CLINICAL STUDY PROTOCOL: PB2452-PT-CL-0002

Part A: A Phase 2A, Randomized, Double-blind, Placebo-controlled, Single Dose, Sequential Group Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PB2452 with Ticagrelor Pretreatment in Older and Elderly Subjects

Version Number: 2 Part A

Study Drug Name: PB2452

Phase 2A IND #: 125267

Sponsor: PhaseBio Pharmaceuticals Inc.
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SIGNATURE PAGE

STUDY TITLE: Part A: A Phase 2A, Randomized, Double-blind, Placebo-controlled, Single Dose, Sequential Group Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PB2452 with Ticagrelor Pretreatment in Older and Elderly Subjects

Study: PB2452-PT-CL-0002

Development Phase: 2A

I have read this protocol and agree that it contains all the necessary information required to conduct the clinical trial in compliance with applicable regulations and Good Clinical Practices (GCP) standards

Chief Medical Officer, Medical Monitor: John Lee, MD, PhD

Signature: _____ *Date:* 7-25-2019

Biostatistician: Sherry Xu, PhD

Signature: _____ *Date:* 7-25-2019

Preclinical and Assay Development: Susan Arnold, PhD

Signature: _____ *Date:* 25 JUL 19

Quality Assurance/ Regulatory Affairs: Lauren Richardson

Signature: _____ *Date:* 25 Jul 19

Clinical Operations: Susan Maloney

Signature: _____ *Date:* 25 JUL 2019

AGREEMENT OF INVESTIGATOR

STUDY TITLE: Part A: A Phase 2A, Randomized, Double-blind, Placebo-controlled, Single Dose, Sequential Group Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PB2452 with Ticagrelor Pretreatment in Older and Elderly Subjects

By signing the Agreement of Investigator Form, I the Principal Investigator agree to:

1. Conduct the study in accordance with the protocol and as subsequently amended by the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects;
2. Conduct the study in accordance with applicable federal, state and local laws and regulations, and in accordance with Good Clinical Practice (GCP) standards;
3. Personally, conduct or supervise the study;
4. Ensure that all associates, colleagues and employees assisting in the conduct of the study are adequately trained on the requirements of the protocol and informed about their obligations related to the conduct of the clinical study;
5. Delegate only those study tasks to my associates who have appropriate training and experience and provide documentation on training and the tasks to be delegated in the study file;
6. Ensure the investigational drug product is dispensed only to individuals who have signed consent, are enrolled in the referenced clinical study, and in accordance with the protocol;
7. Ensure the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in 21 CFR, § 50 and 56;
8. Report to the Sponsor (or designee) any AEs that occur in the course of the study, in accordance with 21 CFR § 312.64;
9. Maintain adequate and accurate records in accordance with 21 CFR § 312.62 and to make those records available for inspection with the Sponsor (or designee) or other applicable regulatory authorities;
10. Ensure that an Institutional Review Board (IRB), responsible for initial and continuing review and approval of the clinical study, complies with the requirements of 21 CFR §56;
11. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports);
12. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects;
13. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in 21 CFR § 312.

Principal Investigator Name: _____ Site ID: _____

Signature/Date: _____

PROTOCOL SYNOPSIS

PROTOCOL NO.: PB2452-PT-CL-0002

TITLE: Part A: A Phase 2A, Randomized, Double-blind, Placebo-controlled Single Dose, Sequential Group Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of PB2452 with Ticagrelor Pretreatment in Older and Elderly Subjects

STUDY PHASE: 2A

STUDY SITE: 1 clinical site in the United States: PPD Phase 1 Clinic, 7551 Metro Center Drive, Suite 200, Austin, Texas 78744

INDICATION: Reversal of ticagrelor anti-platelet activity

DURATION OF STUDY: The estimated duration of the study for each subject, excluding Screening, is approximately 35 days.

OBJECTIVES:

Primary:

- To evaluate the safety and tolerability of intravenous (IV) doses of PB2452 vs matching placebo with oral ticagrelor plus acetylsalicylic acid (ASA) pretreatment in older and elderly subjects
- To assess the efficacy/pharmacodynamics (PD) of intravenous (IV) doses of PB2452 vs matching placebo in reversing ticagrelor antiplatelet activity by measuring $P2Y_{12}$ reaction units (PRU) with VerifyNow® $P2Y_{12}$ assay in older and elderly subjects

Secondary:

- To determine the pharmacokinetics (PK) of PB2452 in the presence of ticagrelor
- To determine the PK of ticagrelor and the ticagrelor active metabolite AR-C124910XX (TAM) in the presence of PB2452
- To evaluate the effect of PB2452 on ticagrelor antiplatelet activity by measuring platelet aggregation with light transmittance aggregometry (LTA) and platelet reactivity index (PRI) with vasodilator-stimulated phosphoprotein (VASP) assay by enzyme-linked immunosorbent assay (ELISA)
- To evaluate the immunogenicity potential of PB2452

Exploratory:

- To evaluate the effect of PB2452 on the PK profile of unbound ticagrelor and unbound TAM plasma concentrations
- To investigate the effect of PB2452 vs matching placebo on circulating biomarkers of platelet activation, such as P-selectin, in subjects pretreated with ticagrelor + ASA
- To examine the correlation between estimated creatinine clearance (CrCl) and the PK of ticagrelor and TAM.

STUDY DESIGN AND METHODOLOGY:

This is Part A of a two-part Phase 2A, randomized, double-blind, placebo-controlled, single dose, sequential group study to evaluate the safety, tolerability, PK, and PD of PB2452 vs matching placebo. Part A investigates various dose levels and regimens of PB2452 administered intravenously to older (ages 50 to 64 years) and elderly (ages 65 to 80 years) male and female subjects pretreated with ticagrelor + aspirin (ASA) as part of dual antiplatelet therapy. Part B investigates various dose levels and regimens of PB2452 administered to healthy male and female subjects (ages 18-50) pretreated with a high dose of ticagrelor alone (180 mg twice daily (BID)). Part B is described in a separate protocol document.

In Part A described herein, up to 5 dose levels and/or administration regimens will be evaluated in up to 5 cohorts. Each cohort will include 8 to 12 subjects randomized in a 3:1 ratio (PB2452:placebo). All references to study drug within the content of the protocol apply to PB2452 or matching placebo.

This initial cohort (Cohort 1) will include approximately 8 subjects ages 50 to 80 years pretreated with ASA + ticagrelor who will be randomized to 18 grams (g) of PB2452 or matching placebo administered as an initial 6 g bolus infused over 10 minutes, followed by 12 g infused over the next 15 hours and 50 minutes to complete a 16 hour regimen. This initial regimen was shown to be safe and well tolerated in healthy young adults (18 to 50 years) in a prior Phase 1 study and provided immediate and sustained reversal of the antiplatelet effects of ticagrelor.

Following completion of Cohort 1, subsequent cohort(s) may test the same, higher or lower dose levels, and/or different infusion regimens of PB2452 or matching placebo in the same population as in Cohort 1, or in different populations such as elderly subjects (65 to 80 years old) as determined by the Sponsor after examination of available PD and safety data from the prior cohort(s). A written Dosing Memo provided by the Sponsor to the clinical site will describe details of the dosing regimen, cohort population, cohort size, sampling schedules and other cohort-specific study activities prior to initiation of each cohort. The maximum total dose of PB2452 administered to any subject will not exceed 30g. Duration of study drug infusions will not exceed 48 hours. The maximum administration rate of PB2452 will not exceed 18g over 30 minutes.

A Safety Review Committee (SRC) will review all available safety data from ongoing or completed cohorts and will document their review and assessment in written SRC minutes prior to initiation of a subsequent cohort. Dose escalation may occur only if the SRC affirms the dose and regimen from the previously completed cohorts were safe and well tolerated and no dose-limiting toxicities (DLTs) were observed.

The study will consist of a Screening period (Days –45 to –4), a Check-in day (Day -3) and Pretreatment Period, an on-site Randomization/Treatment day (Day 1), 3 days on-site for treatment and safety monitoring, a Follow-up Visit (Day 7), and a Final Follow-up visit (Day 28 [±2 days]). Seven days prior to Randomization (Day -7), subjects will be administered ASA 81 mg orally once daily (QD) until the final dose on the morning of Day 1 before receiving study drug. A ticagrelor 180 mg oral loading dose will be administered on the morning of Day -2 followed by 90 mg every 12 hours until the 5th dose has been administered on the morning of Day 1. After completion of Cohort 1, the Sponsor may choose to have a 6th dose of ticagrelor administered 24 hours after the initiation of study drug in a subsequent cohort.

Subjects will check in to the clinical site (PPD) on Day -3. In the morning on Day -2, subjects will begin pretreatment with ticagrelor as described in the preceding paragraph. On Day 1, subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized in a ratio 3:1 (PB2452:placebo), to receive an IV dose of PB2452 or placebo 2 hours following the 5th ticagrelor dose. Subjects may be discharged from the clinical site between Days 3 and 7 inclusive and will return for a Follow-up visit on Day 7, if already discharged, and on Day 28 (±2 days).

Serum and plasma sampling times for PB2452, ticagrelor, and TAM PK and PD assessments will be described in a detailed Dosing Memo for each cohort. Hour 0 will be the time for initiation of study drug infusion (2 hours following administration of the 5th ticagrelor dose). PK and PD time points for subsequent cohorts may be adjusted as needed based on available PK, PD, and safety data from prior cohorts. In any cohort subsequent to Cohort 1, there will be no more than 6 additional sampling time points. The written Dosing Memo provided by the Sponsor prior to initiation of each cohort will include the following instructions:

- Number of subjects to be randomized
- Total PB2452 dose and administration regimen

- Whether or not a 6th ticagrelor dose will be administered 24 hours after the 5th ticagrelor dose
- The PK and PD sampling schedule
- Safety electrocardiogram (ECG) schedule
- Biomarkers

Safety and tolerability will be carefully monitored throughout the study. Immunogenicity samples will be collected from all subjects at Baseline and at Days 7 and 28 (±2 days) following administration of study drug.

Dose Escalation

An SRC will be formed to conduct a blinded review of all safety and tolerability data (e.g., clinical laboratory test results, adverse events [AEs], ECGs, Holter monitoring report, vital signs) after each cohort- prior to initiation of a subsequent cohort. Escalation to a higher total dose of PB2452 will occur only if the SRC affirms the safety, tolerability, and absence of dose limiting toxicity (DLTs) in the preceding cohort(s).

The SRC will be minimally composed of the on-site PPD investigator/medical monitor, PhaseBio medical monitor, and PhaseBio clinical operations lead. Changes to the administration regimen (rate and duration) without escalation of the total dose or without increasing the infusion rate will not require formal SRC approval. Similarly, reductions in the total dose or the infusion rate will not require SRC approval.

Stopping Criteria

Dose escalation or ongoing infusions will be suspended, pending investigation by the SRC, if any of the following occur after confirmation the subject has received PB2452:

- Any preclinical or clinical events that, in the opinion of the SRC, contraindicate further dosing of additional subjects with PB2452
- Any serious adverse event (SAE) occurring prior to discharge from the clinical site
- Data from previous cohorts indicate safety concerns for dosing at a higher level, such as unanticipated adverse responses (e.g., clinically significant [CS] changes in clinical laboratory test data, 12 lead ECGs, continuous 12-lead electrocardiogram (Holter monitor) results, vital signs, physical examinations)
- Two or more subjects in a cohort experience any DLT, or 1 subject experiences a ≥Grade 2 AE (DLT) that, in the opinion of the SRC, warrants suspension of dose escalation
- Two or more subjects have >3 x upper limit of normal (ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or >2 x ULN of bilirubin or alkaline phosphatase (ALP) when no other reason can be found to explain the increases
- One or more subjects experiences a ≥Grade 2 infusion-related reaction (IRR) despite having been premedicated for IRRs

Continuation of dosing following suspension will be determined by the SRC and documented in an ad hoc SRC Safety Report. Dosing may also be suspended if, in the opinion of the SRC or Sponsor, any new or unexpected significant safety or tolerability issues related to ticagrelor or PB2452 are identified that warrant further evaluation before additional subjects are dosed. This may include emerging nonclinical data, clinically relevant AEs, or relevant data from other sources indicating safety concerns, even if the event(s) per se does not meet the protocol-specified definition of a DLT.

INCLUSION CRITERIA:

1. The subject provides written informed consent and agrees to comply with all protocol requirements.

2. The subject is male or female between 50 and 80 years of age, inclusive.
3. The subject has a body mass index (BMI) between 18 and 35 kg/m^2 and a weight of ≥50 kg but ≤120 kg, inclusive, at Screening.
4. The subject is considered by the investigator to be in good general health, as determined by medical history, clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings at Screening. Subjects with chronic, stable, and well-controlled medical conditions are eligible provided they meet all other inclusion/exclusion criteria. Some examples of stable and well-controlled medical conditions include but are not limited to:
   - Hypertension (HTN) controlled with ≤2 antihypertensive drugs
   - Diabetes controlled with diet/exercise or treated with up to 2 oral diabetes medications
   - Subjects with diabetes must have a glycosylated hemoglobin HbA1c ≤8 mg/dL at Screening.
   - Mild hepatic enzyme elevation (AST or ALT <1.5 x ULN or total bilirubin <1.2 x ULN)
   - Controlled hyperlipidemia (defined with a Screening low density lipoprotein LDL <160 mg/dL)
5. Specific inclusionary laboratory values at Screening and Check-in require:
   - White blood cell (WBC) count, platelet count, hemoglobin (Hgb) level within normal range, as defined by the clinical laboratory
   - Thyroid stimulating hormone (TSH) level within normal range, as defined by the clinical laboratory at Screening
   - Prothrombin time (PT) and partial thromboplastin time (PTT) level within normal range, as defined by the clinical laboratory
6. Subjects taking medications for well-controlled medical conditions must have been on a stable dose (meaning no changes in dose) for at least 30 days prior to Screening visit.
7. Subjects entering the study who are not already taking daily ASA must be willing to start an 81 mg daily dose of ASA on Day -7 and continue daily dosing until the final dose is administered on the morning of Day 1. Subjects entering the study who are already taking ASA daily will be administered 81 mg ASA daily between Day -7 and Day 1 and must suspend further ASA dosing until discharge from the clinical facility.
8. Female subjects of childbearing potential must not be pregnant, lactating, or planning to become pregnant for 3 months after the last dose of study drug, and have a negative serum pregnancy test at Screening and Check-in. Female subjects of childbearing potential must use 2 effective methods of birth control from 30 days before study drug administration through to the end of the study.
   - Effective birth control methods include oral, implantable, patch, or injectable contraceptive hormone treatment, hormone-containing intrauterine device that has been in place ≥2 months prior to Screening, sponge, diaphragm, or cervical cap with spermicidal gel or cream for female subjects or condom or vasectomy for male subjects.
   - Women are considered to not be of childbearing potential if they have fulfilled one of these criteria: documentation of irreversible surgical sterilization (i.e., hysterectomy or bilateral oophorectomy [not tubal ligation]) or are postmenopausal (defined as amenorrhea for 12 consecutive months following cessation of all exogenous hormonal treatments, and documented plasma follicle-stimulating hormone (FSH) level >40 IU/mL) or amenorrhea for 24 consecutive months.

- Male subjects with partners of childbearing potential must agree to use appropriate and effective measures of contraception (e.g., condom plus diaphragm with spermicide, condom plus spermicide) during the study and for 30 days after the last dose of study drug, and refrain from donating sperm for ≥90 days following the last dose of study drug.

EXCLUSION CRITERIA:

1. Concern the subject may be unable to comply with study procedures and/or follow-up, or, in the opinion of the investigator, the subject is not suitable for entry into the study
2. History of any acute or chronic medical disorder expected to decrease the life expectancy of the subject
3. History or presence of gastrointestinal (GI), hepatic (with the exception of Gilbert's syndrome), or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs
4. Significant renal insufficiency, as indicated by estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) equation
5. Any CS acute illness, medical/surgical procedure, or trauma within 4 weeks of administration of study drug or any planned surgical procedure that will occur during the study (from Screening through the Day 28 [±2 days] Follow-up visit)
6. Any CS abnormal findings in physical examination, vital signs, laboratory assessments, and ECG parameters identified during Screening or Check-in. Note: abnormal results may be repeated for confirmation immediately after the first out of range measurement. Abnormal vital signs may be repeated twice if needed, immediately after the first abnormal result and/or after the subject has rested for at least 10 minutes.

   Specific vital sign exclusionary criteria occurring after 10 minutes of supine rest are any of the following:

   - Systolic blood pressure (SBP) <100 or >160 mm Hg
   - Diastolic blood pressure (DBP) <40 or >95 mm Hg
   - Resting heart rate (HR) <50 or >100 beats per minute (bpm)

   Specific exclusionary criteria for ECG parameters at Screening or Check-in include any of the following:

   - Prolonged Fridericia-corrected QT interval (QTcF) >450 milliseconds (msec), shortened QTcF <340 msec, or pause >3 seconds, or family history of long QT syndrome
7. Any specific contraindication to Brilinta® as described in the Brilinta® prescribing information and:
   - History of intracranial hemorrhage, active bleeding, or hypersensitivity or allergic reaction to ticagrelor or any component of the product
   - Any history of severe head trauma, intracranial neoplasm, arteriovenous malformation, aneurysm, or proliferative retinopathy
   - Any history of intraocular, retroperitoneal, or spinal bleeding
   - Have taken, within 30 days of Screening, any oral or parenteral anticoagulant, including low molecular-weight heparin
   - Stool sample testing positive for occult blood within 3 months of Screening or at any time during the Screening Period
8. Receiving chronic treatment with nonsteroidal anti-inflammatory drugs (NSAIDS; [including ASA >100 mg daily]), anticoagulants, or other antiplatelet agents that cannot be discontinued

14 days prior to randomization (including clopidogrel, prasugrel, ticlopidine, dipyridamole, or cilostazol)

9. Positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) types 1 or 2 antibodies at Screening
10. Concomitant oral or IV therapy with strong cytochrome P450 3A4 (CYP3A) inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers, which cannot be stopped within at least 5 half-lives, but not fewer than 10 days, before randomization (a list of examples may be found in Appendix 7.2)
11. Consumption of grapefruit or grapefruit juice, Seville orange or Seville orange-containing products (e.g., marmalade), or xanthine-containing products within 48 hours before dosing with study drug
12. Prescription or over-the-counter (OTC) medications within 14 days before the first dose of study drug unless specifically allowed by protocol. (Permitted medications include multivitamins, paracetamol [up to 2g per day], and/or treatments for chronic stable diseases, provided the drug and dose have been stable for ≥30 days prior to administration of study drug)
13. Has received another investigational drug (defined as a small molecule or biologic compound which has not been approved for marketing) within 30 days of the administration of study drug in this study or within 5 half-lives of the prior study drug, whichever is longer
14. Positive test result for alcohol or drugs of abuse at Screening or Check-in
15. Participated in strenuous activity or contact sports within 24 hours before the infusion of study drug or while confined in the clinical site
16. History of severe or ongoing allergy/hypersensitivity to any drug or biologic therapeutic agent
17. Involvement with any PhaseBio or study site employee or their close relatives (e.g., spouse, parents, siblings, or children whether biological or legally adopted)
18. Previously received PB2452 or had been randomized to receive study drug in an earlier cohort for this study

EVALUATION CRITERIA:

Safety Endpoints:

Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), vital sign measurements (systolic blood pressure (SBP) and diastolic blood pressure (DBP), oral body temperature, respiratory rate [RR], and HR), 12-lead ECG, immunogenicity, biomarkers and physical examination findings.

