence of clinically significant cardiac, hepatic, renal, pulmonary, endocrine, neurologic, infectious, gastrointestinal (including gallbladder disease or surgery), hematologic, or oncologic disease as determined by screening history, physical examination, laboratory test results or 12-lead ECG assessment. History or current evidence of liver function tests greater than 50% of the upper limit of normal (ULN) or renal function tests (serum creatinine) greater than 1.5 mg/dl and based on PI discretion. History or current evidence of QTc (QTcF) greater than normal (450 msec for males or 470 msec for females).
2. History of unexplained syncope

3. History of major bleeding, trauma, or surgical procedure of any type based on PI discretion
4. Vaginal delivery within six months prior to screening
5. History of peptic ulcer, gastrointestinal bleeding (including hematemesis, melena, rectal bleeding) within one year prior to screening
6. Long standing history of bleeding episodes such as epistaxis, bruising or gingival bleeding or if not long standing, within 1 month prior to screening
7. Personal or family history of clotting disorder or abnormality, excessive bleeding, joint hematoma, thrombovascular disease or any hematologic disorder involving platelets or clotting abnormalities or any condition requiring treatment with transfusions, or history of thrombocytopenia
8. Females with a history of dysfunctional uterine bleeding who have not undergone hysterectomy, including history of menorrhagia (heavy menstrual bleeding), menometrorrhagia or polymenorrhea
9. Smokers or use of tobacco and/or nicotine containing products within 3 months prior to dosing as determined by the subject's verbal history
10. Pregnant or breast-feeding
11. Males with a history of hormone therapy within 3 months prior to screening
12. Administration of any blood product or anticoagulant within 3 months prior to study entry or any non-steroidal anti-inflammatory drug or cyclooxygenase inhibitor within 2 weeks prior to dosing
13. Taking any type of chronic medication (including vitamin, nutritional and herbal supplements) for more than 14 consecutive days within the 4 weeks prior to study entry (use of hormonal contraceptives is acceptable except for oral contraceptives)
14. Positive serologic test for human immunodeficiency virus (HIV), Hepatitis C virus antibody (HCV-Ab), or Hepatitis B surface antigen (HBsAg)
15. Donation of blood or blood products within 56 days prior to screening
16. Participation in any study with an investigational compound or device within 30 days prior to signing informed consent
17. Active drug or alcohol dependence within the prior 12 months or any condition that, in the opinion of the Investigator, would interfere with adherence to study protocol
18. Allergic to apixaban

5 STUDY TREATMENT(S)

5.1 Description of Treatment(s)

The following dosage forms will be provided for this study:

- Ciraparantag for IV injection
- Placebo for IV injection
- Apixaban 5 mg tablets (commercial formulation Eliquis®, Pfizer/BMS) for oral administration

All doses of study drug (ciraparantag or placebo) will be administered by IV injection (over a minimum of 10 minutes) e.g. 60 mg ciraparantag (10 ml) will be administered at a rate of approximately 1 mL/min and 360 mg (60 ml) will be administered at a rate of approximately 6 mL/min into an indwelling catheter that is not attached to an IV solution and will not result in dilution of the study drug. The indwelling catheter will be flushed with 5.0 mL of sterile 0.9% Sodium Chloride Injection, USP before and after administration of study drug. All doses of study drug will be administered in a single-blinded-fashion.

5.2 Treatments Administered

5.2.1 Ciraparantag

The investigational drug product is a sterile, isotonic, pH neutral solution for injection containing 6 mg/mL ciraparantag (10 mg/mL ciraparantag acetate) + 6.4 mg/mL sodium chloride to be administered by IV injection (See the Ciraparantag Investigator Brochure for complete description of the chemical structure).

5.2.2 Placebo

Sterile 0.9% Sodium Chloride Injection, USP will be administered as the placebo in the same method as ciraparantag.

5.2.3 Apixaban

All doses of apixaban (trade name Eliquis®; Pfizer/BMS) will be administered in an open-label manner. The ingestion of apixaban tablets will be witnessed by clinical site personnel.

Apixaban 10 mg administered twice daily Q12 as two 5 mg oral tablets for 3.5 consecutive days is a standard, FDA approved dose and is considered safe and well-tolerated in this population.

5.3 Selection and Timing of Dose for Each Volunteer Subject

The doses of ciraparantag utilized in this study were selected based on the clinical findings in PER977-01-001.

The 10 mg dose for apixaban for 7 days is recommended for treatment of deep vein thrombosis and pulmonary embolism and is a FDA approved dose considered safe and well-tolerated in this population.

All doses of apixaban will be administered in an open-label manner. All doses of study drugs (ciraparantag or placebo) will be administered in a single-blind manner (study site personnel performing coagulation testing and subjects will be blinded).

5.4 Method of Assigning Patients to Treatment Groups

The Investigator will identify all subjects who will meet all inclusion/exclusion criteria and who will be enrolled in the study. Subjects will be enrolled in cohorts of 16 subjects each and will be sequentially assigned Randomization Numbers 1001 to 1016 prior to dosing of study drug on Day 4, after confirmation of eligibility. The next 16 such subjects will be enrolled in Cohort 2, and will be sequentially assigned Randomization Numbers 2001 to 2016. This method of assignment will continue through all three cohorts. Replacement subjects, if applicable will be assigned the same treatment, using the number of the withdrawing subject +100 (e.g. if subject 1001 withdraws, the replacement subject would be 1101).

The assignment of treatment will be based on Randomization Schedules to be generated by the CRO. Each cohort will have a different, independently generated randomization schedule.

5.5 Blinding

This is a single-blind study in which the subjects will be blinded to treatment of the study drug (ciraparantag or placebo) and the study personnel assigned to conducting coagulation testing (WBCT) must be blinded as well.

5.6 Concomitant Therapy

Use of concomitant medications (including vitamin, nutritional and herbal supplements) is prohibited as per Exclusion criteria, during screening and for the course of the study. Acetaminophen up to 1 gram/24 hours may be administered for management of AEs at the discretion of the Investigator. As needed use of over-the-counter antihistamines is permitted following screening and prior to admission on Day -1 and following discharge from the clinical site on Day 4. Use of hormonal contraceptives is acceptable except for oral contraceptives.

5.7 Meals and Study Restrictions

5.7.1 Dietary Guidelines Prior to Check-in

The purpose of the required diet is to prevent a false positive reading for the fecal blood test.

Begin at least 2 days before check-in at the clinical site for overnight visits.

When to begin diet restriction?	Do not eat and drink	What are some suggested foods that are ok to eat and drink?
At least 2 days before check-in	Any red or rare meat. Horseradish, cantaloupe, raw turnips, broccoli, cauliflower, red radishes, and parsnips. NO alcohol (beer, wine or liquor)	Pasta, rice, potato, dairy, and vegetables Non-alcoholic beverages like sparkling cider, ginger-ale, Sprite, Crystal-light with no caffeine, whole milk (cow, goat, soy)

5.7.2 Dietary Guidelines during the Study

Meals and an evening snack will be provided for each overnight stay. Subjects will be instructed on when to fast, what times to eat meals and snacks, and when water may be consumed. Identical meals will be served for each treatment. The calorie content, as well as the percent of calories from protein, carbohydrate, and fat, will be uniform for each meal during the study (i.e., breakfast uniform to breakfast, lunch uniform to lunch). Substitutions of food are not allowed. The calories from fat for the day will not exceed 30% per day.

5.7.3 Lifestyle Restrictions

During the study, subjects will be advised against using manual razors and dental flosses. Electric razors and soft toothbrushes will be allowed.

Subjects will not perform any physical activity outside of their normal living activities and will not engage in strenuous activity from screening to study completion.

Except when ECGs must be taken in supine position, subjects will remain in the semi-erect or upright position with minimal ambulation (i.e. only to and from the washroom, lounge or for study procedures) for the first 8 hours after study drug dosing on Day 4.