Pharmacodynamic Endpoints:

VerifyNow® $P2Y_{12}$:

- Minimum %inhibition of PRU within 4 hours after the initiation of study drug. %inhibition of PRU is calculated as 100 * [(PRU_{bsl} – PRU_{trt})/PRU_{bsl}]. PRU_{bsl} refers to the PRU value measured before treatment with ticagrelor and PRU_{trt} refers to the PRU value measured posttreatment with the study drug.
- PRU area under the curve (AUC) for the first 4 hours.
- Proportion of patients with normalized platelet reactivity units within 4 hours after the initiation of study drug. Normalized platelet reactivity is defined as PRU ≥ 180.
- Proportion of patients with ≥60%, ≥80%, and 100% of PRU response rate within 4 hours after the initiation of study drug. A PRU response rate is defined as the 100 * (PRU_{trt}/PRU_{bsl}).

- Time to 60%, 80%, 100% of PRU response rate within 4 hours after the initiation of study drug
- Duration of 80% and 100% of PRU response rate by PRU.

LTA:

- Minimum %inhibition of LTA within 4 hours after the initiation of study drug.
- LTA AUC for the first 4 hours.
- Proportion of patients with ≥60%, ≥80%, and 100% of LTA response rate within 4 hours after the initiation of study drug. LTA response rate is defined as the 100 * (LTA_{trt}/LTA_{bsl}).
- Time to 60%, 80%, 100% LTA response rate within 4 hours after the initiation of study drug.
- Duration of 80% and 100% of LTA response rate.

VASP by ELISA:

- Minimum %inhibition of PRI within 4 hours after the initiation of study drug.
- PRI AUC for the first 4 hours.
- Proportion of patients with ≥60%, ≥80%, and 100% of PRI response rate within 4 hours after the initiation of study drug. A PRI response is defined as the 100 * (PRI_{trt}/PRI_{bsl}).
- Time to 60%, 80%, 100% PRI response rate within 4 hours after the initiation of study drug
- Duration of 80% and 100% of PRI response rate

For Cohorts receiving a 6^{th} dose of ticagrelor 24 hours following study drug, PD parameters will be calculated for Days 1 and Day 2 separately. Additional PD parameters may be generated, if needed.

Pharmacokinetic Endpoints:

Plasma PK

Plasma concentrations of total PB2452, unbound PB2452, total Ticagrelor, total TAM, unbound Ticagrelor, and unbound TAM, will be assessed at predetermined timepoints.

PK parameters for PB2452 include:

- Observed maximum plasma concentration (C_{max})
- Area under the plasma concentration versus time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC_{0-t})
- Time to reach the observed maximum plasma concentration (T_{max})
- AUC from time zero to 24 hours post-dose (AUC_{0-24})
- AUC from time zero to 48 hours post-dose (AUC_{0-48})
- Area under the plasma concentration versus time curve (AUC) from time zero to the time of the end of the dosing period(AUC_{0-tau})
- AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$; if data permit)
- Terminal elimination half-life ($t_{½}$; if data permit)
- Clearance (CL; if data permit)
- Volume of distribution (Vd)

PK parameters for Ticagrelor/TAM include:

- C_{max}
- AUC_{0-t}
- T_{max}
- AUC_{0-24}

- AUC_{0-48}
- AUC_{0-tau}
- $AUC_{0-\infty}$; if data permit
- $t_{½}$; if data permit

For Cohorts receiving a 6th dose of ticagrelor 24 hours following study drug initiation, AUC_{0-48} will not be calculated for neither plasma PB2452 nor ticagrelor/TAM. The remaining PK parameters may be calculated for Days 1 and 2 separately. Additional PK parameters may be generated, if needed. Details will be provided in a separate document, the statistical analysis plan (SAP).

Urine PK

Pooled urine samples to assess urine PB2452, ticagrelor, and TAM concentrations will be collected over these intervals: before dosing (within 60 minutes prior to the first ticagrelor dose on Day -2) and 0 to 6, 6 to 12, and 12 to 24 hours. In patients receiving a 6th dose of ticagrelor, pooled urine samples to assess urine ticagrelor and TAM concentrations will be collected over these intervals beginning with the 6th ticagrelor dose: 0 to 6, 6 to 12, 12 to 24 hours.

Pharmacokinetic parameters for PB2452, ticagrelor, and TAM concentrations in urine for all subjects in the PK population to be calculated are:

- Total amount of drug excreted in urine at 24 hours after dosing (Ae_{24}) and at 48 hours after dosing (Ae_{48})
- Total amount of drug excreted in urine from time t1 to t2 (Ae_{t1-t2}) hours when the values of t1 to t2 are 0 to 6, 6 to 12, 12 to 24 and 24 to 48 hours
- Fraction excreted in urine from 1 to 24 hours after dosing (Fe_{24}) and from 1 to 48 hours after dosing (Fe_{48})
- Renal clearance (CLr) for 24 hours after dosing

For Cohorts receiving a 6th dose of ticagrelor 24 hours following study drug initiation, Fe_{48} and Ae_{24-48} will not be calculated. Other urine PK parameters may be calculated for Day 1 and 2 separately.

Additional PK parameters may be generated, if needed. Details will be provided in a separate document, the SAP.

STUDY DRUG, DOSAGE, AND ROUTE OF ADMINISTRATION:

PB2452:

PB2452 IV infusion, prepared according to the Pharmacy Manual, will be administered on Day 1 for up to 48 hours. The total dose for each subject will not exceed 30 g. The infusion rate will not exceed 18 g over 30 minutes and the concentration will not exceed 24g in 250mL. Subjects will not receive more than 250 mL of study drug infusion within any 1-hour period.

For each cohort, the dose, infusion rate, and duration will be communicated from the Sponsor to PPD in a Dosing Memo issued prior to initiation of each treatment cohort.

Matching Placebo:

0.9% sodium chloride single IV infusion, to be delivered at a rate and volume matching the active infusion.

Ticagrelor:

Ticagrelor 90 mg oral tablet (immediate release) will be administered as a180 mg (2 × 90 mg tablets) loading dose plus 90 mg every 12 hours for 4 additional doses. In successive cohorts following cohort 1, if indicated in a Dosing Memo from Sponsor to site, one or more cohorts may also receive an additional single oral dose of 90 mg ticagrelor 24 hours after the initiation of the study drug infusion (6^{th} ticagrelor dose).

Aspirin (acetylsalicylic acid; ASA):

Aspirin (ASA) 81 mg oral tablet (enteric coated) will be administered daily between Day -7 and in the morning before receiving study medication on Day 1. Subjects may resume ASA after discharge from the study. Subjects entering the study who are already taking ASA daily must be willing to document a daily 81 mg dose between Day -7 and Day 1 and must suspend further ASA doses until discharge from the clinical facility.

STATISTICAL METHODS:

Sample Size:

The sample size for this study is based on clinical and practical considerations and not on a formal statistical power calculation. The sample size will provide preliminary safety, efficacy and PK information in a dose/regimen finding fashion.

Analysis Populations:

- The *Safety Population* will include all subjects who receive any amount of study drug.
- The *PK Population* will include subjects in the safety population who have ≥1 measurable PK concentration.
- The *PD Population* will include subjects in the safety population who receive ≥1 dose of ticagrelor and have ≥1 measurable post dose PRU value.

Safety Analyses:

Adverse events will be coded by preferred term and system-organ-class (SOC) using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). All AE data will be presented in Data Listings. Treatment-emergent AEs (TEAEs) will be summarized by treatment and overall, as well as by severity and relationship to study drug. All SAEs and AEs leading to discontinuation of study drug will be presented in the Data Listings.

Actual values and changes from Baseline in clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, standard deviation [SD], median, minimum, and maximum). Clinical laboratory test results, vital sign measurements, 12-lead ECGs, Holter monitor report data, immunogenicity results, and physical examination findings will be presented in Data Listings.

Pharmacokinetic Analyses:

Plasma concentrations will be listed and summarized descriptively (number of subjects, arithmetic mean, SD, coefficient of variation [CV], median, minimum, and maximum). Plasma concentration versus time profiles for each subject will be presented graphically. The mean plasma concentration versus scheduled time profiles will be presented graphically by dose.

Pharmacokinetic parameters will be summarized by time point for each dose level using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum). Geometric means will be reported for AUCs and C_{max}.

Pharmacodynamic Analyses:

Pharmacodynamic data will be summarized for each time point using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum). Pharmacodynamic parameters will also be summarized for each cohort.

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See Appendices, Section 7.

LIST OF ABBREVIATIONS AND DEFINITIONS

AA	arachidonic acid
ACS	acute coronary syndrome
ADA	anti-drug antibodies
ADP	adenosine diphosphate
AE	adverse event
Ae_{48}	total amount of drug excreted in urine at 48 hours after dosing
Ae_{24}	total amount of drug excreted in urine at 24 hours after dosing
$Ae_{t1\text{-}t2}$	Ae from time t1 to t2 hours
$Ae_{t1\text{-}t2}$	Ae from time t1 to t2 hours
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASA	acetylsalicylic acid, aspirin
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-}12}$	AUC from time zero to 12 hours after dosing
$AUC_{0\text{-}24}$	AUC from time zero to 24 hours after dosing
$AUC_{0\text{-}48}$	AUC from time zero to 48 hours after dosing
$AUC_{0\text{-}\infty}$	area under the plasma concentration versus time curve from time zero extrapolated to infinity
$AUC_{0\text{-}\tau}$	area under the concentration versus time curve from time zero to the time of the last quantifiable concentration
bid	twice daily
BL	baseline
BLQ	below the limit of quantification
BMI	body mass index
BP	Blood Pressure
Bpm	beats per minute
BUN	Blood Urea Nitrogen
CABG	coronary artery bypass graft
CFR	Code of Federal Regulations
CL	clearance
CLr	renal clearance
C_{max}	observed maximum plasma concentration
CrCl	creatinine clearance
CS	clinically significant
CSR	Clinical Study Report

CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP3A	cytochrome P450 3A4
DAPT	dual antiplatelet therapy
DBP	diastolic blood pressure
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
FDA	Food and Drug Administration
Fe_{24}	Fraction excreted in urine from 1 to 24 hours after dosing
Fe_{48}	fraction excreted in urine from 1 to 48 hours after dosing
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
HbA1c	glycosylated Hemoglobin Hgb
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high-density lipoprotein
Hgb	hemoglobin
HIV	human immunodeficiency virus
HR	resting heart rate
HTN	hypertension
IB	Investigators' Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
INR	international normalized ratio
IPA	inhibition of platelet aggregation
IRB	institutional review board
IRR	infusion-related reaction
IV	Intravenous- (ly)
LDH	lactate dehydrogenase
LDL	low-density lipoprotein

LTA	light transmittance aggregometry
MAP	mean arterial pressure
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDMA	methylenedioxymethamphetamine
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary FOR Regulatory Activities
MI	Myocardial infarction
MPV	Mean platelet volume
msec	millisecond
MTD	maximum tolerated dose
N	sample size
NCS	not clinically significant
NOAEL	no adverse effect level
OTC	Over the counter
PD	Pharmacodynamic
PEF	Peak expiratory flow
PK	pharmacokinetic
PO	by mouth
PRI	platelet reactivity index
PRU	$P2Y_{12}$ reaction units
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QTcF	Fridericia-corrected QT interval
RBC	red blood cell(erythrocyte)
RR	respiration rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	System- organ- class
SOP	standard operating procedure
SpGr	specific gravity
SRC	Safety Review Committee
$t_{1/2}$	terminal elimination half-life
TAM	ticagrelor active metabolite AR-C124910XX
TEAE	treatment-emergent adverse event

T_{max}	time to reach the observed maximum (peak) concentration
TRAP	thrombin receptor activating peptide
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
VASP	vasodilator-stimulated phosphoprotein
WBC	white blood cell

1. INTRODUCTION

1.1 PRODUCT AND BACKGROUND INFORMATION

PB2452 (molecular weight 47.4 kDa) is a specific and selective recombinant human neutralizing antibody IgG1λ monoclonal fragment antigen-binding antibody that binds with high affinity to ticagrelor and to AR-C124910XX (TAM), the major active circulating ticagrelor metabolite. It is expressed in *Escherichia coli* cells.

PB2452 is intended to reverse the antiplatelet effects of ticagrelor in patients who experience major bleeding or who require urgent surgery or intervention.
Platelet transfusion has appeared to be inferior to standard care for those taking antiplatelet therapy.(Baharoglu, 2016)

A strategy is needed to re-establish the integrity of the clotting cascade for the many patients who have abnormal coagulation due to pharmacological anticoagulation.(Beshay, 2010) Antiplatelet medications and anticoagulants pose a significant treatment dilemma since no direct reversal agents currently exist to reverse or mitigate antithrombotic properties.(Dornbos III, 2018) Accordingly, the current lack of an effective therapy to mitigate ticagrelor-induced platelet inhibition in patients who have life-threatening bleeding or require urgent surgery or intervention represents a significant unmet need.

Ticagrelor is an orally available, direct-acting cyclopentyltriazolopyrimidine, a selective and reversibly binding $P2Y_{12}$ receptor antagonist.(Storey, 2007) TAM, the ticagrelor active metabolite (30% to 40% plasma exposure relative to parent in humans, (Storey, 2007) has potency similar to ticagrelor versus $P2Y_{12}$. In addition to $P2Y_{12}$, ticagrelor also inhibits the equilibrative nucleoside transporter-1, thereby providing an enhanced adenosine response.(Armstrong, 2014; Beshay JE, Morgan H, Madden C, Yu W, et al. Emergency reversal of anticoagulation and antiplatelet therapies in neurosurgical patients. J Neurosurg 2010 Feb;112(2):307-18.

Catteneo, 2014) Ticagrelor in combination with low-dose aspirin (acetylsalicylic acid; ASA) is indicated for the prevention of thrombotic events (e.g., cardiovascular death, myocardial infarction [MI], and stroke) in patients with acute coronary syndrome (ACS) or a history of MI. Ticagrelor also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS. In the management of ACS, ticagrelor treatment is initiated with a 180 mg loading dose, followed by 90 mg twice daily (bid) during the first year after an ACS event. After one year, the prescribed dosage is decreased to 60 mg bid.

Therapy with ASA plus an oral antiplatelet agent such as clopidogrel, prasugrel, or ticagrelor is known as dual antiplatelet therapy (DAPT). Although DAPT is strongly recommended in the early management of patients experiencing an ACS event, it also increases the risk of bleeding.(Storey, 2011) Patients with ACS may require urgent or emergent coronary artery bypass

graft (CABG) surgery. In such patients, DAPT is associated with a 2-fold increase in risk of blood transfusion, a 5-fold increase in risk of reoperation, and a 50% increased risk of wound infection.(Bell, 2011; Fitchett, 2011) Consequently, guidelines and guidance statements recommend the $P2Y_{12}$ receptor antagonist be stopped ≥5 days prior to the procedure, a recommendation that is not possible in patients who require urgent surgery.

There are no approved drugs or biological agents capable of reversing the $P2Y_{12}$ inhibition produced by ticagrelor or other $P2Y_{12}$ inhibitors; therefore, in the event of major bleeding in a patient on DAPT, there are limited treatment options. Although platelet transfusion restores platelet function in patients on ASA,(Taylor, 2013) it does not reverse the antiplatelet effect of ticagrelor in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding.(Teng, 2016)

1.1.1 Non-clinical Pharmacology

Non-clinical pharmacology studies have demonstrated that PB2452 binds with high affinity and selectivity to the $P2Y_{12}$ receptor antagonist ticagrelor and its active metabolite, TAM, (equilibrium dissociation constant [K_D] 20 pmol/L). PB2452 rapidly neutralizes the unbound plasma fraction of ticagrelor and TAM, thereby reversing ticagrelor- and TAM-mediated inhibition of adenosine diphosphate (ADP)-induced platelet aggregation in a concentration- and dose-dependent manner in vitro (in human platelet-rich plasma) and in vivo (mouse and pig, dose-dependency data in mouse only). In mice dosed with ticagrelor to a supratherapeutic plasma exposure, those dosed with PB2452 before a tail cut had reduced bleeding to a degree not statistically different from the observation in mice not treated with ticagrelor. The activity in vitro and the rapid onset of effect observed in vivo translated to a reduction of bleeding in ticagrelor-treated mice to a degree that was not statistically significantly different from mice not treated with ticagrelor. Detailed descriptions of the non-clinical pharmacology of PB2452 may be found in the Investigators' Brochure (IB) for PB2452.

1.1.2 Summary of Human Data

The first-in-human Phase 1 study (PB2452-PT-CL-0001) has been clinically completed, the database is locked, and final analyses are complete with the exception of exploratory endpoints. The safety, PK, and PD data described herein will be incorporated into a clinical study report. This study was a single-center, randomized, double-blind, placebo-controlled, single ascending dose study to evaluate the safety, tolerability, PK, and PD of PB2452 with and without ticagrelor pretreatment in healthy male and female subjects ages 18-50 years. Ten sequential dose cohorts were evaluated. Cohorts 1, 2, and 3 assessed 30 min IV infusions of PB2452 without ticagrelor pretreatment while Cohorts 4-10 assessed IV infusions of

PB2452 after ticagrelor pretreatment. Detailed descriptions of the clinical safety, PK, and PD profiles of PB2452 may be found in the Investigators' Brochure (IB) for PB2452.

PB2452 appeared generally safe and well tolerated across a dose range of 0.1 g to 18 g. A total of 30 adverse events occurred after initiation of PB2452 or placebo and were reported by 19 of the 64 volunteers (30%). Of the 48 volunteers who received PB2452, 17 (35%) reported 27 adverse events; of the 16 volunteers who received placebo, 2 (12%) reported 3 adverse events. There were no dose-limiting toxicity (DLTs)effects or infusion-related reactions (IRRs). There were no deaths or adverse events that led to discontinuation of the trial drug. One volunteer had 2 serious adverse events (alcohol poisoning and acute respiratory failure) 4 days after discharge from the clinical site. Except for 2 volunteers, in cohorts 1 and 3, all volunteers with adverse events had received ticagrelor pretreatment. Changes in mean clinical laboratory test results, vital signs, and electrocardiographic results were similar across cohorts among volunteers who received different doses or regimens of PB2452 and were similar among those who received PB2452 and those who received placebo. Of the 48 volunteers who received PB2452, 21 (44%) had detectable anti-drug antibodies in blood obtained 7 and/or 28 days after exposure; 15 (31%) had been positive before they received PB2452 and 6 (12%) became positive after they received PB2452, albeit with low titers of 40 (in 5 volunteers) and 160 (in 1 volunteer). Of the 16 volunteers who received placebo, 3 (19%) were positive for anti-drug antibodies, with 2 (12%) having preexisting antibodies. The presence of these antibodies had no observed effect on the safety or efficacy of PB2452.

The PK profile of PB2452 demonstrated that mean plasma concentrations of PB2452 rapidly declined following the end of infusion across all cohorts. In cohorts 1-3 when PB2452 was administered as a 30-minute intravenous infusion in the absence of ticagrelor, elimination appeared to be biphasic with half-life values ranging from 1.5 to 9.2 hours for the dose range 0.1 g to 1 g. In the presence and absence of ticagrelor, geometric mean observed maximum plasma concentration (C_{max}) values and geometric mean area under the plasma concentration versus time curve (AUC) from time zero extrapolated to infinity ($AUC_{0-\infty}$))values of total PB2452 appeared to increase in a dose-proportional manner. The inter-individual variability (geometric mean coefficient of variation [CV%]) for C_{max} and $AUC_{0-\infty}$ was low, ranging from 4.8% to 28.9% across Cohorts 1-3. PB2452 appeared to increase mean total plasma concentrations of ticagrelor and TAM compared to placebo, and this effect was dependent on the dose of PB2452. Additionally, PB2452 increased the renal CL of ticagrelor and TAM in a dose-dependent manner.

The PD profile of PB2452 demonstrated that for subjects receiving steady-state ticagrelor, IV infusion of PB2452 (3 to18 g) restored platelet activity to approximately 100% of baseline using multiple assays of platelet function. The onset of reversal was rapid, occurring at the first assessment of platelet function following initiation of PB2452 infusion (30 minutes in cohorts 4-6 and 5 minutes in cohorts 7-10). The duration of ticagrelor reversal appeared to be dependent on the total dose and infusion duration of PB2452.

1.1.3 Benefit/Risk Assessment

The first in human study of PB2452 in healthy volunteers (PB2452-PT-CL-0001) demonstrated that PB2452 appears to be generally safe and well tolerated when administered intravenously across a dose range of 0.1-18 g. The healthy volunteers who were 18-50 years in age were not expected to nor received any benefit from administration of PB2452. Platelet function analyses showed that PB2452 delivered immediate and sustained reversal of ticagrelor, occurring as early as 5 minutes after initiation of PB2452 infusions and lasting for 20-24 hours. Rapid and sustained ticagrelor reversal by PB2452 may provide clinically significant benefit in patients taking ticagrelor who experience serious bleeding or require urgent surgical procedures by supporting rapid hemostasis or prevention of procedure-related bleeding.

Although treatment emergent adverse events associated with PB2452 in the Phase 1 study were mostly mild and infrequent with no infusion-related or hypersensitivity reactions observed, in the older and elderly subjects in this Phase 2A study, there remain potential risks of infusion-related reactions (IRRs), infusion site reactions, and hypersensitivity-type reactions which can result from exposure to recombinant protein drugs administered intravenously (IV). These risks may be mitigated by predefined exclusion criteria and by close monitoring during and after administration. Risks may also be mitigated by premedication prior to receiving PB2452 which will be implemented if a study subject develops a Grade ≥2 IRR.

The older and elderly subjects in this study will be administered dual anti-platelet therapy with ASA and ticagrelor which carries a risk of bleeding. The bleeding risk in study subjects is considered very low because the duration of dual antiplatelet therapy is only 48 hours. Among those patients taking ticagrelor for therapeutic benefit, the potential risk of disease-related thrombosis upon reversal of the antiplatelet effect of ticagrelor will be evaluated in future clinical studies and by thorough monitoring of hemostasis parameters. In the current study, three platelet function assays and multiple platelet agonists will be used to monitor platelet function which will demonstrate both the reversal profile of PB2452 and also a potential prothrombotic rebound increase in platelet function. The risk of a platelet rebound effect is considered low and was not observed in the Phase 1 study.

Based on available information concerning the risks of PB2452 and the precautions included in this clinical study, the risks are considered acceptable.

1.2 RATIONALE FOR STUDY

Current recommendations for management of bleeding in patients treated with antiplatelet therapies are suboptimal; they are mostly supportive and non-specific. Platelet transfusion, while useful for some antiplatelet agents, exposes patients to the known risks of blood products. Further, the efficacy of transfused platelets may be limited by exposure to circulating antiplatelet drug or metabolites, if present. Moreover, it has been demonstrated that platelet transfusions do not reverse the effects of ticagrelor.(Dalen, 2013; Godier, 2015; Maillard, 2015; Teng, 2016)

An agent to rapidly reduce the anti-platelet aggregation (IPA) associated with effects of ticagrelor, and the metabolite TAM, would fulfill an important unmet clinical need for those patients:

- who have major bleeding with ticagrelor possibly contributing
- who are taking ticagrelor and require urgent surgery or intervention associated with a high risk of bleeding
- who are taking ticagrelor for conditions with a high risk of thrombosis, require major surgery, and/or need to minimize the time when they are not receiving ticagrelor

1.3 RATIONALE FOR DOSE SELECTION

In the first in human Phase 1 study of PB2452, 18 g administered as an initial 6 g bolus followed by a prolonged infusion of the remaining 12 g over 16 hours in healthy subjects aged 18-50 years old was considered generally safe and well tolerated. There were no PB2452-related adverse effects, injection site reaction (ISRs), or DLTs observed as determined by the study investigator and SRC. The profile of rapid and sustained ticagrelor reversal delivered by the 18 g dose level is potentially clinically meaningful and considered ideal for patients on ticagrelor with acute major bleeding or who need urgent surgery.

The 18 g dose level and prolonged infusion regimen administered in the Phase 1 study will be repeated in the current study in older and elderly subjects who are more similar in age and background comorbidities to the actual patient population treated with ticagrelor. Potentially longer infusions of PB2452 may be investigated in this study, using potentially higher total doses of PB2452. To mitigate any risks related to dose escalation, a Safety Review Committee (SRC) will be assembled to review all emergent safety and tolerability data and available PK data after each cohort is completed to determine whether dose escalation and/or prolongation of infusion duration is warranted. PK/PD modeling will be used to simulate potential doses, infusion regimens, and C_{max} and AUC exposure profiles prior to dose-escalation or adjustment of infusion regimen to ensure that no dose or infusion regimen

investigated in this study will exceed C_{max} or AUC exposures achieved at the no observed adverse effect level (NOAEL) in GLP toxicity study in rats.

In the rat GLP toxicity study, there were no adverse effects observed following single doses of PB2452 at the highest dose level tested of 2000 mg/kg given IV, alone or in combination with oral ticagrelor (20 mg/kg). Therefore, 2000 mg/kg was considered NOAEL with a maximum plasma concentration (C_{max}) of 18100 µg/mL and an area under the plasma concentration versus time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$) of 23100 µg*h/mL.

2. STUDY OBJECTIVES AND METHODOLOGY

2.1 OBJECTIVES

Primary:

- To evaluate the safety and tolerability of intravenous (IV) doses of PB2452 vs matching placebo with oral ticagrelor plus acetylsalicylic acid (ASA) pretreatment in older and elderly subjects
- To assess the efficacy/ pharmacodynamic (PD) of IV doses of PB2452 vs matching placebo in reversing ticagrelor antiplatelet activity by measuring $P2Y_{12}$ reaction units (PRU) with VerifyNow® $P2Y_{12}$ assay in older and elderly subjects

Secondary:

- To determine the pharmacokinetic (PK) of PB2452 in the presence of ticagrelor
- To determine the PK of ticagrelor and TAM in the presence of PB2452
- To evaluate the effect of PB2452 on ticagrelor antiplatelet activity by measuring platelet aggregation with light transmittance aggregometry (LTA) and platelet reactivity index (PRI) with vasodilator-stimulated phosphoprotein (VASP) assay by enzyme-linked immunosorbent assay (ELISA)
- To evaluate the immunogenicity potential of PB2452

Exploratory:

- To evaluate the effect of PB2452 on the PK profile of unbound ticagrelor and unbound TAM plasma concentrations
- To investigate the effect of PB2452 vs matching placebo on circulating biomarkers of platelet activation, such as P-selectin, in subjects pretreated with ticagrelor + ASA
- To examine the correlation between estimated creatinine clearance (CrCl) and the PK of ticagrelor and TAM.

2.2 EVALUATION CRITERIA

2.2.1 Safety Endpoints

Safety and tolerability will be assessed by monitoring and recording of Adverse Events (AEs), clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), vital sign measurements (systolic blood pressure [SBP] and diastolic blood pressure [DBP], oral body temperature, respiratory rate [RR], and resting heart rate [HR]), 12-lead electrocardiogram (ECG), continuous 12-lead ECG (Holter monitoring), immunogenicity, and physical examination findings.

2.2.2 Pharmacodynamic Endpoints

VerifyNow® $P2Y_{12}$:

- Minimum %inhibition of PRU within 4 hours after the initiation of study drug. %inhibition of PRU is calculated as 100 * [(PRU_{bsl} – PRU_{trt})/PRU_{bsl}]. PRU_{bsl} refers to the PRU value measured before treatment with ticagrelor and PRU_{trt} refers to the PRU value measured posttreatment with the study drug.
- PRU AUC for the first 4 hours.
- Proportion of patients with normalized platelet reactivity units within 4 hours after the initiation of study drug. Normalized platelet reactivity is defined as PRU ≥ 180.
- Proportion of patients with ≥60%, ≥80%, and 100% of PRU response rate within 4 hours after the initiation of study drug. A PRU response rate is defined as the 100 * (PRU_{trt}/PRU_{bsl}).
- Time to 60%, 80%, 100% of PRU response rate within 4 hours after the initiation of study drug
- Duration of 80% and 100% of PRU response rate by PRU.

LTA:

- Minimum %inhibition of LTA within 4 hours after the initiation of study drug.
- LTA AUC for the first 4 hours.
- Proportion of patients with ≥60%, ≥80%, and 100% of LTA response rate within 4 hours after the initiation of study drug. LTA response rate is defined as the 100 * (LTA_{trt}/LTA_{bsl}).
- Time to 60%, 80%, 100% LTA response rate within 4 hours after the initiation of study drug.
- Duration of 80% and 100% of LTA response rate.

VASP by ELISA:

- Minimum %inhibition of PRI within 4 hours after the initiation of study drug.
- PRI AUC for the first 4 hours.
- Proportion of patients with ≥60%, ≥80%, and 100% of PRI response rate within 4 hours after the initiation of study drug. A PRI response is defined as the 100 * (PRI_{trt}/PRI_{bsl}).
- Time to 60%, 80%, 100% PRI response rate within 4 hours after the initiation of study drug
- Duration of 80% and 100% of PRI response rate

For Cohorts receiving a 6th dose of ticagrelor 24 hours following study drug, PD parameters will be calculated for Day 1 and Day 2 separately. Additional PD parameters may be generated, if needed.

2.2.3 Pharmacokinetic Endpoints

Plasma PK

Plasma concentrations of total PB2452, unbound PB2452, total Ticagrelor, total TAM, unbound Ticagrelor, and unbound TAM, will be assessed at predetermined timepoints.

PK parameters for PB2452 include:

- Observed maximum plasma concentration (C_{max})
- Area under the plasma concentration versus time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC_{0-t})
- Time to reach the observed maximum plasma concentration (T_{max})
- AUC from time zero to 24 hours post-dose (AUC_{0-24})
- AUC from time zero to 48 hours post-dose (AUC_{0-48})
- Area under the plasma concentration versus time curve (AUC) from time zero to the time of the end of the dosing period(AUC_{0-tau})
- AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$; if data permit)
- Terminal elimination half-life ($t_{½}$; if data permit)
- Clearance (CL; if data permit)
- Volume of distribution (Vd)

PK parameters for Ticagrelor/TAM include:

- C_{max}
- AUC_{0-t}
- T_{max}
- AUC_{0-24}
- AUC_{0-48}
- AUC_{0-tau}
- $AUC_{0-\infty}$; if data permit
- $t_{½}$; if data permit

For Cohorts receiving a 6th dose of ticagrelor 24 hours following study drug initiation, AUC_{0-48} will not be calculated for neither plasma PB2452 nor ticagrelor/TAM. The remaining PK

parameters might be calculated for Days 1 and 2 separately. Additional PK parameters may be generated, if needed. Details will be provided in a separate document, the statistical analysis plan (SAP).

Urine PK

Pooled urine samples to assess urine PB2452, ticagrelor, and TAM concentrations will be collected over these intervals: before dosing (within 60 minutes prior to the first ticagrelor dose on Day -2) and 0 to 6, 6 to 12, and 12 to 24 hours. In patients receiving a 6^{th} dose of ticagrelor, pooled urine samples to assess urine ticagrelor and TAM concentrations will be collected over these intervals beginning with the 6th ticagrelor dose: 0 to 6, 6 to 12, 12 to 24 hours.

Pharmacokinetics parameters for PB2452, ticagrelor, and TAM concentrations in urine for all subjects in the PK population to be calculated are:

- Total amount of drug excreted in urine at 24 hours after dosing (Ae_{24}) and at 48 hours after dosing (Ae_{48})
- Ae from time t1 to t2 hours when the values of t1 to t2 are 0 to 6, 6 to 12, 12 to 24 and 24 to 48 hours ($Ae_{t1\text{-}t2}$)
- Fraction excreted in urine from 1 to 24 hours after dosing (Fe_{24}) and from 1 to 48 hours after dosing (Fe_{48})
- Renal clearance (CLr) for 24 hours after dosing

For Cohorts receiving a 6th dose of ticagrelor 24 hours following study drug initiation, Fe_{48} and $Ae_{24\text{-}48}$ will not be calculated. Other urine PK parameters may be calculated for Days 1 and 2 separately.

3. INVESTIGATION PLAN

3.1 STUDY DESIGN AND METHODOLOGY

This is Part A of a two-part Phase 2A, randomized, double-blind, placebo-controlled, single dose, sequential group study to evaluate the safety, tolerability, PK, and PD of PB2452 vs matching placebo. Part A investigates various dose levels and regimens of PB2452 administered intravenously to older (ages 50 to 64 years) and elderly (ages 65 to 80 years) male and female subjects pretreated with ticagrelor + aspirin (ASA) as part of dual antiplatelet therapy. Part B investigates various dose levels and regimens of PB2452 administered to healthy male and female subjects (ages 18-50) pretreated with a high dose of ticagrelor alone (180 mg BID). Part B is described in a separate protocol document.

In Part A described herein, up to 5 dose levels and/or administration regimens will be evaluated in up to 5 cohorts. Each cohort will include approximately 8 to 12 subjects randomized in a 3:1 ratio, PB2452:placebo. All references to study drug within the content of the protocol apply to PB2452 or matching placebo.

This initial cohort (Cohort 1) will include approximately 8 subjects ages 50 to 80 years pretreated with ASA + ticagrelor who will be randomized to 18 grams (g) of PB2452 or matching placebo administered as an initial 6 g bolus infused over 10 minutes, followed by 12 g infused over the next 15 hours and 50 minutes to complete a 16 hour administration regimen. This initial regimen was shown to be safe and well tolerated in healthy young adults (18 to 50 years) in a prior Phase 1 study and provided immediate and sustained reversal of the antiplatelet effects of ticagrelor. Following completion of Cohort 1, subsequent cohort(s) may test the same, higher, or lower dose levels, and/or different infusion regimens of PB2452 or matching placebo in the same population as in Cohort 1 or in different populations, such as, elderly subjects (65 to 80 years old) as determined by the Sponsor after examination of available PD and safety data from the prior cohort(s). A written Dosing Memo provided by the Sponsor to the clinical site will describe details of the dosing regimen, cohort population, cohort size, sampling schedules, and other cohort-specific study activities prior to initiation of each cohort. The maximum total dose of PB2452 administered to any subject will not exceed 30g. Duration of study drug infusions will not exceed 48 hours. The maximum administration rate of PB2452 will not exceed 18g over 30 minutes.

A SRC will review all available safety data from ongoing or completed cohorts and will document their review and assessment in written SRC minutes prior to initiation of a subsequent cohort. Dose escalation may occur only if the SRC affirms the dose and regimen from the previously completed cohorts were safe and well tolerated and no DLTs were observed.

The study will consist of a Screening period (Days –45 to –4), a Check-in day (Day -3) and Pretreatment Period, an on-site Randomization/Treatment day (Day 1), 3 days on-site for treatment and safety monitoring, a Follow-up Visit (Day 7), and a Final Follow-up visit (Day 28 [±2 days]). Seven days prior to Randomization (Day -7), subjects will be administered ASA 81 mg orally once daily (QD) until the final dose on the morning of Day 1 before receiving study drug. A ticagrelor 180 mg oral loading dose will be administered on the morning of Day -2 followed by 90 mg every 12 hours until the 5th dose has been administered on the morning of Day 1. After completion of Cohort 1, the Sponsor may choose to have a 6th dose of ticagrelor administered 24 hours after the initiation of study drug in a subsequent cohort.

Subjects will check in to the clinical site (PPD) on Day -3. In the morning on Day -2, subjects will begin pretreatment with ticagrelor as described in the preceding paragraph. On Day 1, subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized in a ratio 3:1 (PB2452:placebo), to receive an IV dose of PB2452 or placebo 2 hours following the 5th ticagrelor dose. Subjects may be discharged from the clinical site between Days 3 and 7 inclusive and will return for a Follow-up visit on Day 7, if already discharged, and on Day 28 (±2 days).

Serum and plasma sampling times for PB2452, ticagrelor, and TAM PK and PD assessments and urine sampling times for urinary PB2452, ticagrelor, and TAM concentrations will be described in a detailed Dosing Memo for each cohort. Hour 0 will be the time for initiation of study drug infusion (2 hours following administration of the 5th ticagrelor dose). PK and PD time points for subsequent cohorts may be adjusted as needed based on available PK, PD, and safety data from prior cohorts. In any cohort subsequent to Cohort 1, there will be no more than 6 additional sampling time points.

- For each cohort, the final dose level, administration regimen, PK/PD sampling and ECG schedule will be conveyed from the Sponsor to the clinical site in a written Dosing Memo 1 to 2 weeks prior to initiation of each cohort, including the following instructions Number of subjects to be randomized
- Total PB2452 dose and administration regimen
- Whether or not a 6th ticagrelor dose will be administered 24 hours after the 5th ticagrelor dose
- The PK and PD sampling schedule
- Safety ECG schedule

Hour 0 on Day 1 for all PK/PD and safety assessment will be the initiation of study drug infusion (2 hours following administration of the 5th ticagrelor dosing).

Safety and tolerability will be carefully monitored throughout the study. Immunogenicity samples will be collected from all subjects at Day -3, Randomization, Days 7 and 28 (±2 days) following administration of study drug.

3.2 SELECTION OF STUDY POPULATION

Male or female subjects will be evaluated in up to 5 cohorts in the US, North America. To ensure the study clinic has sufficient subjects available for dosing for any cohort, additional subjects may be asked to present to the clinic for check in. The number of subjects brought in for check-in and pre-dosed with ticagrelor will be at the discretion of the study clinic personnel/ principal investigator to ensure there is a sufficient number of subjects available for dosing with study drug for a given cohort. Subjects who check in to the clinic may be dosed with ticagrelor in preparation for dosing with the study drug according to the Schedule of Events (Appendix 7.1). Extra subjects may be dosed with ticagrelor, so on the day of randomization there is a sufficient number of subjects available to fill the cohort.