5.8 Treatment Compliance

All study drug will be administered by clinical site personnel by IV injection over a minimum of 10 minutes into an indwelling catheter that is not attached to an IV solution and will not result in dilution of the study drug. Following administration of the study drug, the indwelling catheter will be flushed with 5.0 mL of sterile 0.9% Sodium Chloride Injection, USP.

All doses of apixaban will be administered after meal with 240 ml of water under the supervision of clinical site personnel. The ingestion of all doses of apixaban will be witnessed by clinical site staff. A mouth and hand check of all subjects will be carried out to ensure that the tablets have been swallowed.

5.9 Dose Escalation/De-Escalation

Review of WBCT results, AEs, clinical laboratory tests, and ECG data will be conducted by a group that includes the Principal Investigator, Medical Monitor(s), and representative(s) of the Sponsor. The group will be responsible for the decision to expand a given dose cohort, escalate (or de-escalate) to a different dose from the planned dose, or stop the study. All meetings will be documented with minutes.

The goal of the study is to explore the dose range of ciraparantag that reverses the anticoagulation induced by therapeutic doses of apixaban at steady state. The study is intended to establish a dose of ciraparantag that fully reverses steady-state apixaban, to evaluate at least one dose above the reversal dose to establish a therapeutic index, and at least one partial or no effect dose.

5.10 Packaging and Labeling

5.10.1 Ciraparantag

Ciraparantag Injection will be supplied as a sterile solution for IV injection containing 6 mg/ml ciraparantag (10 mg/mL ciraparantag acetate) and supplied in 30 clear vials (5 mL each). Vials will be labeled for clinical study use including study number, contents, quantity, lot number, date of manufacture and stability retest date, and storage conditions as well as a caution statement according to 21CFR 312.6(a).

5.10.2 Apixaban

Apixaban will be provided in bottles containing 60 tablets per bottle (NDC 0003-0894-21). Bottles will be labeled for clinical study use including study number.

5.11 Storage and Accountability

Drug supplies must be stored in a secure, limited access storage area under the recommended storage conditions.

5.11.1 Ciraparantag

Ciraparantag will be stored refrigerated at 2-8°C (36-46°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 2-8°C (36-46°F) until prior to administration.

5.11.2 Placebo

Placebo solution will be provided by the CRO and stored at room temperature prior to preparation.

5.11.3 Apixaban

Following the product Prescription Information, apixaban tablets must be stored at 20-25°C (68-77°F) with excursions permitted to 15-30°C (59-86°F). Temperature measurements will be recorded.

5.12 Investigational Product Retention at Study Site

Investigational study drug will be labeled with the following statement – Caution: New Drug--Limited by Federal (or United States) law to investigational use. The Principal Investigator will maintain accurate records of receipt of all test articles, including dates of receipt. In addition, accurate records will be kept regarding when and how much of each test article is dispensed to and used by each individual subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. A Drug Dispensing Form will be provided for this purpose and will be signed by the Principal Investigator at the conclusion of the study. To satisfy regulatory requirements regarding drug accountability and destruction, following instruction from the Sponsor, the Principal Investigator will arrange for return or destruction of all used, unused, empty and partially used study drug and containers to the Sponsor for final accountability and disposal.

6 STUDY PROCEDURES

6.1 Informed Consent

The Investigator or designee will obtain written informed consent from all subjects prior to initiation of any study-related procedures as per Section 10.5.

6.2 Medical History

The Investigator or designee will obtain a complete medical history including medication and surgical history will be obtained at the screening visit. To ensure subject safety, the Investigator may ask the subject to sign a medical release form allowing him to contact the subject's doctor for more information about subject's medical history

6.3 Physical Examination

The Investigator will perform a complete physical examination at screening and abbreviated physical examination will be performed on check-in and prior to discharge.

The full physical examination will consist of the following:

- General physical well-being will be assessed by evaluation of the head, eyes, ears, nose, throat, neck, heart, chest, lungs, abdomen, extremities, neurological status (including, but not limited to, consciousness, facial symmetry, strength/sensation symmetry, gait), skin, and other conditions of note
- Measurement of height in street clothes and without shoes (to the nearest 0.5 cm) at screening only
- Measurement of weight in street clothes and without shoes (to the nearest 0.1 kg). Weight will be assessed by standard objective means (e.g., weight scale). There are no adjustments in dose if changes in weight should occur
- Body mass index is based on height and weight calculated at screening and first check-in for eligibility purposes using the following formula:

$$\text{BMI} = \frac{\text{Weight in kilograms}}{\text{Height in meters}^2}$$

The abbreviated physical examination will consist of the following:

- General appearance, heart, lungs, abdomen.
- Additional physical examinations may be conducted at any time throughout the study, if deemed necessary by the Investigator.

6.4 Vital Signs

All vital sign measurements will be taken after the subject is supine for 5 minutes.

Vital signs (including blood pressure and pulse [radial or brachial to be measured over 30 seconds if performed manually]), respiration rate, and body temperature (oral) will be measured at screening. Vital signs will be measured on Day -1, prior to administration of apixaban on the morning of Days 1-4, 30 minutes prior to study drug, at 1.5, 4, 8 and 24 hours post-study drug. Please see below for tolerance window to perform vital sign assessments:

Vital Signs Tolerance Window

Vital Sign Time Point	**Tolerance Window**
Pre-dose	-60 minutes to 0 hour
>0 hour - 4 hour	-10 minutes to +10 minutes
>4 hour - 12 hour	-20 minutes to +20 minutes
>12 hour - 24 hour	-30 minutes to +30 minutes
Study Exit/Early Termination	-30 minutes to +30 minutes

Vital signs, respiratory rate, and body temperature will be re-assessed at the discretion of the investigator if warranted by the subject's condition and/or in the following situations:

- Systolic blood pressure less than 90 mmHg or greater than 180 mmHg
- Diastolic blood pressure less than 50 mmHg or greater than 100 mmHg
- Pulse less than 40 beats per minute or greater than 110 beats per minute
- Respiratory rate less than 10 breaths per minute or greater than 30 breaths per minute
- Body temperature less than 36.1°C (97.0°F) or greater than 37.3°C (99.2°F)

An abnormal vital sign that is considered clinically significant by the Investigator will be recorded as an adverse event. Additional vital sign measurements may be conducted at any time throughout the study, if deemed necessary by the Investigator.

6.5 Stroke Assessments

Stroke assessments will be performed by PI or designee at approximately 3 hours post-apixaban dose on the morning (±1-hour window) on Day 1 to 4. PI or designee will check for stroke warning signs and physical symptoms:

Stroke warning signs:

- Sudden weakness or numbness of the face, arm or leg, especially on one side
- Sudden confusion or difficulty understanding
- Trouble speaking, walking or seeing
- Dizziness or loss of balance
- Sudden onset of severe headache

Physical symptoms:

- Facial smiling or showing of teeth on one side
- One arm does not move or drifts compared to the other on extension
- Abnormal slurred speech, improper choice of words, inability to speak or acute confusion and disorientation

6.6 Clinical Laboratory Tests

Blood and urine samples for safety laboratory tests will be collected at screening, at check-in, and prior to discharge from the clinical site. Safety laboratory tests may also be done at any time during the study at the discretion of the Investigator to monitor AEs. Subjects will be in a seated or supine position during blood collection.

6.6.1 Fecal Occult Blood Tests

Fecal occult blood tests will be done at check-in. Fecal occult blood kits will be given to all subjects at screening to provide stool samples for testing at check-in. In the event occult blood kits are not returned, a rectal exam for stool sample may be performed at the discretion of the Investigator. Occult blood test results must be negative during check-in to continue study participation. Additional fecal occult blood testing may be conducted at any time throughout the study, if deemed necessary by the Investigator.

6.6.2 Laboratory Parameters

Values for the clinical laboratory tests listed below will be determined by accredited laboratory facility(ies).