3.2.1 Inclusion Criteria

Subjects must meet ALL the following criteria to be eligible for inclusion in the study:

1. The subject provides written informed consent and agrees to comply with all protocol requirements.
2. The subject is male or female between 50 and 80 years of age, inclusive.
3. The subject has a body mass index (BMI) between 18 and 35 kg/m^2 and a weight of ≥50 kg but ≤120 kg, inclusive, at Screening.
4. The subject is considered by the investigator to be in good general health, as determined by medical history, clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings at Screening. Subjects with chronic, stable, and well-controlled medical conditions are eligible provided they meet all other inclusion/exclusion criteria. Some examples of stable and well-controlled medical conditions include but are not limited to:
   - Hypertension (HTN) controlled with ≤2 antihypertensive drugs
   - Diabetes controlled with diet/exercise or treated with ≤2 oral diabetes medications
   - Subjects with diabetes must have a glycosylated hemoglobin HbA1c ≤8 mg/dL at Screening
   - Mild hepatic enzyme elevation (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] <1.5 x upper limit of normal [ULN] or total bilirubin <1.2 x ULN)

- Controlled hyperlipidemia (defined as a Screening low density lipoprotein [LDL] <160 mg/dL)

5. Specific inclusionary laboratory values at Screening and Check-in require:
   - White blood cell (WBC) count, platelet count, hemoglobin (Hgb) level within normal range as, defined by the clinical laboratory
   - Thyroid stimulating hormone (TSH) level within normal range, as defined by the clinical laboratory at Screening
   - Prothrombin time (PT) and partial thromboplastin time (PTT) level within normal range, as defined by the clinical laboratory
6. Subjects taking medications for well-controlled medical conditions must have been on a stable dose (meaning no changes in dose) for at least 30 days prior to Screening visit.
7. Subjects entering the study who are not already taking daily ASA must be willing to start an 81 mg daily dose of ASA on Day -7 and continue daily dosing until the final dose is administered on the morning of Day 1. Subjects entering the study who are already taking ASA daily will be administered a ASA 81 mg daily between Day -7 and Day 1 and must suspend further ASA dosing until discharge from the clinical facility.
8. Female subjects of childbearing potential must not be pregnant, lactating, or planning to become pregnant for 3 months after the last dose of study drug, and have a negative serum pregnancy test at Screening and Check-in. Female subjects of childbearing potential must use 2 effective methods of birth control from 30 days before study drug administration through to the end of the study.
   - Effective birth control methods include oral, implantable, patch, or injectable contraceptive hormone treatment, hormone-containing intrauterine device that has been in place ≥2 months prior to Screening, sponge, diaphragm, or cervical cap with spermicidal gel or cream for female subjects or condom or vasectomy for male subjects.
   - Women are considered to not be of childbearing potential if they have fulfilled one of these criteria: documentation of irreversible surgical sterilization (i.e., hysterectomy or bilateral oophorectomy [not tubal ligation]) or are postmenopausal (defined as amenorrhea for 12 consecutive months following cessation of all exogenous hormonal treatments, and documented plasma follicle-stimulating hormone (FSH) level >40 IU/mL) or amenorrhea for 24 consecutive months.
   - Male subjects with partners of childbearing potential must agree to use appropriate and effective measures of contraception (e.g., condom plus diaphragm with spermicide, condom plus spermicide) during the study and for 30 days after the last

dose of study drug, and refrain from donating sperm for ≥90 days following the last dose of study drug.

3.2.2 Exclusion Criteria

Subjects will be excluded from this study if they meet ANY of the following criteria:

1. Concern the subject may be unable to comply with study procedures and/or follow-up, or, in the opinion of the investigator, the subject is not suitable for entry into the study
2. History of any acute or chronic medical disorder expected to decrease the life expectancy of the subject
3. History or presence of gastrointestinal (GI), hepatic (with the exception of Gilbert's syndrome), or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs
4. Significant renal insufficiency, as indicated by estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) equation
5. Any clinically significant (CS) acute illness, medical/surgical procedure, or trauma within 4 weeks of administration of study drug or any planned surgical procedure that will occur during the study (from Screening through the Day 28 [±2 days] Follow-up visit).
6. Any CS abnormal findings in physical examination, vital signs, laboratory assessments, and ECG parameters identified during Screening or Check-in. Note: abnormal results may be repeated for confirmation immediately after the first out of range measurement. Abnormal vital signs may be repeated twice if needed, immediately after the first abnormal result and/or after the subject has rested for at least 10 minutes.

   Specific vital sign exclusionary criteria occurring after 10 minutes of supine rest are any of the following:

   - SBP <100 or >160 mm Hg
   - DBP <40 or >95 mm Hg
   - Resting HR <50 or >100 beats per minute (bpm)

   Specific exclusionary criteria for ECG parameters at Screening or Check-in include any of the following:

   - Prolonged Fridericia-corrected QT interval (QTcF) >450 milliseconds (msec), shortened QTcF <340 msec, or pause >3 seconds, or family history of long QT syndrome

7. Any specific contraindication to Brilinta® as described in the Brilinta prescribing information and:
   - History of intracranial hemorrhage, active bleeding, or hypersensitivity or allergic reaction to ticagrelor or any component of the product
   - Any history of severe head trauma, intracranial neoplasm, arteriovenous malformation, aneurysm, or proliferative retinopathy
   - Any history of intraocular, retroperitoneal, or spinal bleeding
   - Have taken, within 30 days of Screening, any oral or parenteral anticoagulant, including low molecular-weight heparin
   - Stool sample testing positive for occult blood within 3 months of Screening or at any time during the Screening Period.
8. Receiving chronic treatment with nonsteroidal anti-inflammatory drugs (NSAIDS; including ASA [>100 mg daily]), anticoagulants, or other antiplatelet agents that cannot be discontinued 14 days prior to randomization (including clopidogrel, prasugrel, ticlopidine, dipyridamole, or cilostazol).
9. Positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) types 1 or 2 antibodies at Screening.
10. Concomitant oral or IV therapy with strong cytochrome P450 3A4 (CYP3A) inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers, which cannot be stopped within at least 5 half-lives, but not fewer than 10 days, before randomization (a list of examples may be found in Appendix 7.2).
11. Consumption of grapefruit or grapefruit juice, Seville orange or Seville orange-containing products (e.g., marmalade), , or xanthine-containing products within 48 hours before dosing with study drug.
12. Prescription or over-the-counter (OTC) medications within 14 days before the first dose of study drug unless specifically allowed by protocol. (Permitted medications include multivitamins, paracetamol [up to 2g per day], and/or treatments for chronic stable diseases provided the drug and dose have been stable for ≥30 days prior to administration of study drug)
13. Has received another investigational drug (defined as a small molecule or biologic compound which has not been approved for marketing) within 30 days of the administration of study drug in this study or within 5 half-lives of the experimental medication, whichever is longer.
14. Positive test result for alcohol or drugs of abuse at Screening or Check-in.

15. Participated in strenuous activity or contact sports within 24 hours before the infusion of study drug or while confined in the clinical site.
16. History of severe or ongoing allergy/hypersensitivity to any drug or biologic therapeutic agent.
17. Involvement with any PhaseBio or study site employee or their close relatives (e.g., spouse, parents, siblings, or children whether biological or legally adopted).
18. Previously received PB2452 or had been randomized to receive study drug in an earlier cohort for this study.

3.2.3 Subject Restrictions During the Study

If a subject is unable to comply with any of the following restrictions before study drug dosing on Day 1, the subject's participation in the study will be re-evaluated by the investigator in consultation with the Sponsor and/or medical monitor on behalf of the Sponsor; the subject may not be eligible to participate in the study:

- Subjects must be willing to remain at the study site from Day -3 through 48 hours following study drug dosing on Day 3.
- Subjects must be willing to return to the clinic for Follow-up visits on Day 7 and Day 28 (±2 days).
- Subjects must refrain from smoking or using nicotine or nicotine-containing products and from drinking alcohol-containing products
- Subjects must refrain from strenuous exercise for 24 hours prior to Check-in and for 7 days after discharge from the study
- Subjects must be willing to maintain their usual caloric intake and to consume only food and beverages provided by the clinical site while confined to the study site.

3.3 WITHDRAWAL OF SUBJECTS FROM THE STUDY

3.3.1 Reasons for Withdrawal

Subjects may withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the Sponsor. The investigator may also withdraw a subject at the request of the Sponsor or if the Sponsor terminates the study.

The investigator may withdraw a subject from the study if the subject:

- Is non-compliant with the protocol;

- Experiences a serious adverse event (SAE) or intolerable adverse event (AE) that, in the investigator's opinion, requires withdrawal from the study;
- Has laboratory safety assessments that reveal CS hematological or biochemical changes from Baseline values;
- During the course of the study and through the end of study (EOS) develops symptoms or conditions listed in the exclusion criteria;
- Requires a medication prohibited by the protocol; or
- Requests an early discontinuation for any reason.

If a subject experiences an SAE or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an AE, the event will be followed until it is resolved or until it is stable.

3.3.2 Handling of Withdrawals

When a subject withdraws from the study, the reason(s) for withdrawal will be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, any subject who withdraws from the study if willing, should continue to be followed according to the protocol. For example, if termination occurs earlier than planned (i.e., after a subject has received all or partial study drug infusion) all efforts should be made to ensure the remaining protocol visits are completed. If a subject refuses to return for the Follow-up visits, the Day 28 (±2 days) visit procedures should be completed. Any subject who fails to return for final assessments will be contacted by the site in an attempt to obtain compliance with the protocol. The status of subjects who fail to complete final assessments will be documented in the eCRF.

3.3.3 Replacement of Subjects

At the discretion of the investigator after consultation with the Sponsor, any subject who withdraws before completing the study, for reasons other than a DLT, may be replaced. Any replacement subject will be assigned to receive the same treatment as the subject he or she is replacing.

3.4 STUDY TREATMENTS

3.4.1 Method of Assigning Subjects to Treatment Groups

On Study Day 1 eligible subjects will be randomly assigned to treatment with either PB2452 or matching placebo in a 3:1 ratio, PB2452:placebo.

3.4.2 Treatments Administered

PB2452:

PB2452 IV infusion, prepared according to the Pharmacy Manual, will be administered on Day 1 for up to 48 hours. The total dose for each subject will not exceed 30g. The infusion rate will not exceed 18g over 30 minutes and the concentration will not exceed 24g in 250mL. Subjects will not receive more than 250 mL of study drug infusion within any 1-hour period.

For each cohort, the dose, infusion rate, and duration will be communicated from the Sponsor to the study site, PPD, in a Dosing Memo issued prior to initiation of each treatment cohort.

Matching Placebo:

0.9% sodium chloride single IV infusion, administered on Day 1, will be delivered at a rate and volume matching the active infusion.

Ticagrelor:

Ticagrelor 90 mg oral tablet (immediate release) administered as 180 mg (2 × 90 mg tablets) loading dose plus 90 mg every 12 hours for 4 additional doses. In successive cohorts following cohort 1, if indicated in a Dosing Memo from Sponsor to site, one or more cohorts may also receive an additional single oral dose of 90

ASA:

During Screening, starting on Study Day -7, subjects will receive ASA (enteric coated) 81 mg QD to be taken through to the morning of Day 1, prior to receiving study medication. Subjects who were already taking ASA daily before entering the study must be willing to document self-administered daily 81 mg dose of ASA between Day -7 and -3, accept ASA 81 mg administered at the clinical site between Day -2 and Day 1, and suspend further ASA doses until discharge from the clinical facility.

3.4.2.1 Dose Escalation

The SRC will conduct a blinded review of all safety and tolerability data from a cohort at least through Day 3 (e.g., clinical laboratory results, AEs, ECGs, Holter monitoring reports if available, vital signs, and available PK data) and available data for each completed dose cohort and will document their review and assessment in written SRC minutes prior to initiation of a subsequent cohort. Dose escalation may occur only if the SRC affirms the dose and regimen from the previously completed cohorts were safe and well tolerated and no DLTs were observed.

The SRC will be minimally composed of the on-site PPD investigator/medical monitor, PhaseBio medical monitor, and PhaseBio clinical operations lead. Changes to the administration regimen (rate and duration) without escalation of the total dose or without

increases in the infusion rate will not require formal SRC approval. Similarly, reductions in the total dose or the infusion rate will not require SRC approval.

The investigator may make a recommendation concerning whether the safety profile is sufficient to proceed to a higher dose level, whether a pause in dosing for review of additional safety and/or PK data is needed, or whether adjustment of the dose of the next dose cohort is needed. The decision to adjust or pause the dose or proceed to the next cohort will be made by the SRC.

3.4.2.2 Infusion-related or Allergic Reactions

The administration of study drug infusion must be performed under supervision of trained medical staff and where facilities to handle allergic reactions are available. Should a subject experience symptoms typical of IRRs seen with some recombinant protein drugs e.g., lightheadedness, nausea, chills, fever(Doessegger 2015) the study drug infusion must be immediately and permanently discontinued. Should a subject experience symptoms typical of an allergic reaction (e.g., shortness of breath, anaphylaxis, urticaria, angioedema), the study drug administration must be immediately and permanently discontinued. Suspected IRRs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.(NCI CTCAE, v5, 2017) Should any one subject develop a ≥Grade 2 IRR to study drug, all subsequent subjects in the study, inclusive of all dose cohorts, must be administered premedication (diphenhydramine 25 mg by mouth [PO] + acetaminophen 650 mg PO) 30 to 60 minutes prior to receiving study drug to mitigate the risk of IRR. If any recipient of PB2452 (after unblinding) develops a ≥Grade 2 IRR in the absence of premedication, the entire dose level must be repeated as an additional cohort in which all subjects must be premedicated (as described above) 30 to 60 minutes prior to administration of study drug.

To monitor for potential IRRs, vital signs, including BP, HR, Temp, RR, will be assessed at Baseline (prior to study drug infusion), every 10 minutes during the first 30 minutes of the infusion, and every 15 minutes thereafter for the first hour after initiation of the infusion. The remaining assessments of vital signs will be performed as described in the Schedule of Events (Appendix 7.1). Suspected allergic (hypersensitivity) reactions and anaphylaxis will be assessed according to the clinical diagnostic criteria outlined by the National Institute of Allergy and Infectious Diseases provided in the CTCAE v5 in Appendix 7.3 (Definition and Management of Anaphylaxis) and Appendix 7.4 (Clinical Criteria for Diagnosing Anaphylaxis). Subjects will receive appropriate medical treatment for these and other medical concerns at the discretion of the investigator.

3.4.2.3 Dose-limiting Toxicities

The SRC will review all AEs and all laboratory and ECG Holter monitoring abnormalities according to CTCAE v5 to determine whether DLT has been identified in a subject who is confirmed to have received PB2452. If the SRC determines an AE is related to administration of ticagrelor or another confirmed cause, the AE will not be considered a DLT. Definitions of DLT are:

- Any AE assessed as ≥Grade 2 based on the CTCAE v5 grading scale and occurred in a subject confirmed to have received PB2452.
- Any ≥Grade 2 laboratory abnormality (outside the clinical laboratory normal reference range) that occurs in a subject confirmed to have received PB2452.
- Note: For a Grade 2 electrolyte abnormality that spontaneously resolves to ≤Grade 1 without intervention within 24 hours, the SRC may decide to exempt the laboratory abnormality from being considered a DLT.
- Any treatment-emergent adverse event (TEAE) that leads to study withdrawal of a subject confirmed to have received PB2452.

3.4.2.4 Stopping Criteria

Dose escalation or ongoing infusions will be suspended, pending investigation by the SRC, if any of the following occur after confirmation the subject has received PB2452:

- Any preclinical or clinical events that, in the opinion of the SRC, contraindicate further dosing of additional subjects with PB2452
- Any serious AE (SAE) occurring prior to discharge from the clinical site
- Data from previous cohorts indicate safety concerns for dosing at a higher level, such as unanticipated adverse responses (e.g., CS changes in clinical laboratory test data, ECGs Holter monitoring results, vital signs, physical examinations)
- Two or more subjects in a cohort experience any DLT, or 1 subject experiences a ≥Grade 2 AE (DLT) that, in the opinion of the SRC, warrants suspension of dose escalation
- Two or more subjects have >3 x ULN of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or >2 x ULN of bilirubin or alkaline phosphatase (ALP) when no other reason can be found to explain the increases
- One or more subjects experiences a ≥Grade 2 IRR despite having been premedicated for IRRs.

Continuation of dosing following suspension will be determined by the SRC and documented in an ad hoc SRC Safety Report. Dosing may also be suspended if, in the opinion of the SRC or Sponsor, any new or unexpected significant safety or tolerability issues related to ticagrelor or PB2452 are identified that warrant further evaluation before additional subjects are dosed. This may include emerging nonclinical data, clinically relevant AEs, or relevant data from other sources indicating safety concerns, even if the event(s) per se does not meet the protocol-specified definition of a DLT.

Dose-limiting toxicities identified during the study will be assessed as potential indicators of cumulative toxicity and provide rationale for defining the maximum tolerated dose (MTD). Although this study is not designed to dose to a MTD, the MTD may be reached if ≥2 subjects in a dose cohort experience a DLT, as defined in Section 3.4.2.3. There will be no further dosing above the MTD.

3.4.3 Identity of Investigational Product

Study drug PB2452 is supplied as a sterile white to off-white lyophilized cake, free from visible foreign particles in a 20R glass vial at a nominal fill volume of 7.5 mL. PB2452 in the reconstituted state is formulated at 100 mg/mL in 25 mM histidine/histidine hydrochloride buffer, 290 mM sucrose, and 0.05% (w/v) polysorbate-80, pH 6.0.

Matching placebo is a sterile, nonpyrogenic liquid product intended for IV administration composed of 0.9% sodium chloride in water for injection, USP. Separate instructions will be provided to the clinic for dose dilution, preparation, storage, and administration.

3.4.4 Management of Clinical Supplies

3.4.4.1 Packaging and Storage

PhaseBio Pharmaceuticals, Inc will provide the investigator and clinical site with adequate quantities of PB2452, and matching placebo. The study site will purchase commercially available ticagrelor 90 mg tablets and ASA 81 mg tablets.

PB2452 will be supplied in a 20R glass vial at a nominal fill volume of 7.5 mL, stoppered with siliconized 20 mm chlorobutyl elastomer, flurotec-coated, single vent lyophilization stopper, and sealed with flip-off cap overseal. Following reconstitution with water for injection, PB2452 is further diluted into 0.9% saline for IV infusion.

The clinical site pharmacy will prepare a single dose for each subject based on the dosing cohort and randomization assignment. The concentration will vary between 0.4 mg/mL up to 72 mg/mL. Separate instructions will be provided to the clinic for dose dilution, preparation, storage, and administration.

PB2452 must be stored in a secure area (e.g., a locked, temperature-controlled unit) at 2°C to 8°C (36°F to 46°F) protected from moisture and light with access restricted to necessary clinic personnel. with access restricted to necessary clinic personnel. The clinical site will be required to keep a temperature log to establish a record of compliance with these storage conditions.

3.4.4.2 Drug Accountability

The investigator will maintain accurate records of receipt of all drug supplies used in this study including lot numbers (if applicable) and dates of receipt. In addition, accurate records

will be kept regarding when and how much drug is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all drugs will be reconciled and retained or destroyed according to applicable regulations.

3.4.5 Blinding

This is a double-blind study. Neither the subjects nor the investigator will be aware of the treatment assignment. Blinding will be maintained throughout the study by use of active and placebo dose forms prepared to be similar in appearance. To maintain the blind, only designated pharmacy staff at the study site will have access to the randomization code and will prepare each dose for each subject. In order to prepare preliminary summaries of safety, PK, and/or PD data, as needed, to make timely decisions concerning adjustment of study procedures, dosing regimens, or potentially early termination of the study, certain designated staff at PhaseBio (e.g. study director, a single biostatistician, and bioanalytical scientist[s]) study drug accountability monitor, will receive unblinded data after each cohort completes Day 3 assessments. Except as noted above, all other members of PhaseBio will remain blinded. Access to the randomization code will be strictly controlled according to PPD SOPs.