CLINICAL CHEMISTRY	**HEMATOLOGY**
The following clinical chemistry tests will be performed at screening, check-in, and discharge from the study:	*The following hematology tests will be performed at screening, check-in, and discharge from the study:*
Alanine aminotransferase (ALT)	Hematocrit
Albumin (ALB)	Hemoglobin
Aspartate aminotransferase (AST)	Platelet count
Blood urea nitrogen (BUN)	RBC
Calcium	WBC / with differential
Chloride	
CO_2	**COAGULATION**
Creatinine (CR)	*The following coagulation tests will be performed at screening, check-in, and discharge from the study:*
Direct bilirubin (DBIL)	
Glucose	
Indirect bilirubin (IBIL)	PT-PTT
Lactose dehydrogenase (LDH)	
Magnesium	**URINALYSIS**
Potassium	*The following urinalysis tests will be performed at screening, check-in, and discharge from the study:*
Sodium	
Total bilirubin (TBIL)	Appearance
Total Protein	Bilirubin
	Blood
	Color
FECAL OCCULT BLOOD TEST	Glucose
Fecal occult blood test (conducted at clinical site at check-in)	Ketones
	Microscopic examination
	pH
	Protein
PREGNANCY SCREEN** (females only)	Specific gravity
Urine pregnancy tests will be performed at screening and at discharge. Serum pregnancy test will be done at check-in on Day -1 FSH and estradiol test will be done on post-menopausal females at screening and check-in on Day -1 **the urine pregnancy tests may be performed in-clinic using CLIA-waived marketed kits.	
	OTHER TEST:
	Urine Random Creatinine test *will be performed at screening, check-in, and discharge from the study*
Saliva Alcohol Test *(to be performed at screening and at check-in using CLIA –waived marketed kits)*	**VIRAL SCREEN***** *(to be performed at screening only):*
Urine Drug Screen *(to be performed at screening and check-in using CLIA –waived marketed kits)*	HBsAg
	HCV antibody test
	HIV antibody test

6.6.3 Experimental Safety Biomarker Assessment

Two aliquots of citrated plasma (1 ml each) for experimental safety biomarker assessments (e.g. D-Dimer, F1.2 tests) will be collected at pre-apixaban (within 1 hr. prior to dosing) on Day 1, and at 2.75 and 8 hrs. post-apixaban on Day 4. Experimental safety biomarker assessment will only be performed at the discretion of the Principal Investigator.

6.7 Electrocardiograms

A resting 12-lead electrocardiogram will be performed at screening, check-in, after administration of apixaban, and prior to discharge from the clinic site. Parameters assessed will include ventricular rate (bpm), PR interval (msec), QRS duration (msec), QT interval (msec) and QTc interval (msec). Additional ECGs may be performed at the discretion of the Principal Investigator.

6.8 Dispensing Study Drug

All study drugs will be prepared by the designated pharmacy personnel at [redacted].

6.8.1 Ciraparantag

The study pharmacist or designated personnel will calculate the final volume of ciraparantag. Ciraparantag should be prepared on the day of dosing and stored at room temperature at least 1 hour before administration. The appropriate volume of Ciraparantag Injection will be withdrawn from the supplied vials.

Throughout this protocol, the active study drug doses are expressed as active drug substance (ciraparantag) (previously study drug doses were expressed as ciraparantag acetate with a content of 10 mg/mL). The administered dose is based on a concentration of 6 mg/mL ciraparantag and translates to the following dose conversions:

Ciraparantag Acetate	Ciraparantag	Dose Volume
600 mg	**360 mg**	60 mL
300 mg	**180 mg**	30 mL
100 mg	**60 mg**	10 mL
50 mg	**30 mg**	5 mL
25 mg	**15 mg**	2.5 mL

Ciraparantag will be prepared and administered by IV injection over a minimum of 10 minutes.

All ciraparantag doses must be labeled with the study number and date.

Study drug may be prepared on the day of dosing and will have an expiration of 4 hours at room temperature or will be refrigerated at 2-8°C (36-46°F) until use. All prepared solutions must be used within 24 hours. All unused drugs will be returned to the pharmacy. A record must be kept of all discarded solutions.

6.8.2 Placebo

An equivalent volume of sterile 0.9% Sodium Chloride Injection, USP will be utilized as the placebo.

All placebo doses must be labeled with the study number and date.

Placebo may be prepared on the day of dosing and will have an expiration of 4 hours at room temperature or will be refrigerated at 2-8°C (36-46°F) until use. All prepared solutions must be used within 24 hours. A record must be kept of all discarded solutions.

6.8.3 Apixaban

Apixaban will be dispensed as one tablet in a container labeled with the study number, subject number and date. All unused tablets will be returned to the pharmacy.

6.9 Efficacy Assessments

Time 0 for all PK and PD assessments will be the end of the study drug injection. Where timing for assessments coincide, PD assessment(s) should be performed first, followed by PK assessment(s), and then ECGs, and vital signs will be performed. The tolerance window to complete PK and PD draws is as follow:

PK/PD Draw Tolerance Window

Sampling Time Point	**Tolerance Window**
Pre-dose	-60 minutes to 0 hour
>0 hour - 24 hour	-10 minutes to +10 minutes

Over the course of the study, the total estimated volume of blood to be sampled from each subject for the combined PK, PD and safety evaluations is approximately 175 mL.

6.9.1 Pharmacokinetic Assessment

Blood samples for PK assessment of ciraparantag and its metabolite, and apixaban, will be analyzed using LC/MS assay methodology.

Apixaban PK time points:

A 4 mL blood sample in potassium EDTA will be collected for each PK assessment of apixaban.

Day 1: pre-apixaban (within 1 hr. prior to dosing)

Day 4: post-apixaban at 2.75 hr and post-study drug at 15, 30, 45 minutes, and 1, 3, 5, 24 hrs.

Ciraparantag and BAP PK time points:

Ciraparantag or placebo is administered 3 hrs. after the apixaban dosing on Day 4.

A 3 mL blood sample with no additive (i.e. **serum** sample) will be collected for each PK assessment of ciraparantag and its metabolite.

Day 4: pre-study drug (within 1 hr. prior to dosing of ciraparantag or placebo) and post-study drug at 15, 30, 45 minutes, and 1, 3, 5, 24 hrs.

6.9.2 Pharmacodynamic Assessment

Blood samples (2 ml) for measuring of clotting time by WBCT will be collected at the following time points:

Day 1: pre-apixaban baseline (within 1 hr. prior to dosing)

Day 4: post-apixaban at 2.75 hr and post-study drug at 15, 30, 45 minutes, and 1, 3, 5, 24 hrs. (only subjects with at least 20% increase of clotting time from the Day 1 pre-apixaban baseline will be randomized).

Triplicate WBCT will be done Day 1 pre-apixaban baseline, post-apixaban at 2.75 hrs. and post-study drug at 1 hr on Day 4.

6.10 Adverse Events Assessments

All AEs and SAEs will be captured by electronic data capture (EDC).

All AEs occurring after the subject signs the ICF up to the time of the Follow-up phone call, whether observed by the Investigator or reported by the subject, will be captured. If in the opinion of the Investigator or the sponsor, an AE meets the criteria of an SAE it is to be reported. SAEs occurring up to 30 calendar days post treatment should be reported. Any AEs and SAEs that occur after the specified reporting period should also be reported if in the opinion of the investigator, there is a reasonable possibility for a causal association with the study product. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to Informed Consent will be recorded as part of medical history. All SAEs are to be reported according to the procedures in Section 6.10.10 SAE Reporting-Procedure for Investigators. Report diagnosis as the AE or SAE term; when the diagnosis is unavailable, report signs and symptoms as individual entries of AE or SAE until the

diagnosis becomes available. For events that are serious due to hospitalization, the reason for hospitalization must be reported as the serious adverse event (diagnosis or symptom requiring hospitalization). A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Pre-planned (prior to signing the Informed Consent Form) procedure or treatment requiring hospitalization for pre-existing conditions which do not worsen in severity should not be reported as SAEs. For deaths, the underlying or immediate cause of death should always be reported as an SAE. In addition, any serious, untoward event that may occur subsequent to the reporting period that the Investigator assesses as related to study drug should also be reported and managed as an SAE.

At each visit, the Investigator will determine whether any AEs have occurred by evaluating the subject. Adverse events may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. Subjects should be questioned in a general way, without asking about the occurrence of any specific symptoms. All abnormal laboratory values must be appraised by the Investigator as to clinical significance. All abnormal laboratory values considered clinically significant by the Investigator must be recorded as an AE on the CRF, and if serious, reported as an SAE following the procedures in Section 6.10.10.

Investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved AEs including significant abnormal laboratory values at the end of study assessment, these events will be followed until resolution or until they become clinically not relevant.

6.10.1 Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study drug discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., ECG or vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Section 6.10.3 and Section 6.10.4, respectively. For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality.

6.10.2 Toxicity Management

Subject safety will be monitored closely. All clinically significant treatment-emergent AEs (TEAEs) denoted by the Investigator will be brought to the attention of the Perosphere medical monitor. All subjects experiencing a TEAE must be monitored periodically until symptoms subside or until there is a satisfactory explanation for the AE. Additionally, treatment-emergent abnormal laboratory values should be monitored

periodically until the abnormality resolves, returns to baseline levels, or is otherwise explained. At the discretion of the Investigator, assessments and/or clinic visits in addition to those scheduled for routine study conduct may be warranted to properly monitor the AE or laboratory abnormality. To ensure subject safety, the Investigator may ask the subject to sign a medical release form allowing him to contact the subject's doctor for more information about subject's medical history. All questions regarding toxicity management should be directed to the Perosphere medical monitor.

6.10.3 Adverse Event (AE)

An AE is any untoward medical occurrence in a subject 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, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A Guideline, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

It is the responsibility of Investigators, based on their knowledge and experience, to determine, those circumstances or abnormal lab findings which should be considered adverse events.

6.10.4 Serious Adverse Event (SAE)

Any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect, or
- Is an important medical event

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe (ICH E2A Guideline, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Oct 1994).

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the

definition above. Examples include allergic bronchospasm, convulsions, and blood dyscrasias or development of drug dependency or drug abuse.

6.10.5 AE Severity

The following definitions should be used to assess intensity of adverse events:

Mild: Awareness of sign or symptom, but easily tolerated, i.e., does not interfere with subject's usual function.

Moderate: Discomfort enough to cause interference with usual activity.

Severe: Incapacitating with inability to work or do usual activity, i.e., interferes significantly with subject's usual function.

Severity should be distinguished from seriousness. Severity is a measure of intensity whereas seriousness is classified by the criteria based on the regulatory definitions. An AE of severe intensity need not necessarily be classified as serious.

6.10.6 Causality Assessment

The Investigator should assess causal relationship between an AE and ciraparantag and/or apixaban (if administered) on the basis or his/her clinical judgment and the following definitions. The causality assessment should be made based on the available information and can be updated as new information becomes available.

1 = Related:

The AE follows a reasonable temporal sequence from study drug administration, and cannot be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

The AE follows a reasonable temporal sequence from study drug administration, and is a known reaction to the drug under study or its chemical group, or is predicted by known pharmacology.

2 = Not Related:

The AE does not follow a reasonable sequence from study product administration, or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

6.10.7 Action Taken Regarding the Study Drug

The following definitions will be used to describe action taken regarding study drug:

1 = Dose Not Changed: No change in study drug dosage was made.

2 = Drug Withdrawn: The study product was permanently stopped.

3 = Dose Reduced: The dosage of study product was reduced.

4 = Drug Interrupted: The study product was temporarily stopped.

5 =Dose Increased: The dosage of study product was increased.

6.10.8 Adverse Event Outcome

The following definitions will be used to describe AE outcomes:

1 = Recovered/Resolved

The subject fully recovered from the AE with no residual effect observed.

2 = Recovered/Resolved with Sequelae

The residual effects of the AE are still present and observable.

Include sequelae/residual effects.

3 = Not Recovered/Not Resolved

The AE itself is still present and observable.

4 = Fatal

5 = Unknown

6.10.9 Other Action Taken for Event

The following definitions will be used to describe other actions taken for an AE:

1 = None.

No treatment was required.

2 = Medication required.

Prescription and/or OTC medication was required to treat the adverse event.

3 = Hospitalization or prolongation of hospitalization required.

Hospitalization was required or prolonged due to the adverse event, whether or not medication was required.

4 = Other.

6.10.10 Serious Adverse Event Reporting–Procedure for Investigators

6.10.10.1 Initial Reports

Within 24 hours of becoming aware of the SAE, the Principal Investigator must contact Perosphere as notification of an SAE and report the SAE via EDC, facsimile or email to:

AMAG Pharmacovigilance
Email: [redacted]
Fax: [redacted]

SAE queries should be addressed as soon as possible.

6.10.10.2 Follow-up Reports

The Investigator will follow all SAEs until the SAE is:

- Resolved, or
- Stabilized (e.g., in the case of persistent impairment), or
- Returned to baseline, if a Baseline value is available, or
- Otherwise justified by the investigator in agreement with the Sponsor and
- All relevant data are received

If NEW information become available on a previously reported SAE, within 24 hours of awareness, the Principal Investigator will contact the sponsor with a follow-up report:

- Report the updated information on the SAE via facsimile as listed above
- For SAEs that resulted in death, provide the autopsy report, if done, via e-mail, fax, or express mail to Perosphere
- Perosphere will review the follow up SAE information and supporting documents and issue additional queries as needed

6.10.11 Notifying Regulatory Authorities, Investigators, and IRB/IEC

Perosphere will report any Suspected Unexpected Serious Adverse Event Reactions (SUSARs) for ciraparantag and apixaban to the FDA and other regulatory authorities globally under the respective Investigational New Drug (IND) and Investigational Medicinal Product Dossier (IMPD) (if applicable). Serious unexpected serious adverse reactions (SUSARs) attributed to both ciraparantag and apixaban will be submitted to both INDs. Perosphere is responsible for submission of ciraparantag and apixaban SUSARs outside of US, respectively, if applicable. Perosphere will notify participating Investigators and IRB/IEC of all SUSARs (ciraparantag and/or apixaban) occurring in this study or other ciraparantag studies.

6.10.12 Pregnancy

Pregnancy tests will be performed at screening and at visits specified in the protocol. Subjects with a positive test at screening or during the study period will be excluded from the study. Women of child-bearing potential will be instructed to practice an acceptable method of birth control for the duration of the study. However, if subject becomes pregnant during the study, the pregnancy, in and of itself, is not considered an AE unless there is suspicion that the study medication may have interfered with the effectiveness of a contraceptive medication or method.

Any pregnancy diagnosed during the study, or that the Investigator becomes aware of within 30 days after stopping study medication, must be reported by the Investigator to the Sponsor using the [redacted] Initial Pregnancy Report Form within 24 hours of awareness. The pregnancy should be followed to term by the Investigator and the outcome of all such pregnancies, i.e., spontaneous miscarriage, elective termination, normal birth, or congenital abnormality, should be reported to the Sponsor using the [redacted] Pregnancy Outcome Report Form.

All live births must be followed for a minimum of 8 weeks or to the first well-baby visit and information reported using the [redacted] Pregnancy Follow-Up Report Form. All reports of congenital abnormalities/birth defects and spontaneous abortions/miscarriages should be reported as an SAE for the study.

Elective abortion procedures, without complications, will not be considered as AEs.

6.11 Concomitant Medication Assessments

Concomitant medication is defined as any medication other than the trial product that is taken during the trial including the screening period.

Details of all medications must be recorded at trial entry. Any changes in concomitant medications must be recorded at each visit.

The information collected for each concomitant medication includes dosage, route, start date, stop date or continuing and indication. Concomitant medications will be summarized and tabulated.

6.12 Removal of Patients from the Trial or Study Drug

Any subject who discontinues from the study treatment for any reason will have their study treatment discontinuation recorded.