3.4.6 Treatment Compliance

All doses of study drug, matching placebo, and ticagrelor will be administered at the clinical site under direct observation of clinic personnel and recorded in the eCRF.

The date, time, and actual dose received of study drug and matching placebo infusion and ticagrelor dosing will be recorded on the appropriate pages of the eCRF. If a subject was scheduled to receive any of these drugs and did not, the reason for the missed or partial dose will be recorded in the eCRF pages.

3.4.7 Breaking the Blind

A subject may be unblinded in the event of a DLT, an SAE, or if there is a medical emergency when the identity of the drug must be known to properly treat a subject. A cohort may be unblinded to determine if dose escalation to the next dose level will or will not proceed. In the event of a medical emergency requiring identification of the study drug administered to an individual subject, the investigator will make every attempt to contact the medical monitor to explain the need for opening the code within 24 hours of performing that task. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

3.4.8 Prior and Concomitant Medication

Prior medications are defined as medications taken prior to the first dose of study medication, regardless of whether they are continued or not after the first dose of study medication. Concomitant medications are defined as medications taken on or after the first dose date of study medication, including those started before the first dose and continued into the treatment period.

3.4.8.1 Prior Medication and Therapies

Information about prior medications taken by the subject within 30 days before he or she provides informed consent will be recorded in the subject's eCRF.

3.4.8.2 Concomitant Medication and Therapies

Subjects are prohibited from taking any additional prescription or OTC medications or nutritional supplements during their participation in the study (with the exception of protocol allowed medications, hormonal birth control and/or chronic medications). Paracetamol/acetaminophen or other medications may be administered at the discretion of the investigator at doses of up to 2 g/day.

Subjects are prohibited from therapy with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers. A list of example inhibitors and inducers of CYP3A4 is presented in Appendix 7.2.

Subjects are prohibited from taking NSAIDs (within 14 days of screening), anticoagulants, or other antiplatelet agents within 30 days of screening.

Concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD). With the exception of drug therapy specified in the protocol, if drug therapy is taken, a joint decision will be made by the investigator and the Sponsor whether to continue or discontinue the subject based on the time the medication was administered, its pharmacology and PK, and whether the use of the medication will compromise the subject's safety or interpretation of the data. It is the investigator's responsibility to ensure that details regarding the medication are accurately recorded in the eCRF.

3.5 STUDY PROCEDURES

After signing the ICF, subjects will have study procedures at the time points specified in the Schedule of Events (Appendix 7.1).

Screening (Days -45 to -4)

- Subjects sign informed consent
- Inclusion/Exclusion criteria

- Demographics
- Medical history
- Urine drug screen, including cotinine
- Urine alcohol screen
- Serum pregnancy test for women of childbearing potential
- Serology test
- Stool occult blood test
- Physical examination, full, including height, weight, and BMI calculation
- Vital signs measured including SBP and DBP, oral body temperature, respiration rate (RR), and HR
- 12-lead ECG
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis

Screening (Day -7)

- Subjects start receiving ASA 81mg QD (Subjects who enter the study already taking ASA daily will document a daily ASA 81 mg dose.)

Screening (Day -6)

- Subjects receive ASA 81mg QD

Screening (Day -5)

- Subjects receive ASA 81mg QD

Screening (Day -4)

- Subjects receive ASA 81mg QD

Check-in/Pretreatment - Baseline (Day -3)

- Subjects receive ASA 81mg QD
- Inclusion/Exclusion criteria
- Urine drug screen, including cotinine
- Urine alcohol screen
- Serum pregnancy test for women of childbearing potential
- Admission to study site
- Physical examination, full, including weight,
- Vital signs measured including SBP and DBP, oral body temperature, RR, and HR
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- Blood sampling for PD (LTA/PRU/VASP)
- Serum immunogenicity
- AEs collected

Pretreatment - Baseline (Day -2)

- Subjects receive ASA 81mg QD

- Administration of ticagrelor begins in the morning, single dose oral ticagrelor 180 mg (2 x 90 mg), followed by oral ticagrelor 90 mg every 12 hours for 4 additional doses through to Day 1 (2 hours before study drug is initiated; for a total of 5 doses of ticagrelor)
- Urine sampling, PK
- Blood sampling for PD (LTA/PRU/VASP)
- AEs collected

Pretreatment - Baseline (Day -1)

- Inclusion/Exclusion criteria
- Subjects receive ASA 81mg QD
- 12-lead ECG
- Biomarkers
- Ticagrelor administered
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- AEs collected

On-site Treatment – Randomization (Day 1)

- Administration of ASA 81mg 2 hours prior to study drug administration
- Administration of ticagrelor 2 hours prior to study drug administration
- 12-lead ECG *before* study drug is administered
- Continuous 12-lead Holter monitor placed 2 hours b*efore* administration of study drug will remain in place for 24 hours *after* initiation of study drug. Subjects should be resting in the supine or semi-recumbent position depending upon Dosing Memo.
- Vital signs (SBP, DBP, oral body temperature, RR, HR) measured 30 to 60 minutes prior to and during infusion of study drug according to Schedule of Events (Appendix 7.1)
- Randomization
- Administration of PB2452 or matching placebo at Hour 0
- Blood sampling for PK: plasma PB2452, ticagrelor, and TAM PK, collected within 10 minutes *before* initiation of PB2452 infusion at Hour 0
- Blood sampling for PK: plasma PB2452, ticagrelor, and TAM PK, collected according to the cohort-specific Dosing Memo
- Blood sampling for PD: LTA/PRU/VASP according to the cohort-specific Dosing Memo
- Urine sampling (PK)
- Infusion site assessment
- Serum immunogenicity prior to dosing
- AEs collected

On-site Treatment (Day 2)

- Vital signs measured
- 12-lead ECG
- Continuous ECG recording (Holter) for ECG evaluation to remain in place for 24 hours *after* initiation of study drug on Day 1
- Administration of ticagrelor in cohorts specifying a 6th dose of ticagrelor
- Blood sampling for plasma PB2452, ticagrelor, and TAM PK, collected according to the cohort-specific Dosing Memo
- PK Urine sampling
- Blood sampling for PD: LTA/PRU/VASP according to the cohort-specific Dosing Memo
- Biomarkers
- Infusion site assessment
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- AEs collected

On-site Treatment (Day 3)

- Physical examination, brief, includes querying the subject concerning any changes from Baseline
- 12-lead ECG
- Vital signs measured
- Blood sampling for PK: plasma PB2452, ticagrelor, and TAM PK collected according to the cohort-specific Dosing Memo
- Urine sampling (PK)
- Blood sampling for PD: LTA/PRU/VASP according to the cohort-specific Dosing Memo
- Infusion site assessment
- AEs collected
- Subjects discharged from site

Out-patient, Return to Study Site, Follow-up (Day 7)

- Physical examination, brief, includes querying the subject concerning any changes from Baseline
- Vital signs measured
- 12-lead ECG
- Blood sampling for PK: plasma PB2452, ticagrelor, and TAM PK, collected according to the cohort-specific Dosing Memo
- Biomarkers
- Serum immunogenicity
- Infusion site assessment
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- AEs collected

Out-patient, Return to Study Site, Follow-up, End of Study (Day 28 ±2 Days)

- Serum pregnancy test
- Physical examination, full, including height, weight, and BMI calculation
- Vital signs measured
- 12-lead ECG
- Blood sampling for PK: plasma PB2452, ticagrelor, and TAM PK, collected according to the cohort-specific Dosing Memo
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- Biomarkers
- Serum immunogenicity
- AEs collected

3.5.1 Pharmacokinetic Sample Collection

Samples for PK analyses should be collected after subjects has been resting supine for ≥10 minutes. Additional details concerning the collection, preparation, and handling of PK blood and urine samples and sample shipping instructions will be provided to the clinical site. The clinical site will store all urine and plasma samples at the designated temperatures until shipped to the appropriate laboratories for analysis. Back-up samples will be maintained by the clinical site under the same conditions or at a designated storage facility until the Sponsor indicates the back-up samples should be shipped to the Sponsor.

PB2452 PK and immunogenicity analysis will be performed by:

PhaseBio Pharmaceuticals, Inc.
1 Great Valley Parkway, Suite 30
Malvern, PA 19355
Telephone: 610-981-6500

Ticagrelor and TAM concentration analysis will be performed by:

Covance
1121 East 3900 South, Suite C-110
Salt Lake City, UT 84124
Telephone: 801-313-6450

3.5.1.1 Bioanalytical Methods

Pharmacokinetic samples for total and free ticagrelor and the metabolite TAM will be analyzed using a validated liquid chromatography coupled with tandem mass spectrometry assay in human plasma. Pharmacokinetic samples for PB2452 will be analyzed using an immunoassay. The methods will be validated according to ICH standards and fit for purpose. Details of the bioanalytical methods and validation will be available in a separate bioanalytical report.

3.5.1.2 Pharmacodynamic Sample Collection

Blood samples for PD analysis will be collected at the following times: Day -3, -2, Day 1 (within 10 minutes prior to the initiation of study drug infusion [Hour 0] and per Dosing Memo), Day 2, and Day 3 if needed.

Collection time points for each cohort will be specified in a Dosing Memo from the Sponsor to PPD prior to initiation of each cohort.

Blood samples will be collected in collection tubes specific for each of the 3 PD assays. Specific instructions referring to the collection, processing, testing and, when applicable, the shipment of PD samples to CirQuest Labs, will be in the laboratory manual provided by CirQuest Labs and must be followed. If there is a discrepancy between the protocol and the lab manual, the lab manual should be followed.

- LTA: 3.2% sodium citrate (blue-top)
- VerifyNow® $P2Y_{12}$: Greiner Bio-One Vacuette® partial fill blood collection tube containing 3.2% sodium citrate
- VASP: 3.2% sodium citrate (blue-top)

3.5.2 Adverse Events

3.5.2.1 Adverse Event Definitions

The investigator is responsible for reporting all AEs observed or reported during the study, regardless of their relationship to study drug or their clinical significance. If there is any doubt whether a clinical observation is an AE, the event should be reported. For the purposes of AE recording when relationship to study drug is assessed, study drug refers to PB2452 or placebo. A separate line on the eCRF is for assessing whether or not an AE is related to the administration of ticagrelor.

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A TEAE is defined as any AE not present before exposure to study drug or any AE already present that worsens in intensity or frequency after exposure to study drug.

A suspected adverse reaction is any AE for which there is a reasonable possibility the study drug caused the AE. For the purposes of investigational new drug (IND) safety reporting, “reasonable possibility” means there is evidence to suggest a causal relationship between the study drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than “adverse reaction,” which means any AE caused by a study drug.

An adverse reaction is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions when there are reasons to conclude the drug caused the event.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or at the specificity or severity that has been observed with the study drug; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions mentioned in the IB that occur with a certain class of drugs or as anticipated based on the pharmacological properties of the drug but are not specifically mentioned as having occurred with the specific drug under investigation.

An AE or suspected adverse reaction is considered an SAE/suspected unexpected serious adverse reaction if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect

Important medical events that may not result in death, may not be life threatening, or may not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered "life threatening" if, in the opinion of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Special attention will be given to DLTs and the MTD, if applicable. DLT is defined in Section 3.4.2.3. The overall safety profile, including but not limited to DLTs and MTDs will be used in the selection of the starting dose(s) in future studies of PB2452 administered by infusion.

3.5.2.2 Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to PhaseBio Pharmaceuticals, Inc. From the time informed consent is signed through to completion of all study procedures and assessments at the Day 28 (±2 days) visit, all AEs will be assessed.

Subjects may spontaneously report and/or will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have used any new medications or changed concomitant medication regimens (both prescription and OTC medications).

In addition to subject observations, AEs will be documented from any data collected on the AE page of the eCRF (e.g., laboratory values, physical examination findings, ECG, Holter monitoring changes) or other documents relevant to subject safety.

3.5.2.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, time of onset, dosage, investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant (NCS). The current version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition present at the time the subject is screened but does not deteriorate should not be reported as an AE. However, if the condition deteriorates at any time during the study, it should be recorded as an AE.

Any AE considered serious by the investigator or that meets SAE criteria (Section 3.5.2.1) must be reported to the Sponsor immediately (after the investigator has confirmed the occurrence of the SAE). The investigator will assess whether there is a reasonable possibility the study drug caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE, as outlined in the US Title 21 Code of Federal Regulations (CFR) Parts 312 and 320. The investigator is responsible for notifying the Institutional Review Board (IRB) directly.

The following contact information is to be used for SAE reporting:

PPD Medical Monitor: Rahul Bhatnagar, MD
PPD 7551 Metro Center Drive, Suite 300

Austin, TX 78744
Telephone (24 hour): 888-483-7729
Fax: 888-529-3580
email: rtpsafety@ppdi.com

3.5.2.4 Assessment of Severity

The severity (or intensity) of an AE will be determined by the investigator and refers to the extent to which it affects the subject's daily activities. Severity will be classified as mild, moderate, or severe using the following criteria:

- *Mild:* These events require minimal to no treatment and do not interfere with the subject's daily activities.
- *Moderate:* These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning.
- *Severe:* These events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow assessment of the duration of the event at each level of intensity. An AE characterized as intermittent requires documentation of onset and duration of each episode. The CTCAE v5 grading scale will be used by the SRC to assess all IRRs to determine whether premedication is required to mitigate future potential IRRs for subsequent study subjects. Additionally, CTCAE v5 will be used by the SRC to assess all AEs and laboratory abnormalities to determine whether a DLT and/or stopping criteria have been reached.

3.5.2.5 Assessment of Causality

The investigator's assessment of the relationship between an AE and study drug or ticagrelor is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality of all AEs and SAEs (i.e., whether there is a reasonable certainty the study drug caused the event). The relationship between an AE and an SAE to study drug (and ticagrelor) will be characterized using the following classifications:

- *Unrelated:* This relationship suggests there is no association between study drug (or ticagrelor) and the reported event.
- *Possible:* This relationship is based on evidence suggesting a causal relationship between the study drug (or ticagrelor) and the AE (i.e., there is a reasonable possibility the drug caused the event). The event follows a reasonable temporal sequence from the time of drug administration or the event follows a known response pattern to study drug (or ticagrelor) but could also have been caused by other factors.
- *Probable:* This relationship suggests a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the

drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with study drug (or ticagrelor) seems likely.

- *Definite:* This relationship suggests that a definite causal relationship exists between study drug (or ticagrelor) administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

3.5.2.6 Follow-up of Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed until it is resolved or stable or judged by the investigator to be not clinically significant (NCS).

3.5.3 Clinical Laboratory Testing

Clinical laboratory tests will be performed by PPD Central Laboratory. Blood will be collected at the time points indicated in the Schedule of Events (Appendix 7.1) and will be prepared using standard procedures. Repeat clinical laboratory tests may be performed at the discretion of the investigator, if necessary, to evaluate inclusion and exclusion criteria or clinical laboratory abnormalities. The clinical laboratory performing the tests will provide the reference ranges for all clinical laboratory parameters.

The following clinical laboratory assessments will be performed:

Hematology	Complete blood count (CBC) with differential hematocrit (hct) hemoglobin (Hgb) mean corpuscular hemoglobin (MCH) mean corpuscular hemoglobin concentration (MCHC) mean corpuscular volume (MCV) mean platelet volume (MPV) platelet count erythrocyte (red blood cell [RBC]) count total and differential leukocyte (white blood cell [WBC]) count
Serum Chemistry	alanine aminotransferase (ALT) albumin alkaline phosphatase (ALP) aspartate aminotransferase (AST) bicarbonate bilirubin (total and direct) blood urea nitrogen (BUN) calcium chloride cholesterol total high-density lipoprotein (HDL) calculated low-density lipoprotein (LDL) creatine phosphokinase creatinine gamma-glutamyl transferase (GGT)

	glucose Hgb A1C lactate dehydrogenase (LDH) magnesium phosphorus potassium sodium thyroid stimulating hormone (TSH; Screening only) total protein triglycerides (repeat fasting triglyceride if TG >500) uric acid
Coagulation	activated partial thromboplastin time (aPTT) international normalized ratio (INR) partial thromboplastin time (PTT) prothrombin time (PT)
Urinalysis (should be aligned to PPD urinalysis)	appearance bilirubin color glucose ketones leukocyte esterase reflex microscopy (at Screening and Check-in only, if dipstick is positive for protein or blood value ≥1+); includes bacteria, casts crystals, epithelial cells RBCs, WBCs nitrites, occult blood pH, protein specific gravity (SpGr), turbidity urobilinogen
Serology	hepatitis B surface antigen (HBsAg) hepatitis C virus (HCV) antibody human immunodeficiency virus (HIV) types 1 and 2 antibodies (Screening only)
Other analyses	urine drug screen (Screening and Check-in only): amphetamines barbiturates benzodiazepines cannabinoids cocaine cotinine methylenedioxymethamphetamine (MDMA) opiates phencyclidine propoxyphene tetrahydrocannabinol urine alcohol (Screening and Check-in only) female subjects: follicle-stimulating hormone (FSH; Screening only) serum pregnancy test (human chorionic gonadotropin [Screening, Check-in, and Day 28 (±2 days) only])

Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter. The investigator will determine whether any of the abnormally high or low results are CS or NCS. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, therapeutic measures). If a CS change from the Screening value is noted, the CS value and etiology or reason for clinical significance will be documented on the AE page of the eCRF. The investigator will continue to monitor the subject with additional assessments until the values have reached either the reference range or the values at Screening or until the investigator determines that follow-up is no longer medically necessary.

When schedule procedures overlap at the same time point (see Schedule of Events (Appendix 7.1). there must be planning to collect the specific information within the designated time window. Accordingly, the importance of these procedures is:

1. *Blood collection* (whether for PD, PK, immunology, or safety) should always be collected at the designated time point (if possible). However, multiple collections (PD, PK, immunology, and safety) may be required at the same time point. Therefore, the recommendation is for blood to be drawn in this order: PD, PK, immunology, and safety (see lab collection manual from CirQuest for additional information related to collection of PD samples).
2. The *12-lead ECG Holter monitoring* has a ±10-minute window (unless otherwise designated in the Schedule of Events, [Appendix 7.1]) when this may be done, either before or after blood collection.
3. If time permits, *vital sign measurements* should be completed just prior to or just after blood collection; this may be still be done within the designated window in the Schedule of Events (Appendix 7.1).

3.5.4 Vital Signs Measurements

Vital signs will be measured at the time points indicated in the Schedule of Events (Appendix 7.1).

Vital sign measurements will include SBP, DBP, oral body temperature, RR, and HR. The subject will have rested in a supine position for ≥10 minutes before all measurements are taken. *Note:* Vital signs collected during the initial 30 minutes of infusion of study drug require only the BP and HR.

The investigator will determine whether any of the vital sign measurements are CS or NCS. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, therapeutic measures). If a CS change from Screening values is noted, the CS value and reason for clinical significance will be documented on the AE page of the eCRF. The investigator will continue to monitor the subject with additional assessments until the value

has reached either the reference range or the value at Screening or until the investigator determines follow-up is no longer medically necessary.