Subjects may be withdrawn from the study after signing informed consent for the following reasons:

- Adverse Event
- Lost to Follow-up
- Withdrawal of Consent by Subject
- Investigator decision
- Death
- Pregnancy
- Study terminated by Sponsor
- Other (any other reason)

If a subject withdraws from the study, the Investigator will complete and report the observations as thoroughly as possible up to the date of withdrawal including the date of last treatment and the reason for withdrawal.

If the subject is withdrawn due to an AE, the Investigator will follow the subject until the AE has resolved or stabilized.

All subjects who are withdrawn from the study should complete protocol specified withdrawal procedures.

6.12.1 Withdrawal Procedures

The subject may withdraw from the study at any time. Subjects who become pregnant or who develop a condition which contraindicates the use of apixaban during the course of the study will be withdrawn. The subject may be withdrawn from the study at the discretion of the Investigator or Sponsor, if judged non-compliant with study procedures or due to safety concerns. These criteria include:

- Unwillingness to continue with the study, or because of unwanted effects due to study drug
- Ingestion of interfering substances at times other than those specified in the protocol during the course of the study or,
- Intercurrent illness or concomitant medication that, in the Investigator's judgment, may interfere with the conduct of the study.
- Study drug will be administered only to those subjects who have a minimum increase in WBCT of 20% from Day 1 pre-apixaban baseline level at the pre-study drug (i.e., 2.75 hours post-apixaban) time point on Day 4. Any subject who does not have a minimum increase in WBCT of 20% from Day 1 pre-apixaban baseline level at the pre-study drug time point on Day 4 will be discontinued from the study and replaced.

Subjects who withdraw from the study prior to completion will undergo abbreviated physical exam, vital signs, ECG, and safety laboratories prior to release from the study center. An additional 2 mL blood sample will be collected for confirmatory coagulation

testing (WBCT). All subjects who discontinue from the study prior to completion will receive a telephone call as follow-up for AEs 3-7 days after discharge.

6.12.2 Subject Replacement

Individual subjects may only participate in one dose-cohort of this study. Any subject who discontinues prior to completion of the dose cohort will be replaced and the replacement subject will receive the same treatment as the original subject. Subjects who discontinue due to an AE that precedes administration of study drug may be replaced at the discretion of the Sponsor. Only those subjects who discontinue due to AEs that follow administration of study drug (ciraparantag or placebo) will not be replaced.

7 STUDY ACTIVITIES

A complete schedule of events is provided in the Synopsis.

Where timing for assessments coincide, PD assessments should be performed first, followed by PK assessment(s) as indicated, and then safety measurements.

Time 0 for PK and PD assessments and post-study drug procedures will be the end of the study drug injection.

7.1 Screening Visit (Days -36 to -1)

The following activities and/or assessments will be performed at/during Screening in all cohorts:

- Written Informed Consent
- Review of Inclusion/Exclusion criteria
- Recording of demographic data, medical/surgical history, medication history
- Vital signs, ECG, and safety laboratory tests (hematology, chemistry, coagulation and urinalysis)
- Complete physical examination
- Height and weight measurement, and BMI calculation
- Blood draw for HIV, HBsAg, HCV-Ab
- Urine pregnancy test for all female subjects
- FSH and Estradiol tests for post-menopausal female subjects
- Saliva alcohol test and urine drug screen
- Each subject will be given an occult blood kit to be returned at the check-in
- Subjects will be provided with a lifestyle and dietary guide
- Adverse events and concomitant medications will be recorded

7.2 Treatment Period (Day -1 to Day 5)

7.2.1 Check-in (Day -1) Procedures

The following activities and/or assessments will be performed on Day -1 in all subjects:

- Check-in to the clinical site
- Review of Inclusion/Exclusion criteria
- An ECG, vital signs, and safety laboratory tests (hematology, chemistry, coagulation and urinalysis)

- Weight and BMI calculation
- Saliva alcohol and urine drug screen
- Serum pregnancy tests in all female subjects
- FSH and estradiol tests for post-menopausal female subjects
- Fecal occult blood analysis
- In the event the occult blood kit is not returned, a rectal exam for stool sample may be performed at the discretion of the Investigator.
- Abbreviated physical examination
- AEs and concomitant medications will be recorded
- If the screening visit for the subject is within 3 weeks of check-in, redundant procedures (ECG, safety laboratory tests, and physical examination) may be omitted at the discretion of the PI.

7.2.2 Day 1 Procedures

The following activities and/or assessments will be performed on Day 1 in all subjects:

- Administration of 10 mg dose of apixaban BID (Q12) after meal; Maintain fast for 4 hours after the apixaban dosing; water allowed ad libitum
- An ECG
- Vital signs prior to apixaban dosing in the morning
- Blood draw for experimental safety biomarker assessment and Day 1 baseline WBCT prior to apixaban administration
- AEs and concomitant medications will be recorded
- Stroke assessment at approximately 3 hours post-apixaban dose on the morning (±1-hour window)

7.2.3 Day 2 and Day 3 Procedures

The following activities and/or assessments will be performed on Day 2 and 3 in all subjects:

- An ECG
- Vital signs prior to apixaban dosing in the morning
- Administration of 10 mg dose of apixaban BID (Q12) after meal; Maintain fast for 4 hours after the apixaban dosing; water allowed ad libitum
- AEs and concomitant medications will be recorded
- Stroke assessment at approximately 3 hours post-apixaban dose on the morning (±1-hour window)

7.2.4 Day 4 Procedures

7.2.4.1 Pre-study drug

The following activities and/or assessments will be performed on Day 4 before administration of study drug in all subjects:

- Administration of a single 10 mg dose of apixaban after breakfast; Maintain fast for 4 hours after the apixaban dosing; Water allowed ad libitum
- An ECG and vital signs
- Blood draw for PK assessment of apixaban and ciraparantag baseline at 2.75 hrs. post-apixaban
- Blood draw for WBCT measurement (triplicates post-apixaban at 2.75 hrs.)
- Blood draw for experimental safety biomarker assessment
- Randomization
- AEs and concomitant medications will be recorded
- Stroke assessment at approximately 3 hours post-apixaban dose on the morning (±1-hour window)

7.2.4.2 Study Drug Administration: Time 0

The following activities and/or assessments will be performed in the order listed on Day 4 in all subjects:

- Vital signs prior to study drug
- I.V. administration of study drug (ciraparantag or placebo)
- AEs and concomitant medications will be recorded

7.2.4.3 Post-study Drug: 15 minutes

The following activities and/or assessments will be performed on Day 4 at 15 minutes post administration of study drug in all subjects:

- Blood draw for WBCT
- Blood draw for PK samples for ciraparantag/metabolite and apixaban
- AEs and concomitant medications will be recorded
- Post-study Drug: 30 minutes

The following activities and/or assessments will be performed on Day 4 at 30 minutes post administration of study drug in all subjects:

- Blood draw for WBCT
- Blood draw for PK samples for ciraparantag/metabolite and apixaban
- AEs and concomitant medications will be recorded

7.2.4.4 Post-study Drug: 45 minutes

The following activities and/or assessments will be performed on Day 4 at 45 minutes post administration of study drug in all subjects:

- Blood draw for WBCT
- Blood draw for PK samples for ciraparantag/metabolite and apixaban
- AEs and concomitant medications will be recorded

7.2.4.5 Post-study Drug: 1 hour

The following activities and/or assessments will be performed on Day 4 at 1 hour post administration of study drug in all subjects:

- Blood draw for WBCT (triplicates)
- Blood draw for PK samples for ciraparantag/metabolite and apixaban
- AEs and concomitant medications will be recorded

7.2.4.6 Post-study Drug: 1.5 hour

- Vital signs

7.2.4.7 Post-study Drug: 3 hours

The following activities and/or assessments will be performed on Day 4 at 3 hours post administration of study drug in all subjects:

- Blood draw for WBCT
- Blood draw for PK samples for ciraparantag/metabolite and apixaban
- AEs and concomitant medications will be recorded

7.2.4.8 Post-study Drug: 4 hours

- Vital signs

7.2.4.9 Post-study Drug: 5 hours

The following activities and/or assessments will be performed on Day 4 at 5 hours post administration of study drug in all subjects:

- Blood draw for WBCT
- Blood draw for PK samples for ciraparantag/metabolite and apixaban
- Blood draw for experimental safety biomarker assessment
- AEs and concomitant medications will be recorded

7.2.4.10 Post-study Drug: 8 hours

- Vital signs

7.2.4.11 Post-study Drug: 24 hours

The following activities and/or assessments will be performed on Day 5 at 24 hours post administration of study drug in all subjects:

- Blood draw for WBCT
- Blood draw for PK samples for ciraparantag/metabolite and apixaban
- Vital signs
- AEs and concomitant medications will be recorded

7.2.5 Day 5 or Early Termination Procedures

The following activities and/or assessments will be performed on Day 5 prior to discharge in all subjects:

- An ECG and safety laboratory tests (hematology, chemistry and urinalysis)
- Vital signs (the vital sign assessment at 24 hr. post-study drug may be used for discharge)
- Urine pregnancy test for female
- AEs and concomitant medications will be recorded
- Abbreviated physical examination
- Discharge from the clinical site if coagulation parameter (WBCT) are not clinically significant. If there is an abnormal laboratory test result or AE, the subject may need to return for repeat testing.

7.3 Follow-up (Day 7-10)

The following activities and/or assessments will be performed during the follow-up in all subjects:

- Telephone follow-up
- AEs and concomitant medications will be recorded
- Discharge from the study

Subjects may be asked to return to the clinical site at the discretion of the Investigator.

8 QUALITY CONTROL AND ASSURANCE

The Investigator/investigational site will permit study-related monitoring, audits, IRB/IEC review and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

8.1 Monitoring and Inspections

The study monitor or delegate and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., case report forms, source data, and other pertinent documents).

The monitor is responsible for visiting site(s) at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to ICH/GCP and local regulations on the conduct of clinical research. The monitor is responsible for inspecting the case report forms and ensuring completeness of the study essential documents. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the case report forms.

The monitor will communicate deviations from the protocol, Standard Operating Procedures (SOPs), GCP and applicable regulations to the Investigator and the Sponsor and will ensure that appropriate action designed to prevent recurrence of the detected deviations is taken and documented.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are addressed and documented.

In accordance with ICH/GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from Perosphere. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories etc.) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH/GCP, and applicable regulatory requirements.

In the event Perosphere elects to conduct an audit onsite, the CRO will be notified in advance, will be given sufficient time to prepare, and will be given an opportunity to participate in the audit.

8.2 Data Collection

Case Report Form (CRF) completion should be kept current to enable the monitor to review the subject's status throughout the course of the study. Case Report Form will be completed, reviewed and signed off or e-signed by the Investigator.

If the study employs paper CRFs, the Investigator will sign and date the indicated places on the case report form. These signatures will indicate that the Investigator inspected or reviewed the data on the case report form, the data queries, and the site notifications, and agrees with the content.

If the study employs EDC, the Investigator e-signs according to the study data flow.

8.3 Data Management

All data recorded during the study will be available for audit against source data and for compliance with GCP and specific protocol requirements. Monitoring of the study progress and conduct will be ongoing.

The Principal Investigator will be responsible for the following:

1. Monitoring study conduct to ensure that the rights of subjects are protected;
2. Monitoring study conduct to ensure trial compliance with GCP guidelines; and
3. Monitoring accuracy, completion and verification from source documents of study data.

8.4 Study Documentation and Storage

The Investigator will maintain a Signature List of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on case report forms will be included on the Signature List.

Source documents are original documents, data, and records from which the subject's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

Case Report Form entries may be considered source data if the CRF is the site of the original recording (i.e., there is no other written or electronic record of data). In this study, CRF pages may be used as source documents.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system (Trial Master File [TMF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from Perosphere and/or applicable regulatory authorities. Essential documents include:

- Subject files containing completed CRFs, ICFs, and supporting copies of source documentation (if kept)
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IRB/IEC and Perosphere.
- Records related to the Investigational Product(s) including acknowledgment of receipt at site, accountability records and final reconciliation and applicable correspondence
- In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

8.5 Record Keeping

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study product, regulatory documents (e.g., protocol and amendments, IRB/EC correspondence and approvals, approved and signed informed consent forms, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other sponsor correspondence pertaining to the study must be kept in appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records will be retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records Perosphere must be notified in writing and be given the opportunity to further store such records.

8.6 Document Retention

All essential documentation will be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have lapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the Investigator/institution as to when these documents no longer need to be retained.

No study document should be destroyed without prior written agreement between Perosphere and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify Perosphere in writing of the new responsible person and/or the new location.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

All data collected will be presented in data listings. Data from subjects excluded from an analysis set will be presented in the data listings, but not included in the calculation of summary statistics. For categorical variables, frequencies, and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum). Data will be tabulated by treatment, across active treatment groups when applicable, with all placebo subjects pooled into a single group.

All evaluable data from subjects in the analysis sets will be included in the analyses. No adjustment or imputation will be utilized for missing values or for subjects who withdraw prior to completing the study, neither will analyses be restricted to subjects with complete data.

Baseline values will be defined as the last assessment prior to investigational product administration and per period if applicable.

Details of all statistical analyses will be specified in a separate statistical analysis plan (SAP) that will be finalized prior to database lock.

9.2 Determination of Sample Size

The study population will consist of healthy male and female adults, age 50-75 years (inclusive).

No formal sample size calculations were performed for this study; sixteen (16) subjects enrolled in each cohort (3:1; active: placebo) is considered an adequate number of subjects to achieve the objectives of the study.

Estimated number of subjects screened:	120
Planned number of subjects randomized/dosed:	48
Planned number of evaluable subjects:	48

9.3 Analysis Populations

The safety analysis set will include all subjects who receive at least 1 administration of investigational product. This set will be used for all safety, demographic, subject and disposition summaries.

The PD analysis set will include all subjects who receive at least 1 administration of investigational product, and provide at least one on-treatment WBCT measurement without protocol deviations with potential to affect these measurements. This set will be used for all PD analyses.

The PK analysis set will include all subjects who receive at least 1 administration of study drug, and provide sufficient data to estimate at least one PK parameter without protocol deviations with potential to affect these measurements. This set will be used for all PK analyses.

9.4 Pharmacokinetics of PER977 and Metabolite (BAP)

PER977 and BAP serum concentration values will be summarized in terms of arithmetic means, standard deviations, and geometric means for each time point. The PK parameters will be computed using WinNonlin (Version 6.3, Princeton, NJ) or other appropriate software. The relationship between each of these PK parameters and dosage will be evaluated and summarized (Table 3).

Table 3 Parameters for Serum PER977 and BAP

Parameter	Units	Description
C_{max}	ng/mL	Maximum concentration in the sampled matrix, obtained directly from the observed concentration versus time data
C_{24}	ng/mL	Observed quantifiable analyte concentration in the sampled matrix at the 24-hour time point
C_{last}	ng/mL	Last observed quantifiable analyte concentration in the sampled matrix
t_{last}	h	Time of C_{last}, obtained directly from the observed concentration versus time data
t_{max}	h	Time of C_{max}, obtained directly from the observed concentration versus time data
$AUC_{(0\text{-}last)}$	ng·h/mL	The area under the concentration-time curve, from time zero to the last quantifiable concentration (C_{last})
$AUC_{(0\text{-}inf)}$	ng·h/mL	Area under the concentration-time curve in the sampled matrix from zero (predose) extrapolated to infinite time by addition of the last quantifiable concentration divided by the elimination rate constant: $AUC_{(0\text{-}last)} + C_{last}/\lambda_z$
λ_z	1/h	Apparent terminal rate constant
$t_{1/2}$	h	Apparent terminal half-life, determined as $\ln(2)/\lambda_z$
CL	L/h	Systemic clearance after IV dosing, calculated for PER977 only
V_z	L	Volume of distribution after IV dosing, calculated for PER977 only
V_{ss}	L	Steady-state volume of distribution after IV dosing, calculated for PER977 only
MR_{Cmax}		Metabolite to parent (BAP/PER977) ratio of C_{max}
$MR_{AUC(0\text{-}last)}$		Metabolite to parent (BAP/PER977) ratio of $AUC_{(0\text{-}last)}$
$MR_{AUC(0\text{-}inf)}$		Metabolite to parent (BAP/PER977) ratio of $AUC_{(0\text{-}inf)}$

Supporting Pharmacokinetic Parameters

The following PK parameters for PER977 and its metabolite, BAP, will be calculated for diagnostic purposes and listed, but will not be summarized.