3.5.5 Twelve-lead Electrocardiogram

Twelve-lead ECGs will be obtained after the subject has rested in the supine position for ≥10 minutes or as clinically indicated based on reported AEs or laboratory findings, as necessary. The investigator should review and sign the ECG for any immediate issues. Electrocardiogram assessments will include comments concerning whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, and any evidence of MI, or ST-segment, T-Wave, and U-Wave abnormalities. In addition, measurements of these intervals will be reported: RR interval, PR interval, QRS width, and and QTcF

The investigator will determine whether any of the 12-lead ECG results are CS or NCS. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, therapeutic measures). If a CS change from Screening is noted, the CS value and reason for CS will be documented on the AE page of the eCRF. The investigator will continue to monitor the subject with additional assessments until either the values have reached either reference range or the values at Screening or until the investigator determines follow-up is no longer medically necessary.

3.5.6 Holter Monitoring (Continuous Twelve-lead ECG)

Holter monitoring (continuous 12-lead ECG recording) for 24 hours will be performed at the time points indicated in the Schedule of Events (Appendix 7.1) to monitor HR and rhythm activity as standard safety measurements. The clinical research site will be responsible for providing trained study personnel for setting up and managing the Holter monitoring system to ensure that reports of Holter findings for each subject will be available for review at the safety review meeting for each cohort. The continuous ECG waveform data recorded by the Holter device will be stored for optional exposure-response QTc analysis. The Holter monitoring system used will be maintained in accordance with the clinical research site SOPs.

The SRC will determine if any of the Holter findings are CS at the safety review meetings. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, therapeutic measures).

If a CS finding from the Holter report is noted, the CS findings and etiology or reason for clinical significance will be documented in the AE page of the eCRF. The SRC may recommend repeat Holter monitoring during the 28-day safety period if clinically indicated.

3.5.7 Physical Examinations

A physical examination will be performed at the time points indicated in the Schedule of Events (Appendix 7.1).

A full physical examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities.

A brief physical examination will include assessment of skin (including any signs of cutaneous erythema), lungs, cardiovascular system, and abdomen (liver, spleen). Interim physical examinations will be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Height and weight will be measured, and BMI will be calculated at Screening and at Day 28 (±2 days).

3.5.8 Infusion Site Assessments

The infusion site will be examined by the investigator or designée concerning pain, tenderness, erythema/redness, and induration/swelling, as indicated in the Schedule of Events (Appendix 7.1). Infusion site reactions will be assessed according to the CTCAE v5 grading scale and will be recorded as AEs; these should be followed until resolution.

3.5.9 Immunogenicity Assessments

Immunogenicity (antibody) samples will be screened for the presence of binding anti-drug antibodies (ADA) at the time points indicated in the Schedule of Events (Appendix 7.1).

Results of immunogenicity samples taken prior to administering study drug do not need to be available prior to dosing nor to confirm subject eligibility. A subject who tests positive for ADAs at the final scheduled visit (Day 28 ±2 days) will be asked to return for follow-up sampling approximately 3 months after the final visit and approximately every 6 months thereafter until ADAs no longer test positive or until levels return to a predose state.

3.6 STATISTICAL CONSIDERATIONS

3.6.1 Sample Size Calculations

The sample size (N) of up to 5 cohorts of approximately for this study is based on clinical and practical considerations rather than on formal statistical power calculation. The sample size will provide preliminary safety, efficacy and PK information in a dose/regimen finding fashion.

3.6.2 Analysis Populations

The *Safety Population* will include all subjects who receive any amount of study drug.

The *PK Population* will include subjects in the safety population who have ≥1 measurable PK concentration.

The *PD Population* will include subjects in the safety population who receive ≥1 dose of ticagrelor and have ≥1 measurable post dose PRU value.

3.6.3 Statistical Analysis

Details concerning all statistical analyses will be described in a separate Statistical Analysis Plan (SAP). All data collected during the study will be presented in Data Listings.

Data from subjects excluded from an analysis population will be presented in the Data Listings but will not be included in the calculation of summary statistics.

Data from subjects who receive placebo will be pooled across cohorts for all presentations.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation [SD], minimum, and maximum).

Demographic and baseline characteristics will be summarized. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

3.6.3.1 Pharmacokinetic Analyses

Plasma concentrations will be listed and summarized descriptively (number of subjects, arithmetic mean, SD, coefficient of variation [CV], median, minimum, and maximum). Plasma concentration versus time profiles for each subject will be presented graphically. The mean plasma concentration versus scheduled time profiles will be presented graphically by dose.

Pharmacokinetic parameters will be summarized by time point for each dose level using descriptive statistics (number of subjects, mean, standard deviation (SD), CV, median, minimum, and maximum). Geometric means will be reported for AUCs and C_{max}. For Cohorts receiving a 6^{th} dose of ticagrelor 24 hours following study drug, PK parameters will be calculated for Days 1 and 2 separately.

The PK parameters of PB2452, ticagrelor, and TAM will be determined with noncompartmental methods using Phoenix® WinNonlin® (Certara, L.P., Princeton, NJ) Version 6.4 or higher or SAS® Version 9.3 or higher (SAS Institute Inc., Cary, NC). Actual

sampling times, rather than scheduled sampling times, will be used in all calculations of PK parameters. However, for ease of presentation, scheduled sampling times will be used to present results in tables, listings, and figures.

3.6.3.2 Pharmacodynamic Analyses

Pharmacodynamic data will be summarized for each time point using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum). Pharmacodynamic parameters will also be summarized for each cohort. For Cohorts receiving a 6th dose of ticagrelor 24 hours following study drug, PD parameters will be calculated for Days 1 and 2 separately.

3.6.3.3 Safety Analyses

Adverse events will be coded by preferred term and system-organ-class (SOC) using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). All AE data will be presented in Data Listings. Treatment-emergent AEs (TEAEs) will be summarized by treatment and overall, as well as by severity and relationship to study drug. All SAEs and AEs leading to discontinuation of study drug will be presented in the Data Listings.

Actual values and changes from Baseline in clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, standard deviation [SD], median, minimum, and maximum). Clinical laboratory test results, vital sign measurements, 12-lead ECG results, Holter monitor results, immunogenicity results, and physical examination findings will be presented in Data Listings.

3.6.4 Handling of Missing Data

Concentrations below the limit of quantification (BLQ) will be treated as zero for descriptive statistics. Mean BLQ concentrations will be presented as BLQ, and the SD and CV will be reported as not applicable. Missing concentrations will be excluded from the calculations.

For the PK analysis, BLQ values will be treated as zero with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing. Missing concentrations will be treated as missing from the PK parameter calculations. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

3.6.5 Interim Analyses

There is no interim analysis planned for this study.

3.7 DATA QUALITY ASSURANCE

This study will be conducted using quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with current ICH guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current GCP, the protocol, and SOPs. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documents, and discussion of the conduct of the study with the investigator and staff.

Electronic CRFs and electronic data capture will be used. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that provides record traceability. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

4. INVESTIGATOR OBLIGATIONS

Administrative items provided in this section are meant to guide the investigator in the conduct of the study and may be subject to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

4.1 CONFIDENTIALITY

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the Sponsor, designee, the US Food and Drug Administration, or the IRB.

The investigator and all employees and coworkers involved in this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or designee must be obtained for the disclosure of any said confidential information to other parties.

4.2 INSTITUTIONAL REVIEW

Federal regulations and ICH guidelines require approval to be obtained from an IRB before human subjects participate in research studies. Before study onset, the protocol, ICF, advertisements to be used for recruitment of study subjects, and any other written information concerning this study must be provided to the subject must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH E6(R2): GCP will be maintained by the site and will be available for review by the Sponsor or designee. All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

4.3 SUBJECT CONSENT

Written informed consent in compliance with US Title 21 CFR Part 50 will be obtained from each subject before he or she enters the study or before any unusual or non-routine procedure is performed that involves risk to the subject. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured the subject understands the implications of participating in the study, the subject will be asked to give his/her consent to participate in the study by signing the ICF. A copy of the ICF will be provided to the subject/legal guardian.

4.4 STUDY REPORTING REQUIREMENTS

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his/her IRB, as appropriate.

4.5 FINANCIAL DISCLOSURE AND OBLIGATIONS

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigator must provide the Sponsor with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for
1 year following completion of the study.

Neither the Sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor PPD is financially responsible for further treatment of the disease under study.

4.6 INVESTIGATOR DOCUMENTATION

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2 and US Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval
- The original signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the principal investigator and each sub-investigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. CVs will be signed and dated by the principal investigators and sub-investigators at study start-up, indicating they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study to be provided to the subject or legal guardians
- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with US Title 42 CFR Part 493.

4.7 STUDY CONDUCT

The investigator will agree to perform all aspects of this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH E6(R2): GCP, the protocol, and all national, state, and local laws or regulations.

4.8 DATA COLLECTION

4.8.1 Case Report Forms and Source Documents

Site personnel will maintain source documentation and enter subject data into the eCRF as accurately as possible and will rapidly respond to any reported discrepancies.

Electronic CRFs and electronic data capture will be used. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved in the study will have an individual identification code and password that provides record traceability. Therefore, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the investigator. This system provides site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information.

4.9 ADHERENCE TO PROTOCOL

The investigator will agree to conduct the study as outlined in this protocol, in accordance with ICH E6(R2) and all applicable guidelines and regulations.

4.10 REPORTING ADVERSE EVENTS

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in this protocol. In addition, the investigator agrees to

submit annual reports to his/her IRB, as appropriate. The investigator also agrees to provide the Sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

4.11 INVESTIGATOR'S FINAL REPORT

Upon completion of the study, the investigator, when applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study outcome and provide the Sponsor and regulatory authority(ies) with any reports required.

4.12 RECORD RETENTION

Essential documents should be retained until ≥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 ≥2 years have elapsed since the formal discontinuation of clinical development of PB2452. 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 Sponsor's responsibility to inform the investigator/institution when these documents no longer need to be retained.

4.13 PUBLICATIONS

After completion of the study, the study data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publications to which it will be submitted, and any other related issues. The Sponsor has final approval authority over all such issues.

Data from this study are the property of the Sponsor and cannot be published without their prior authorization; however, data and any publication thereof will not be unduly withheld.

5. ETHICS

5.1 ETHICAL CONDUCT OF THE STUDY

PhaseBio Pharmaceuticals, Inc and designées carried out all aspects of this study in accordance with the US Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), IRBs (21 CFR 56), and the obligations of clinical investigators (21 CFR 312). U.S. Title 21 CFR on Good Clinical Practice (GCP) is consistent with principles set forth by the Declaration of Helsinki and the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. The study will be registered on Clinicaltrials.gov in accordance with Section 801 of the FDA Amendments Act of 2007 (FDAAA).

All Investigators were required to review and sign a Food and Drug Administration (FDA) Form 1572 and Sponsor-provided Study Operations Manual which described the Investigator's responsibility according to ICH/GCP guidelines.

5.2 INSTITUTIONAL REVIEW BOARD

The study protocol and amendments, ICFs, advertisements, and other information given to study subjects and/or their guardians will be reviewed and approved by the Institutional Review Board (IRB) of each study center prior to use. Each investigator will be responsible for informing the IRB of the progress of the study and submitting annual reports. This study will be conducted in the US, North America.

6. STUDY MANAGEMENT

6.1 MONITORING

6.1.1 Monitoring the Study

The clinical monitor, as a representative of the Sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documents, and discussion of the conduct of the study with the investigator and staff. All aspects of the study will be carefully monitored by the Sponsor or designee in compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and SOPs.

6.1.2 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the Sponsor, their representatives, the FDA, or other regulatory agency access to all study records.

The investigator should promptly notify the Sponsor and study site(s) of any audits scheduled by any regulatory authorities and promptly forward to the Sponsor copies of any audit reports received.

6.2 MANAGEMENT OF PROTOCOL AMENDMENTS AND DEVIATIONS

6.2.1 Modification of the Protocol

Any changes in this clinical study, except those necessary to remove an apparent immediate hazard to a subject, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol must be submitted in writing to the investigator's IRB and approved before subjects are enrolled into an amended protocol.

6.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from or a change to the protocol without prior IRB approval to eliminate an immediate hazard to study subjects. As soon as possible after such an event, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be

submitted to the IRB for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important protocol deviation (sometimes referred to as a protocol violation or a major protocol deviation) is a subset of protocol deviations that might significantly affect the reliability of study data or might significantly affect subject safety. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH E6(R2) guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified by the monitor of deviations in writing. The IRB should be notified of protocol deviations, if appropriate, in a timely manner.

6.3 STUDY TERMINATION

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue at any time for clinical or administrative reasons.

The EOS is defined as the date on which the last subject completes the last visit; this includes the EOS visit and any additional long-term follow-up required for monitoring the resolution of an AE; the finding may be appended to the Clinical Study Report CSR.

6.4 FINAL REPORT

Whether the study is completed or prematurely terminated, the Sponsor will ensure CSRs are prepared and provided to regulatory agency(ies) according to the applicable regulatory requirement(s). The Sponsor will also ensure CSRs in marketing applications meet the standards of the ICH E3: Structure and Content of Clinical Study Reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for approval of the CSR. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have an opportunity to review complete study results.

Upon completion of the CSR, the investigator(s) will be provided with the final approved CSR, as appropriate.

7. APPENDICES

This section presents the following:

Appendix 7.1 Schedule of Events

Appendix 7.2 Examples of Inhibitors and Inducers of CYP3A4

Appendix 7.3 Definition and Management of Anaphylaxis Summary Report

Appendix 7.4 Clinical Criteria for Diagnosing Anaphylaxis

7.1 SCHEDULE OF EVENTS

Procedure	Screening[a]		Check-in/ Pretreatment			Rand		Subjects Discharged	FUP	FUP/End of Study (EOS)
Study Day(s)	**–45 to –4**	**-7**	**–3**	**-2**	**–1**	**1**	**2**	**3**	**7**	**28 (±2)**
Sign informed consent	X									
Inclusion/exclusion criteria	X		X		X					
Demographics	X									
Medical history	X									
Urine drug screen	X		X							
Urine alcohol screen	X		X							
Serum pregnancy test[b]	X		X							X
Serology testing	X									
Stool occult blood test	X									
Admission to study site clinic			X							
Physical examination[c,d]	X[c]		X[c]					X[d]	X[d]	X[c]
Vital sign measurements[e]	X		X			X	X	X	X	X
12-lead ECG[f]	X				X	X	X	X	X	X
Continuous ECG recording (Holter)						X	X[j]			
Clinical laboratory testing	X		X		X		X		X	X
Randomization						X				
Drug administration										
Ticagrelor[g]				X	X	X	(X)*			
PB2452/Placebo[h]						X				
ASA 81 mg QD[i]	X	X	X	X	X	X				
PK blood sampling**										
Plasma PB2452						X	X	X	X	X
Plasma ticagrelor/TAM						X	X	X	X	X
Free plasma ticagrelor/TAM						X	X	X	X	X
PK urine sampling***				X		X	X	X		
PD sampling (LTA/PRU/VASP)[k]			X	X		X	X	X		
Biomarkers**					X		X		X	X
Infusion site assessment[l]						X	X	X	X	
Serum immunogenicity[m]			X			X[m]			X	X
Adverse events			X	X	X	X	X	X	X	X
Discharge from clinical site								X[n]		

Abbreviations: ADA=anti-drug antibody; ASA=acetaminophen, aspirin; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; EOS=end of study; FUP=follow-up; HR=heart rate; LTA=light transmittance aggregometry; PD=pharmacodynamics; PK=pharmacokinetics; PRU=$P2Y_{12}$ reaction units; QD=once daily; Rand=Randomization; RR=respiratory rate; SBP=systolic blood pressure; TAM=ticagrelor active metabolite AR-C124910XX; VASP=vasodilator-stimulated phosphoprotein

(Continued)

Schedule of Events (Cohort 1) *(continued)*

* In successive cohorts following Cohort 1, if indicated in a Dosing Memo from Sponsor to site, one or more cohorts may also receive a 6th dose of ticagrelor 90 mg, 24 hours after initiation of PB2452 (or placebo) infusion on Day 1.

** Modifications to this schedule may be made in a Dosing Memo from Sponsor to site prior to initiation of each cohort. For cohorts receiving a 6th ticagrelor dose only: Sampling times will be specified in a Dosing Memo from Sponsor to site.

*** Modifications to this schedule may be made in a Dosing Memo from Sponsor to site prior to initiation of each cohort. For cohorts receiving a 6th ticagrelor dose only: Pooled urine samples to assess urine ticagrelor and TAM concentrations will be collected over the following intervals beginning with the 6th ticagrelor dose: 0 to 6, 6 to 12, and 12 to 24 hours.

a=Screening Period=Days -45 to -4 (including Day -7, when ASA is started).

b=Serum pregnancy test for women of childbearing potential

c= A full physical examination is conducted at Screening, Day -3 and Day 28. Height and BMI calculation are completed at Screening and Day 28 only. Weight is collected at Screening, Day -3 and Day 28.

d=Brief physical examination (querying the subject concerning any changes from Baseline)

e= Vital sign measurements (SBP and DBP, oral body temp, RR, and HR) will be collected at screening, check-in, before dosing (30 to 60 minutes prior to the initiation of the study drug infusion) and at 10, 20, 30, 45, 60 min, 24 and 48 hours following initiation of study drug. Vital Signs are also collected on Day 7 and 28. Vital signs at 10, 20 and 30 minutes following infusion require only SBP and DBP, and HR.

f=12-lead ECGs will be obtained at Screening before initiation of PB2452 (or placebo), pre-treatment Day 1, and on treatment
Days 1, 2, 3, 7 and 28. The specific time points for 12-lead ECG on Day 1 and 2 will be pre-dose, after bolus, end of infusion, and after 24 hours. If there is change to this schedule it will be communicated in a Dosing Memo. ECGs will be collected anytime on Day 3, 7, and 28.

g=Beginning in the morning on Day –2, a single dose of oral ticagrelor 180 mg will be given, followed by oral ticagrelor 90 mg every 12 hours for 4 additional doses through to Day 1 (2 hours before study drug is initiated; this will be 5 total doses of ticagrelor).

h=PB2452 (or placebo) will be administered at Hour 0 of Day 1.

i=ASA will be taken on Days -7, -6, -5, -4, -3, -2, -1, and on Day 1 (2 hours before study drug is started). Subjects who enter the study already taking ASA daily must document a daily ASA 81 mg dose between Day -7 and Day -3. Patients will receive daily ASA 81 mg between Day -3 (or Day -2 if the patient took ASA 81mg on Day -3 prior to Check-in) and Day 1 at the clinical facility and will suspend further ASA dosing until discharge from the clinical facility.

j=Continuous 12-lead Holter monitor placed 2 hours *before* administration of study drug will remain in place for 24 hours *after* initiation of study drug to Day 2. The resting schedule for Holter monitors will be aligned with PK draws

k=PD samples may be tested for additional hematologic biomarkers, such as P-selectin.

l=Infusion site assessments will be performed for all subjects within 15 minutes before initiation of PB2452 (or placebo) infusion at Hour 0, and at 1, 3, 24, and 48hours after initiation of PB2452 (or placebo) infusion, and on Day 7.

m= Subjects may be required to return to the site for collection of additional follow-up samples, if the sample collected at Day 28 tests positive for treatment-emergent ADAs. These visits may occur approximately 3 months after the final study visit and approximately every 6 months thereafter or until antibody levels return to Baseline level.

Schedule of Events (Cohort 1) ***(continued)***

n=Subjects are discharged from the clinic on Day 3. Subjects are permitted, if necessary/convenient to the subject to remain housed at PPD following discharge through Day 7 visit. There are no study assessments to be completed on Days 4, 5, and 6.

7.2 EXAMPLES OF INHIBITORS AND INDUCERS OF CYP3A4

Strong Inhibitors (≥5-fold increase in AUC or >80% decrease in oral clearance):
Boceprevir
Clarithromycin
Conivaptan
Grapefruit juice
Indinavir
Itraconazole
Ketoconazole
Lopinavir/ritonavir
Mibefradil
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Voriconazole

Strong Inducers (≥80% decrease in AUC):
Avasimibe
Carbamazepine
Phenytoin
Rifampin
St John's wort

Note: This list is not all-inclusive. Please refer to the following website for further guidance: http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

7.3 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

The common terminology criteria for adverse events, V5 can be found at the following link: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Clinical criteria for diagnosing anaphylaxis are presented in Appendix 7.4

7.4 CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis is highly likely when any ONE of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
    b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal (GI) symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic blood pressure (SBP; age specific) or >30% decrease in SBP*
    b. Adults: SBP <90 mm Hg or >30% decrease from that person's Baseline

* Low SBP for children from 1 month to 1 year is defined as <70 mm Hg (<70 mmHg + [2 x age]); <70 mmHg + [2 x age] from 1 to 10 years; and <90 mm Hg from 11 to 17 years.

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CLINICAL STUDY PROTOCOL: PB2452-PT-CL-0002

Part B: A Phase 2A, Randomized, Double-Blind, Placebo-Controlled, Single Dose, Sequential Group Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PB2452 with High-Dose Ticagrelor Pretreatment in Healthy Subjects

Version Number: 2 Part B

Study Drug Name: PB2452

Phase 2A

IND #: 125267

Sponsor: PhaseBio Pharmaceuticals Inc.
1 Great Valley Parkway, Suite 30
Malvern, PA 19355

Chief Medical Officer: John Lee, MD, PhD
PhaseBio Pharmaceuticals Inc.
Phone: 610-981-6505

SIGNATURE PAGE

STUDY TITLE: Part B: A Phase 2A, Randomized, Double-Blind, Placebo-Controlled, Single Dose, Sequential Group Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PB2452 with High-Dose Ticagrelor Pretreatment in Healthy Subjects

Study: PB2452-PT-CL-0002

Development Phase: 2A

I have read this protocol and agree that it contains all the necessary information required to conduct the clinical trial in compliance with applicable regulations and Good Clinical Practices (GCP) standards

Chief Medical Officer, Medical Monitor: John Lee, MD, PhD

Signature: _____ *Date:* 7-25-2019

Biostatistician: Sherry Xu, PhD

Signature: _____ *Date:* 7-25-2019

Preclinical and Assay Development: Susan Arnold, PhD

Signature: _____ *Date:* 25 JUL 19

Quality Assurance/ Regulatory Affairs: Lauren Richardson

Signature: _____ *Date:* 25Jul19

Clinical Operations: Susan Maloney

Signature: _____ *Date:* 25JUL2019

AGREEMENT OF INVESTIGATOR

STUDY TITLE: Part B: A Phase 2A, Randomized, Double-blind, Placebo-controlled, Single Dose, Sequential Group Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PB2452 with Ticagrelor Pretreatment in Older and Elderly Subjects

By signing the Agreement of Investigator Form, I the Principal Investigator agree to:

1. Conduct the study in accordance with the protocol and as subsequently amended by the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects;
2. Conduct the study in accordance with applicable federal, state and local laws and regulations, and in accordance with Good Clinical Practice (GCP) standards;
3. Personally, conduct or supervise the study;
4. Ensure that all associates, colleagues and employees assisting in the conduct of the study are adequately trained on the requirements of the protocol and informed about their obligations related to the conduct of the clinical study;
5. Delegate only those study tasks to my associates who have appropriate training and experience and provide documentation on training and the tasks to be delegated in the study file;
6. Ensure the investigational drug product is dispensed only to individuals who have signed consent, are enrolled in the referenced clinical study, and in accordance with the protocol;
7. Ensure the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in 21 CFR, § 50 and 56;
8. Report to the Sponsor (or designee) any AEs that occur in the course of the study, in accordance with 21 CFR § 312.64;
9. Maintain adequate and accurate records in accordance with 21 CFR § 312.62 and to make those records available for inspection with the Sponsor (or designee) or other applicable regulatory authorities;
10. Ensure that an Institutional Review Board (IRB), responsible for initial and continuing review and approval of the clinical study, complies with the requirements of 21 CFR §56;
11. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports);
12. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects;
13. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in 21 CFR § 312.

Principal Investigator Name: _____ Site ID: _____

Signature/Date: _____

PROTOCOL SYNOPSIS

PROTOCOL NO.: PB2452-PT-CL-0002

TITLE: Part B: A Phase 2A, Randomized, Double-Blind, Placebo-Controlled Single Dose, Sequential Group Study to Evaluate the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of PB2452 with High-Dose Ticagrelor Pretreatment in Healthy Subjects

STUDY PHASE: 2A

STUDY SITE: 1 clinical site in the United States: PPD Phase 1 Clinic, 7551 Metro Center Drive, Suite 200, Austin, Texas 78744

INDICATION: Reversal of ticagrelor anti-platelet activity

DURATION OF STUDY: The estimated duration of the study for each subject, excluding Screening, is approximately 35 days.

OBJECTIVES:

Primary:

- To evaluate the safety and tolerability of intravenous (IV) doses of PB2452 vs matching placebo with a high-dose of oral ticagrelor (180 mg BID) pretreatment in healthy subjects
- To assess the efficacy/pharmacodynamics (PD) of IV doses of PB2452 vs matching placebo in reversing a high dose of ticagrelor's antiplatelet activity by measuring $P2Y_{12}$ reaction units (PRU) with VerifyNow® $P2Y_{12}$ assay in healthy subjects

Secondary:

- To determine the pharmacokinetics (PK) of PB2452 in the presence of a high dose of ticagrelor
- To determine the PK of ticagrelor and the ticagrelor active metabolite AR-C124910XX (TAM) in the presence of PB2452
- To evaluate the effect of PB2452 on ticagrelor antiplatelet activity by measuring platelet aggregation with light transmittance aggregometry (LTA) and platelet reactivity index (PRI) with vasodilator-stimulated phosphoprotein (VASP) assay by enzyme-linked immunosorbent assay (ELISA)
- To evaluate the immunogenicity potential of PB2452

Exploratory:

- To evaluate the effect of PB2452 on the PK profile of unbound ticagrelor and unbound TAM plasma concentrations
- To investigate the effect of PB2452 vs matching placebo on circulating biomarkers of platelet activation, such as P-selectin, in subjects pretreated with high-dose ticagrelor
- To examine the correlation between estimated creatinine clearance (CrCl) and the PK of ticagrelor and TAM.

STUDY DESIGN AND METHODOLOGY:

This is Part B of a two-part Phase 2A, randomized, double-blind, placebo-controlled, single dose, sequential group study to evaluate the safety, tolerability, PK, and PD of PB2452 vs matching placebo. Part A investigated various dose regimens of PB2452 administered intravenously to older (ages 50 to 64 years) and elderly (ages 65 to 80 years) male and female subjects pretreated with ticagrelor + aspirin (ASA) as part of dual antiplatelet therapy. Part B investigates various dose levels and regimens of PB2452 administered to healthy male and female subjects (ages 18-50) pretreated with a high dose of ticagrelor alone (180 mg) twice daily (BID). Part A is described in a separate protocol document.

In Part B described herein, up to 3 dose levels and/or administration regimens of PB2452 will be evaluated in up to 3 cohorts. Each cohort will include up to 12 subjects randomized in a 3:1 ratio (PB2452:placebo). All references to study drug within the content of the protocol apply to PB2452 or matching placebo.

This initial cohort of Part B will include healthy subjects pretreated with 180 mg of oral ticagrelor twice daily for 48 hours prior to randomization to a dose and regimen of PB2452 (or matching placebo) described in a cohort-specific Dosing Memo. The written Dosing Memo provided by the Sponsor to the clinical site will include details of the dosing regimen, cohort size, sampling schedules, and other cohort-specific study activities prior to initiation of each cohort. The dose level of the initial regimen in Part B will not exceed twice the total dose level (36 g) shown to be safe and well tolerated in older and elderly subjects (50-80 years) in Part A of this Phase 2A study and in the Phase 1 study of PB2452 in healthy subjects (PB2452-PT-CL-0001).

Following completion of Cohort 3, subsequent cohort(s) may test the same, higher or lower dose levels, and/or different infusion regimens of PB2452 or matching placebo as determined by the Sponsor after examination of available PD and safety data from the prior cohort(s) and described in a subsequent Dosing Memo. Duration of study drug infusions will not exceed 48 hours.

A Safety Review Committee (SRC) will review all available safety data from ongoing or completed cohorts and will document their review and assessment in written SRC minutes prior to initiation of a subsequent cohort. Dose escalation may occur only if the SRC affirms the dose and regimen from the previously completed cohorts were safe and well tolerated and no dose-limiting toxicities (DLTs) were observed.

The study will consist of a Screening period (Days –45 to –4), a Check-in day (Day -3), a 48 hour Pretreatment Period starting on Day -2, an on-site Randomization/Treatment day (Day 1), 3 days on-site for treatment and safety monitoring, a Follow-up Visit (Day 7), and a Final Follow-up Visit (Day 28 [±2 days]). Two days prior to Randomization (Day -2), subjects will be administered ticagrelor 180 mg orally twice daily (BID) until the final dose on the morning of Day 1 before receiving study drug. The first ticagrelor 180 mg oral dose will be administered on the morning of Day -2 followed by 180 mg every 12 hours until the 5th dose has been administered on the morning of Day 1.

Subjects will check in to the clinical site (PPD) on Day -3. In the morning on Day -2, subjects will begin pretreatment with ticagrelor as described in the preceding paragraph. On Day 1, subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized in a ratio 3:1 (PB2452:placebo), to receive an IV dose of PB2452 or placebo 2 hours following the 5th ticagrelor dose. Subjects may be discharged from the clinical site between Days 3 and 7 inclusive and will return for a Follow-up visit on Day 7, if already discharged, and on Day 28 (±2 days).

Serum and plasma sampling times for PB2452, ticagrelor, and TAM PK and PD assessments will be described in the detailed Dosing Memo for each cohort. Hour 0 will be the time for initiation of study drug infusion (2 hours following administration of the 5th ticagrelor dose). PK and PD time points for subsequent cohorts may be adjusted as needed based on available PK, PD, and safety data from prior cohorts. In any cohort subsequent to the initial cohort in Part B, there will be no more than 6 additional sampling time points. The written Dosing Memo provided by the Sponsor prior to initiation of each cohort will include the following instructions:

- Number of subjects to be randomized
- Total PB2452 dose and administration regimen
- The PK and PD sampling schedule
- Safety ECG schedule
- Biomarkers schedule

Safety and tolerability will be carefully monitored throughout the study. Immunogenicity samples will be collected from all subjects at Baseline and at Days 7 and 28 (±2 days) following administration of study drug.

Dose Escalation

The SRC will conduct a blinded review of all safety and tolerability data from a cohort at least through Day 3 (e.g., clinical laboratory test results, adverse events [AEs], ECGs, Holter monitoring report, vital signs) prior to initiation of a subsequent cohort. Escalation to a higher total dose of PB2452 will occur only if the SRC affirms the safety, tolerability, and absence of DLTs in the preceding cohort(s).

The SRC will be minimally composed of the on-site PPD investigator/medical monitor, PhaseBio medical monitor, and PhaseBio clinical operations lead. Changes to the administration regimen (rate and duration) without escalation of the total dose or without increasing the infusion rate will not require formal SRC approval. Similarly, reductions in the total dose or the infusion rate will not require SRC approval.

Stopping Criteria

Dose escalation or ongoing infusions will be suspended, pending investigation by the SRC, if any of the following occur after confirmation the subject has received PB2452:

- Any preclinical or clinical events that, in the opinion of the SRC, contraindicate further dosing of additional subjects with PB2452
- Any serious AE (SAE) occurring prior to discharge from the clinical site
- Data from previous cohorts indicate safety concerns for dosing at a higher level, such as unanticipated adverse responses (e.g., clinically significant [CS] changes in clinical laboratory test data, 12 lead ECGs, continuous 12-lead electrocardiogram (Holter monitor) results, vital signs, physical examinations)
- Two or more subjects in a cohort experience any DLT, or 1 subject experiences a ≥Grade 2 AE (DLT) that, in the opinion of the SRC, warrants suspension of dose escalation
- Two or more subjects have >3 x upper limit of normal (ULN) of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or >2 x ULN of bilirubin or alkaline phosphatase (ALP) when no other reason can be found to explain the increases
- One or more subjects experiences a ≥Grade 2 infusion-related reaction (IRR) despite having been premedicated for IRRs

Continuation of dosing following suspension will be determined by the SRC and documented in an ad hoc SRC Safety Report. Dosing may also be suspended if, in the opinion of the SRC or Sponsor, any new or unexpected significant safety or tolerability issues related to ticagrelor or PB2452 are identified that warrant further evaluation before additional subjects are dosed. This may include emerging nonclinical data, clinically relevant AEs, or relevant data from other sources indicating safety concerns, even if the event(s) per se does not meet the protocol-specified definition of a DLT.

INCLUSION CRITERIA:

1. The subject provides written informed consent and agrees to comply with all protocol requirements.
2. The subject is male or female between 18 and 50 years of age, inclusive.
3. The subject has a body mass index (BMI) between 18 and 35 kg/m^2 and a weight of ≥50 kg but ≤120 kg, inclusive, at Screening.

4. The subject is considered by the investigator to be in good general health, as determined by medical history, clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings at Screening.
5. Specific inclusionary laboratory values at Screening and Check-in require:
   - White blood cell (WBC) count, platelet count, hemoglobin (Hgb) level within normal range, as defined by the clinical laboratory
   - Thyroid stimulating hormone (TSH) level within normal range, as defined by the clinical laboratory at Screening
   - Prothrombin time (PT) and partial thromboplastin time (PTT) level within normal range, as defined by the clinical laboratory
6. Female subjects of childbearing potential must not be pregnant, lactating, or planning to become pregnant for 3 months after the last dose of study drug, and have a negative serum pregnancy test at Screening and Check-in. Female subjects of childbearing potential must use 2 effective methods of birth control from 30 days before study drug administration through to the end of the study.
   - Effective birth control methods include oral, implantable, patch, or injectable contraceptive hormone treatment, hormone-containing intrauterine device that has been in place ≥2 months prior to Screening, sponge, diaphragm, or cervical cap with spermicidal gel or cream for female subjects or condom or vasectomy for male subjects.
   - Women are considered to not be of childbearing potential if they have fulfilled one of these criteria: documentation of irreversible surgical sterilization (i.e., hysterectomy or bilateral oophorectomy [not tubal ligation]) or are postmenopausal (defined as amenorrhea for 12 consecutive months following cessation of all exogenous hormonal treatments, and documented plasma follicle-stimulating hormone (FSH) level >40 IU/mL) or amenorrhea for 24 consecutive months.
   - Male subjects with partners of childbearing potential must agree to use appropriate and effective measures of contraception (e.g., condom plus diaphragm with spermicide, condom plus spermicide) during the study and for 30 days after the last dose of study drug, and refrain from donating sperm for ≥90 days following the last dose of study drug.

EXCLUSION CRITERIA:

1. Concern the subject may be unable to comply with study procedures and/or follow-up, or, in the opinion of the investigator, the subject is not suitable for entry into the study
2. History of any acute or chronic medical disorder expected to decrease the life expectancy of the subject
3. History or presence of gastrointestinal (GI), hepatic (with the exception of Gilbert's syndrome), or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs
4. Significant renal insufficiency, as indicated by estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) equation
5. Any CS acute illness, medical/surgical procedure, or trauma within 4 weeks of administration of study drug or any planned surgical procedure that will occur during the study (from Screening through the Day 28 [±2 days] Follow-up visit)
6. Any CS abnormal findings in physical examination, vital signs, laboratory assessments, and ECG parameters identified during Screening or Check-in. Note: abnormal results may be repeated for

confirmation immediately after the first out of range measurement. Abnormal vital signs may be repeated twice if needed, immediately after the first abnormal result and/or after the subject has rested for at least 10 minutes.

Specific vital sign exclusionary criteria occurring after 10 minutes of supine rest are any of the following:

- Systolic blood pressure (SBP) <100 or >160 mm Hg
- Diastolic blood pressure (DBP) <40 or >95 mm Hg
- Resting heart rate (HR) <50 or >100 beats per minute (bpm)

Specific exclusionary criteria for ECG parameters at Screening or Check-in include any of the following:

- Prolonged Fridericia-corrected QT interval (QTcF) >450 milliseconds (msec), shortened QTcF <340 msec, or pause >3 seconds, or family history of long QT syndrome

7. Any specific contraindication to Brilinta® as described in the Brilinta® prescribing information and:
   - History of intracranial hemorrhage, active bleeding, or hypersensitivity or allergic reaction to ticagrelor or any component of the product
   - Any history of severe head trauma, intracranial neoplasm, arteriovenous malformation, aneurysm, or proliferative retinopathy
   - Any history of intraocular, retroperitoneal, or spinal bleeding
   - Have taken, within 30 days of Screening, any oral or parenteral anticoagulant, including low molecular-weight heparin
   - Stool sample testing positive for occult blood within 3 months of Screening or at any time during the Screening Period
8. Receiving chronic treatment with nonsteroidal anti-inflammatory drugs (NSAIDS; [including ASA >100 mg daily]), anticoagulants, or other antiplatelet agents that cannot be discontinued 14 days prior to randomization (including clopidogrel, prasugrel, ticlopidine, dipyridamole, or cilostazol)
9. Positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) types 1 or 2 antibodies at Screening
10. Concomitant oral or IV therapy with strong or moderate cytochrome P450 3A4 (CYP3A) inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers, which cannot be stopped within at least 5 half-lives, but not fewer than 10 days, before randomization (a list of examples may be found in Appendix 7.2)
11. Consumption of grapefruit or grapefruit juice, Seville orange or Seville orange-containing products (e.g., marmalade), or xanthine-containing products within 48 hours before dosing with study drug
12. Prescription or over-the-counter (OTC) medications within 14 days before the first dose of study drug unless specifically allowed by protocol. (Permitted medications include multivitamins, paracetamol [up to 2g per day], and/or treatments for chronic stable diseases, provided the drug and dose have been stable for ≥30 days prior to administration of study drug)
13. Has received another investigational drug (defined as a small molecule or biologic compound which has not been approved for marketing) within 30 days of the administration of study drug in this study or within 5 half-lives of the prior study drug, whichever is longer
14. Positive test result for alcohol or drugs of abuse at Screening or Check-in

15. Participated in strenuous activity or contact sports within 24 hours before the infusion of study drug or while confined in the clinical site
16. History of severe or ongoing allergy/hypersensitivity to any drug or biologic therapeutic agent
17. Involvement with any PhaseBio or study site employee or their close relatives (e.g., spouse, parents, siblings, or children whether biological or legally adopted)
18. Previously received PB2452 or had been randomized to receive study drug in an earlier cohort for this study

EVALUATION CRITERIA

Safety Endpoints:

Safety and tolerability will be assessed by monitoring and recording of Adverse Events (AEs), clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), vital sign measurements (SBP and DBP, oral body temperature, respiratory rate [RR], and HR), 12-lead ECG, immunogenicity, biomarkers and physical examination findings.