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

9.5 Plasma Apixaban Pharmacokinetics

Blood samples for determination of apixaban plasma concentrations will be obtained at specified times before and up to 24 hours following dose administration of apixaban. PK parameters will include C_{max}, T_{max}, $AUC_{(0\text{-last})}$, $t_{½}$, Kel, CL/F and Vz/F, if data allow.

9.6 Dose Proportionality

The dose proportionality of exposure PK parameters for PER977 and BAP ($AUC_{(0\text{-inf})}$, $AUC_{(0\text{-last})}$, and C_{max}), over the administered dose range will be investigated using the following power model:

log (PK parameter) = a + b * log (dose)
where ‘a’ is the intercept and ‘b’ is the slope.

Dose proportionality will be assessed graphically and statistically using the above power model approach with the logarithm of PK parameters as the dependent variables and the logarithm of the dose as the independent variable for subjects who receive one dose at a given dose interval. The intercept (a) and the slope (b) together with their 90% CI will be estimated and presented for each PK parameter. Parameters ‘a’ and ‘b’ will be estimated using an ordinary least-squares approach or the equivalent. Dose proportionality will be declared if the 90% CI for the slope parameter ‘b’ lies entirely within the critical region (0.80, 1.25) using the maximal dose ratio I = 3 (highest dose/lowest dose), a lower equivalence limit of 0.80, and an upper equivalence limit of 1.25.

Additionally, the geometric means for the primary PK parameters between adjacent dose levels will be compared using an analysis of covariance (ANCOVA) model including dose, gender and weight as fixed effects for subjects who receive one administration at a given dose interval. Geometric mean ratios for adjacent administrations (higher

dose/lower dose) and corresponding 90% CI will be presented. PER977 and BAP exposure parameters (C_{max}, $AUC_{(0\text{-inf})}$, and $AUC_{(0\text{-last})}$) will be plotted versus dose on linear and log-log scales for subjects who receive one administration at a given dose level using a scatterplot with individual exposures, regression line and corresponding confidence bands.

9.7 Pharmacodynamic Analyses

The contract research organization's ([redacted]) SOPs and Work Instructions will be used as the default methodology if not otherwise specified. All PD computations will be performed using Phoenix® WinNonlin® 6.3, or SAS® Version 9.2 (SAS Institute, Inc., Cary, North Carolina). Graphics will be prepared with SAS® Version 9.2 or SigmaPlot® 12.5. Actual times will be used in the calculation of PD parameters.

The PD endpoint will be WBCT. The WBCT will be summarized at observed time points and as change from baseline using descriptive statistics and graphical presentations.

Data handling for PD measurements below the limit of quantitation (BLQ) will be specified in the SAP. In the actual analysis, BLQ values will be set to the lower limit of quantitation (LLOQ) for PD data summaries and calculations.

Change-from-baseline and percent-of-baseline will be calculated for all PD endpoints. Baseline for all PD endpoints will be defined as the pre-apixaban sample (approximately four hours before PER977 or placebo administration on Day 3).

The anticoagulant effect of apixaban will be evaluated by comparing WBCT measured at pre-PER977 (about three hours post-apixaban on the morning of Day 4) versus baseline (pre-apixaban on the morning of Day 1). For the purposes of the PD analyses, subjects with percent-of-baseline WBCT at pre-PER977 <120% (i.e., <20% increase) will be considered as apixaban non-responders and will be excluded from all PD summaries and assessments.

Listings of individual PD variable collection times, as well as derived sampling time deviations (where applicable), will be provided.

Individual observed and change from baseline values at scheduled time points will be summarized by treatment and listed for each subject. In addition, the nature of reversal of anticoagulation (no effect, partial reversal, complete or complete and sustained) based on the definition of reversal of anticoagulation below using WBCT will be summarized by treatment and listed for each subject.

9.8 Analysis of the Primary PD Endpoint (WBCT)

Definition of Reversal of Anticoagulation

- Complete reversal is achieved for a treatment group or for a subject if the mean WBCT is ≤ 110% of baseline at any post-baseline time point up to and including 1 hour following test article administration. Complete reversal is achieved if WBCT is <=110% of baseline at any post-baseline time point up to and including 1 hour following test article administration
- Complete and sustained reversal of anti-coagulation is achieved for a treatment group if the mean WBCT is ≤ 115% of baseline at all time points between 1 and 5 hours (inclusive) following test article administration. Complete and sustained reversal of anti-coagulation is achieved for a subject if WBCT is ≤ 115% of baseline at all time points between 1 and 5 hours (inclusive) following test article administration

Statistically Significant Complete Reversal

- Statistically significant complete reversal, relative to mean placebo WBCT, is defined as $p< 0.05$, (one tailed) from the comparison of means between treatment and placebo at 15, 30, 45 minutes or 1 hour post study drug administration as measured by one-way Analysis of Variance at study completion. Distribution diagnostics will be performed to assure assumptions associated with using ANOVA are met. Analysis of Means (ANOM) methods will be used to compare means and variances across groups. These methods will be appropriate to test if any of the group means are statistically different from the overall mean or if the group standard deviations are statistically different from the root mean square error (RMSE). Tukey HSD multiple comparison procedure will be used to test for all pairwise differences among the means (Tukey 1953, Kramer 1956). This test is an exact alpha-level test if the sample sizes are the same, and conservative if the sample sizes are different (Hayter 1984).

9.9 Pharmacodynamic Parameters

Pharmacodynamic parameters will be calculated for observed and percent-of-baseline values using actual times relative to the start of injection of first study drug (PER977 or placebo) dose using Phoenix® WinNonlin® (version 6.3 or higher version) or SAS® Version 9.2 (SAS Institute, Inc., Cary, North Carolina). All PD parameters will be derived over the time window from the first study drug administration (zero hour) to the last collection (i.e., 24 hours after the final administration of the study drug).

The following PD parameters will be determined for the endpoint WBCT.

- E_{min}: minimum value over the two minute to 24 hour interval
- tE_{min}: time of E_{min}
- $E_{min(0-6h)}$: minimum value over the two minute to six hour interval post-final dose
- $tE_{min(0-6h)}$: time of $E_{min(0-6h)}$
- E_{max}: maximum value over the two minute to 24 hour interval
- tE_{max}: time of E_{max}
- ΔE_{max}: maximum value minus the baseline value (observed only)

9.10 Demographics and Baseline Characteristics

Subject disposition, demographics, and baseline characteristics will be listed and summarized. Screening assessments and concomitant mediations used during study conduct will be listed.

9.11 Safety Endpoints

Individual vital signs, ECG parameters, and clinical laboratory data will be listed and tabulated with descriptive statistics. For the laboratory safety data, out of range values will be tabulated in shift tables. Abnormal and clinically noteworthy ECGs will be tabulated.

Treatment-emergent AEs will be tabulated by MedDRA system organ class and preferred term, and further by severity and relatedness to study drug. SAEs and adverse events that lead to discontinuation will be listed.

Physical examination results will be listed. New onset abnormalities after dosing will be recorded as adverse events.

9.12 Interim Analysis

No formal interim analyses are planned.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

10.1.1 Sponsor

Perosphere Inc., a wholly-owned subsidiary of AMAG Pharmaceutical

[redacted]

Perosphere Clinical Study Leader

[redacted]

10.1.2 Clinical Research Organization

[redacted]

Clinical Project Manager

[redacted]

Principal Investigator

[redacted]

Sub-Investigator

[redacted]

[redacted]

10.1.3 Clinical Study Drug Supplies

10.1.4 Drug Safety

Perosphere will be responsible for the pharmacovigilance of this study drug and timely reporting to appropriate regulatory agencies. Any AEs and SAEs occurring in the study will be evaluated and collected by [redacted] and documented in the source documents. Dose escalation decisions in the study will be collectively made by the Principal Investigator, Medical Monitor, and Sponsor.

10.1.5 Pharmacokinetics

Apixaban and ciraparantag samples will be shipped to:

10.2 Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be communicated to the Investigator by Perosphere. All protocol amendments will undergo the same review and approval process as the original protocol. A protocol amendment may be implemented after it has been approved by the IRB/EC and submitted to the FDA (and other health authorities as required), unless immediate implementation of the change is necessary for subject safety. In this case, the situation must be documented and reported to the IRB/EC within five working days. The sponsor will assure the timely submission of amendments to regulatory authorities.

10.3 Institutional Review Board Approval

The study and any amendments will be reviewed by an IRB/IEC prior to implementation. All IRB/IEC reviews will be conducted in accordance with GCP and copies of all communication will be maintained in the TMF.

10.4 Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the ICH consolidated Guideline E6 for GCP (CPMP/ICH/135/95), and applicable regulatory requirement(s) and FDA GCP Regulations: Code of Federal Regulations (CFR) Title 21, parts 11, 50, 54, 56 and 312 as appropriate

10.5 Patient Information and Consent

Before a subject's participation in the study, it is the Investigator or designee's responsibility to obtain freely given consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any study drugs are administered. The written ICF must be prepared in the local language(s) of the potential subject population.

In obtaining and documenting informed consent, the Investigator or designee must comply with the applicable regulatory requirements, and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. The consent form and any revision(s) must be approved by the IRB/IEC prior to being provided to potential subjects.

The subject's written informed consent must be obtained prior to his/her participation in the study, and must be documented in the subject's medical records, as required by 21 CFR Part 312.62. The ICF should be signed and personally dated by the subject, and by the person who conducted the informed consent discussion (not necessarily the Investigator). The original signed ICF must be retained in accordance with institutional policy, and a copy of the signed consent form must be provided to the subject or legal representative. The date and time (if applicable) that informed consent was given must be recorded on the CRF.

If the subject cannot read, then according to ICH/GCP Guideline, Section 4.8.9, an impartial witness should be present during the entire informed consent discussion. This witness should sign the ICF after the subject or the legally acceptable representative has orally consented to the subject's participation and, if possible, signed the ICF. By signing the ICF, the witness attests that the information in the ICF and any other written information was adequately explained to and apparently understood by the subject or the legally acceptable representative and that informed consent was freely given by the subject or the legally acceptable representative.

Additional consent is required for the Health Insurance Portability and Accountability Act (HIPAA).

10.6 Patient Confidentiality

The Investigators, the Clinical Research Organization (CRO) and the Sponsor (Perosphere) will preserve the confidentiality of all subjects taking part in the study, in accordance with GCP and local regulations.

The Investigator must ensure that the subject's anonymity is maintained. On the CRFs or other documents submitted by the CRO or Sponsor subjects should be identified by a unique subject identifier as defined by the sponsor. Documents that are not for submission to other entities (e.g., signed ICFs) should be kept in strict confidence by the Investigator.

In compliance with US Federal regulations and ICH/GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study-related procedures and data. The Investigator is obligated to inform the subject that his/her study-related records will be reviewed by the above named representatives without violating the confidentiality of the subject.

10.7 Regulatory Compliance

The study protocol, subject information and ICF, the Investigator Brochure, any subject diary card or written instructions to be given to the subject, available safety information, subject recruitment procedures (e.g., advertisements), information about payments and compensation available to the subjects and documentation evidencing the Investigator's qualifications should be submitted to the IRB/IEC for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Changes in the conduct of the study or planned analysis will be documented in a protocol amendment and/or the SAP.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC and/or Sponsor for all subsequent protocol amendments and changes to the informed consent document or changes of the investigational site, facilities or personnel. The Investigator should notify the IRB/IEC of deviations from the protocol or SAEs occurring at the site and other AE reports received from the CRO, in accordance with local procedures.

As required by local regulations, the Sponsor's local Regulatory Affairs group will insure all legal aspects are provided, and approval of the appropriate regulatory bodies obtained, prior to study initiation, and that implementation of changes to the initial protocol and other relevant study documents happen only after the appropriate notification of or approval by the relevant regulatory bodies.

10.8 Case Report Forms and Study Records

Study data will be recorded using electronic data capture (EDC).

10.9 Protocol Violations/Deviations

The Investigator should conduct the study in compliance with the protocol agreed to by Perosphere and, if required, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC.

A deviation to any protocol procedure or waiver to any stated criteria will not be allowed in this study except where necessary to eliminate immediate hazard(s) to the subject. Perosphere must be notified of all intended or unintended deviations to the protocol (e.g., inclusion/exclusion criteria, dosing, missed study visits) on an expedited basis.

The Investigator, or person designated by the Investigator, should document and explain any deviation from the approved protocol.

If a subject was ineligible or received the incorrect dose or investigational treatment, and had at least one administration of investigational product, data should be collected for safety purposes.

The Investigator should notify the IRB/IEC of deviations from the protocol in accordance with local procedures.

10.10 Financial Disclosure

Prior to starting the study, the Principal Investigator and/or institution will sign a clinical study agreement with Perosphere. This agreement will include financial information agreed upon by the parties and full financial disclosure (if applicable) and conflict of interest on the part of the clinical investigator, sub-investigator, their spouses and dependent children.

10.11 Publication and Disclosure Policy

A study site may not publish results of a study without the written permission of Perosphere and provided that Perosphere has had the opportunity to review and approve the study site's proposed publication prior to its being submitted.

10.12 Reimbursement, Indemnity, and Insurance

Reimbursement, indemnity and insurance shall be addressed in a separate agreement on terms agreed upon by the parties.

11 REFERENCE LIST

Ansell J, Bakhru SH, Laulicht BE, et al. Use of PER977 to Reverse the Anticoagulant Effect of Edoxaban. New Eng J Med. 2014, 371:2141-2142. Epub. November 5. DOI:10.1056/NEJMc1411800

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Safety Alerts for Human Medical Products. Pradaxa (dabigatran etexilate mesylate): Drug Safety Communication - Safety Review of Post-Market Reports of Serious Bleeding Events. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm282820.htm?source=govdelivery

Appendix 1 Sponsor and Investigator Signatures

Study Title:	Phase 2 Placebo-Controlled, Single-Site, Single-Blind Study of Apixaban Reversal by Ciraparantag as Measured by WBCT
Study Number:	PER977-02-011
Final Date:	02May2019

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed: [redacted] Date: [redacted]

[redacted] D.
Vice President, Clinical Development
AMAG Pharmaceutical
[redacted]

Investigator's Signature

Study Title: Phase 2 Placebo-Controlled, Single-Site, Single-Blind Study of Apixaban Reversal by Ciraparantag as Measured by WBCT

Study Number: PER977-02-011

Final Date: 02May2019

I have fully discussed the objectives of this study and the contents of this protocol with the Sponsor's (Perosphere, Inc ["Perosphere"]) representative.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorization from the CRO, the study sponsor, Perosphere. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Conference on Harmonization guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

I agree to make available to Perosphere personnel, their representatives and relevant regulatory authorities, my subjects' study records in order to verify the data that I have entered into the case report forms. I am aware of my responsibilities as a Principal Investigator as provided by Perosphere Inc.

I understand that Perosphere may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to Perosphere.

Signed:_____ Date:_____

[redacted]
Principal Investigator
[redacted]