Pharmacodynamic Endpoints

VerifyNow®P2Y$_{12}$:

- Minimum %inhibition of PRU within 4 hours after the initiation of study drug. %inhibition of PRU is calculated as 100 * [(PRU_{bsl} – PRU_{trt})/PRU_{bsl}]. PRU_{bsl} refers to the PRU value measured before treatment with ticagrelor and PRU_{trt} refers to the PRU value measured posttreatment with the study drug.
- PRU AUC for the first 4 hours.
- Proportion of patients with normalized platelet reactivity units within 4 hours after the initiation of study drug. Normalized platelet reactivity is defined as PRU ≥ 180.
- Proportion of patients with ≥60%, ≥80%, and 100% of PRU response rate within 4 hours after the initiation of study drug. A PRU response rate is defined as the 100 * (PRU_{trt}/PRU_{bsl}).
- Time to 60%, 80%, 100% of PRU response rate within 4 hours after the initiation of study drug
- Duration of 80% and 100% of PRU response rate by PRU.

LTA:

- Minimum %inhibition of LTA within 4 hours after the initiation of study drug.
- LTA AUC for the first 4 hours.
- Proportion of patients with ≥60%, ≥80%, and 100% of LTA response rate within 4 hours after the initiation of study drug. LTA response rate is defined as the 100 * (LTA_{trt}/LTA_{bsl}).
- Time to 60%, 80%, 100% LTA response rate within 4 hours after the initiation of study drug.
- Duration of 80% and 100% of LTA response rate.

VASP by ELISA:

- Minimum %inhibition of PRI within 4 hours after the initiation of study drug.
- PRI AUC for the first 4 hours.
- Proportion of patients with ≥60%, ≥80%, and 100% of PRI response rate within 4 hours after the initiation of study drug. A PRI response is defined as the 100 * (PRI_{trt}/PRI_{bsl}).
- Time to 60%, 80%, 100% PRI response rate within 4 hours after the initiation of study drug
- Duration of 80% and 100% of PRI response rate

Additional PD parameters may be generated, if needed.

Pharmacokinetic Endpoints:

Plasma PK

Plasma concentrations of total PB2452, unbound PB2452, total Ticagrelor, total TAM, unbound Ticagrelor, and unbound TAM, will be assessed at predetermined timepoints.

PK parameters for PB2452 include:

- Observed maximum plasma concentration (C_{max})
- Area under the plasma concentration versus time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC_{0-t})
- Time to reach the observed maximum plasma concentration (T_{max})
- AUC from time zero to 24 hours post-dose (AUC_{0-24})
- AUC from time zero to 48 hours post-dose (AUC_{0-48})
- Area under the plasma concentration versus time curve (AUC) from time zero to the time of the end of the dosing period(AUC_{0-tau})
- AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$; if data permit)
- Terminal elimination half-life ($t_{½}$; if data permit)
- Clearance (CL; if data permit)
- Volume of distribution (Vd)

PK parameters for Ticagrelor/TAM include:

- C_{max}
- AUC_{0-t}
- T_{max}
- AUC_{0-24}
- AUC_{0-48}
- AUC_{0-tau}
- $AUC_{0-\infty}$; if data permit
- $t_{½}$; if data permit

Urine PK

Pooled urine samples to assess urine PB2452, ticagrelor, and TAM concentrations will be collected over these intervals: before dosing (within 60 minutes prior to the first ticagrelor dose on Day -2) and 0 to 6, 6 to 12, and 12 to 24 hours.

Pharmacokinetic parameters for PB2452, ticagrelor, and TAM concentrations in urine for all subjects in the PK population to be calculated are:

- Total amount of drug excreted in urine at 24 hours after dosing (Ae_{24}) and at 48 hours after dosing (Ae_{48})
- Total amount of drug excreted in urine from time t1 to t2 (Ae_{t1-t2}) hours when the values of t1 to t2 are 0 to 6, 6 to 12, 12 to 24 and 24 to 48 hours
- Fraction excreted in urine from 1 to 24 hours after dosing (Fe_{24}) and from 1 to 48 hours after dosing (Fe_{48})

- Renal clearance (CLr) for 24 hours after dosing

Additional PK parameters may be generated, if needed. Details will be provided in a separate document, the SAP.

STUDY DRUG, DOSAGE, AND ROUTE OF ADMINISTRATION:

PB2452:

PB2452 IV infusion, prepared according to the Pharmacy Manual, will be administered on Day 1 for up to 48 hours. The total dose for each subject will not exceed 30 g. The infusion rate will not exceed 18 g over 30 minutes and the concentration will not exceed 24g in 250mL. Subjects will not receive more than 250 mL of study drug infusion within any 1-hour period.

For each cohort, the dose, infusion rate, and duration will be communicated from the Sponsor to PPD in a Dosing Memo issued prior to initiation of each treatment cohort.

Matching Placebo:

0.9% sodium chloride single IV infusion, to be delivered at a rate and volume matching the active infusion.

Ticagrelor:

Ticagrelor 90 mg oral tablets (immediate release) will be administered as a 180 mg (2 × 90 mg tablets) oral dose every 12 hours for 5 total doses.

STATISTICAL METHODS:

Sample Size:

The sample size (N) of up to 3 cohorts for Part B of this study is based on clinical and practical considerations and not on a formal statistical power calculation. The sample size will provide preliminary safety, efficacy and PK information in a dose/regimen finding fashion.

Analysis Populations:

- The *Safety Population* will include all subjects who receive any amount of study drug.
- The *PK Population* will include subjects in the safety population who have ≥1 measurable PK concentration.
- The *PD Population* will include subjects in the safety population who receive ≥1 dose of ticagrelor and have ≥1 measurable post dose PRU value.

Safety Analyses:

Adverse events will be coded by preferred term and system-organ-class (SOC) using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). All AE data will be presented in Data Listings. Treatment-emergent AEs (TEAEs) will be summarized by treatment and overall, as well as by severity and relationship to study drug. All SAEs and AEs leading to discontinuation of study drug will be presented in the Data Listings.

Actual values and changes from Baseline in clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, standard deviation [SD], median, minimum, and maximum). Clinical laboratory test results, vital sign measurements, 12-lead ECGs, Holter monitor report data, immunogenicity results, and physical examination findings will be presented in Data Listings.

Efficacy Analyses:

Pharmacodynamic data will be summarized using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum) for each treatment group or by cohort at each time point

if applicable. Inferential analysis maybe carried out to compare the % inhibition of PRU, LTA, PRI between PB2452 vs Placebo individually. However due to the limited sample size, efficacy analysis results will be considered descriptive.

Pharmacokinetic Analyses:

Plasma concentrations will be listed and summarized descriptively (number of subjects, arithmetic mean, SD, coefficient of variation [CV], median, minimum, and maximum). Plasma concentration versus time profiles for each subject will be presented graphically. The mean plasma concentration versus scheduled time profiles will be presented graphically by dose.

Pharmacokinetic parameters will be summarized by time point for each dose level using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum). Geometric means will be reported for AUCs and C_{max}.

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See Appendices, Section 7.

LIST OF ABBREVIATIONS AND DEFINITIONS

AA	arachidonic acid
ACS	acute coronary syndrome
ADA	anti-drug antibodies
ADP	adenosine diphosphate
AE	adverse event
Ae_{48}	total amount of drug excreted in urine at 48 hours after dosing
Ae_{24}	total amount of drug excreted in urine at 24 hours after dosing
$Ae_{t1\text{-}t2}$	Ae from time t1 to t2 hours
$Ae_{t1\text{-}t2}$	Ae from time t1 to t2 hours
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASA	acetylsalicylic acid, aspirin
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-}12}$	AUC from time zero to 12 hours after dosing
$AUC_{0\text{-}24}$	AUC from time zero to 24 hours after dosing
$AUC_{0\text{-}48}$	AUC from time zero to 48 hours after dosing
$AUC_{0\text{-}\infty}$	area under the plasma concentration versus time curve from time zero extrapolated to infinity
$AUC_{0\text{-}\tau}$	area under the concentration versus time curve from time zero to the time of the last quantifiable concentration
bid	twice daily
BL	baseline
BLQ	below the limit of quantification
BMI	body mass index
BP	Blood Pressure
Bpm	beats per minute
BUN	Blood Urea Nitrogen
CABG	coronary artery bypass graft
CFR	Code of Federal Regulations
CL	clearance
CLr	renal clearance
C_{max}	observed maximum plasma concentration
CrCl	creatinine clearance
CS	clinically significant
CSR	Clinical Study Report

CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP3A	cytochrome P450 3A4
DAPT	dual antiplatelet therapy
DBP	diastolic blood pressure
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
FDA	Food and Drug Administration
Fe_{24}	Fraction excreted in urine from 1 to 24 hours after dosing
Fe_{48}	fraction excreted in urine from 1 to 48 hours after dosing
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
HbA1c	glycosylated Hemoglobin Hgb
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high-density lipoprotein
Hgb	hemoglobin
HIV	human immunodeficiency virus
HR	resting heart rate
HTN	hypertension
IB	Investigators' Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
INR	international normalized ratio
IPA	inhibition of platelet aggregation
IRB	institutional review board
IRR	infusion-related reaction
IV	Intravenous- (ly)
LDH	lactate dehydrogenase
LDL	low-density lipoprotein

LTA	light transmittance aggregometry
MAP	mean arterial pressure
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDMA	methylenedioxymethamphetamine
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary FOR Regulatory Activities
MI	Myocardial infarction
MPV	Mean platelet volume
msec	millisecond
MTD	maximum tolerated dose
N	sample size
NCS	not clinically significant
NOAEL	no adverse effect level
OTC	Over the counter
PD	Pharmacodynamic
PEF	Peak expiratory flow
PK	pharmacokinetic
PO	by mouth
PRI	platelet reactivity index
PRU	$P2Y_{12}$ reaction units
PT	prothrombin time
PTT	partial thromboplastin time
QD	once daily
QTcF	Fridericia-corrected QT interval
RBC	red blood cell(erythrocyte)
RR	respiration rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	System- organ- class
SOP	standard operating procedure
SpGr	specific gravity
SRC	Safety Review Committee
$t_{1/2}$	terminal elimination half-life
TAM	ticagrelor active metabolite AR-C124910XX
TEAE	treatment-emergent adverse event

T_{max}	time to reach the observed maximum (peak) concentration
TRAP	thrombin receptor activating peptide
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US	United States
VASP	vasodilator-stimulated phosphoprotein
WBC	white blood cell

1. INTRODUCTION

1.1 PRODUCT AND BACKGROUND INFORMATION

PB2452 (molecular weight 47.4 kDa) is a specific and selective recombinant human neutralizing antibody IgG1λ monoclonal fragment antigen-binding antibody that binds with high affinity to ticagrelor and to AR-C124910XX (TAM), the major active circulating ticagrelor metabolite. It is expressed in *Escherichia coli* cells.

PB2452 is intended to reverse the antiplatelet effects of ticagrelor in patients who experience major bleeding or who require urgent surgery or intervention.
Platelet transfusion has appeared to be inferior to standard care for those taking antiplatelet therapy.(Baharoglu, 2016)

A strategy is needed to re-establish the integrity of the clotting cascade for the many patients who have abnormal coagulation due to pharmacological anticoagulation.(Beshay, 2010) Antiplatelet medications and anticoagulants pose a significant treatment dilemma since no direct reversal agents currently exist to reverse or mitigate antithrombotic properties.(Dornbos III, 2018) Accordingly, the current lack of an effective therapy to mitigate ticagrelor-induced platelet inhibition in patients who have life-threatening bleeding or require urgent surgery or intervention represents a significant unmet need.

Ticagrelor is an orally available, direct-acting cyclopentyltriazolopyrimidine, a selective and reversibly binding $P2Y_{12}$ receptor antagonist.(Storey, 2007) TAM, the ticagrelor active metabolite (30% to 40% plasma exposure relative to parent in humans, (Storey, 2007) has potency similar to ticagrelor versus $P2Y_{12}$. In addition to $P2Y_{12}$, ticagrelor also inhibits the equilibrative nucleoside transporter-1, thereby providing an enhanced adenosine response.(Armstrong, 2014; Beshay JE, Morgan H, Madden C, Yu W, et al. Emergency reversal of anticoagulation and antiplatelet therapies in neurosurgical patients. J Neurosurg 2010 Feb;112(2):307-18.

Catteneo, 2014) Ticagrelor in combination with low-dose aspirin (acetylsalicylic acid; ASA) is indicated for the prevention of thrombotic events (e.g., cardiovascular death, myocardial infarction [MI], and stroke) in patients with acute coronary syndrome (ACS) or a history of MI. Ticagrelor also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS. In the management of ACS, ticagrelor treatment is initiated with a 180 mg loading dose, followed by 90 mg twice daily (bid) during the first year after an ACS event. After one year, the prescribed dosage is decreased to 60 mg bid.

Therapy with ASA plus an oral antiplatelet agent such as clopidogrel, prasugrel, or ticagrelor is known as dual antiplatelet therapy (DAPT). Although DAPT is strongly recommended in the early management of patients experiencing an ACS event, it also increases the risk of bleeding.(Storey, 2011) Patients with ACS may require urgent or emergent coronary artery bypass

graft (CABG) surgery. In such patients, DAPT is associated with a 2-fold increase in risk of blood transfusion, a 5-fold increase in risk of reoperation, and a 50% increased risk of wound infection.(Bell, 2011; Fitchett, 2011) Consequently, guidelines and guidance statements recommend the $P2Y_{12}$ receptor antagonist be stopped ≥5 days prior to the procedure, a recommendation that is not possible in patients who require urgent surgery.

There are no approved drugs or biological agents capable of reversing the $P2Y_{12}$ inhibition produced by ticagrelor or other $P2Y_{12}$ inhibitors; therefore, in the event of major bleeding in a patient on DAPT, there are limited treatment options. Although platelet transfusion restores platelet function in patients on ASA,(Taylor, 2013) it does not reverse the antiplatelet effect of ticagrelor in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding.(Teng, 2016)

1.1.1 Non-clinical Pharmacology

Non-clinical pharmacology studies have demonstrated that PB2452 binds with high affinity and selectivity to the $P2Y_{12}$ receptor antagonist ticagrelor and its active metabolite, TAM, (equilibrium dissociation constant [K_D] 20 pmol/L). PB2452 rapidly neutralizes the unbound plasma fraction of ticagrelor and TAM, thereby reversing ticagrelor- and TAM-mediated inhibition of adenosine diphosphate (ADP)-induced platelet aggregation in a concentration- and dose-dependent manner in vitro (in human platelet-rich plasma) and in vivo (mouse and pig, dose-dependency data in mouse only). In mice dosed with ticagrelor to a supratherapeutic plasma exposure, those dosed with PB2452 before a tail cut had reduced bleeding to a degree not statistically different from the observation in mice not treated with ticagrelor. The activity in vitro and the rapid onset of effect observed in vivo translated to a reduction of bleeding in ticagrelor-treated mice to a degree that was not statistically significantly different from mice not treated with ticagrelor. Detailed descriptions of the non-clinical pharmacology of PB2452 may be found in the Investigators' Brochure (IB) for PB2452.

1.1.2 Summary of Human Data

The first-in-human Phase 1 study (PB2452-PT-CL-0001) has been clinically completed, the database is locked, and final analyses are complete with the exception of exploratory endpoints. The safety, PK, and PD data described herein will be incorporated into a clinical study report. This study was a single-center, randomized, double-blind, placebo-controlled, single ascending dose study to evaluate the safety, tolerability, PK, and PD of PB2452 with and without ticagrelor pretreatment in healthy male and female subjects ages 18-50 years. Ten sequential dose cohorts were evaluated. Cohorts 1, 2, and 3 assessed 30 min IV infusions of PB2452 without ticagrelor pretreatment while Cohorts 4-10 assessed IV infusions of

PB2452 after ticagrelor pretreatment. Detailed descriptions of the clinical safety, PK, and PD profiles of PB2452 may be found in the Investigators' Brochure (IB) for PB2452.

PB2452 appeared generally safe and well tolerated across a dose range of 0.1 g to 18 g. A total of 30 adverse events occurred after initiation of PB2452 or placebo and were reported by 19 of the 64 volunteers (30%). Of the 48 volunteers who received PB2452, 17 (35%) reported 27 adverse events; of the 16 volunteers who received placebo, 2 (12%) reported 3 adverse events. There were no dose-limiting toxicity (DLTs)effects or infusion-related reactions (IRRs). There were no deaths or adverse events that led to discontinuation of the trial drug. One volunteer had 2 serious adverse events (alcohol poisoning and acute respiratory failure) 4 days after discharge from the clinical site. Except for 2 volunteers, in cohorts 1 and 3, all volunteers with adverse events had received ticagrelor pretreatment. Changes in mean clinical laboratory test results, vital signs, and electrocardiographic results were similar across cohorts among volunteers who received different doses or regimens of PB2452 and were similar among those who received PB2452 and those who received placebo. Of the 48 volunteers who received PB2452, 21 (44%) had detectable anti-drug antibodies in blood obtained 7 and/or 28 days after exposure; 15 (31%) had been positive before they received PB2452 and 6 (12%) became positive after they received PB2452, albeit with low titers of 40 (in 5 volunteers) and 160 (in 1 volunteer). Of the 16 volunteers who received placebo, 3 (19%) were positive for anti-drug antibodies, with 2 (12%) having preexisting antibodies. The presence of these antibodies had no observed effect on the safety or efficacy of PB2452.

The PK profile of PB2452 demonstrated that mean plasma concentrations of PB2452 rapidly declined following the end of infusion across all cohorts. In cohorts 1-3 when PB2452 was administered as a 30-minute intravenous infusion in the absence of ticagrelor, elimination appeared to be biphasic with half-life values ranging from 1.5 to 9.2 hours for the dose range 0.1 g to 1 g. In the presence and absence of ticagrelor, geometric mean observed maximum plasma concentration (C_{max}) values and geometric mean area under the plasma concentration versus time curve (AUC) from time zero extrapolated to infinity ($AUC_{0-\infty}$))values of total PB2452 appeared to increase in a dose-proportional manner. The inter-individual variability (geometric mean coefficient of variation [CV%]) for C_{max} and $AUC_{0-\infty}$ was low, ranging from 4.8% to 28.9% across Cohorts 1-3. PB2452 appeared to increase mean total plasma concentrations of ticagrelor and TAM compared to placebo, and this effect was dependent on the dose of PB2452. Additionally, PB2452 increased the renal CL of ticagrelor and TAM in a dose-dependent manner.

The PD profile of PB2452 demonstrated that for subjects receiving steady-state ticagrelor, IV infusion of PB2452 (3 to18 g) restored platelet activity to approximately 100% of baseline using multiple assays of platelet function. The onset of reversal was rapid, occurring at the first assessment of platelet function following initiation of PB2452 infusion (30 minutes in cohorts 4-6 and 5 minutes in cohorts 7-10). The duration of ticagrelor reversal appeared to be dependent on the total dose and infusion duration of PB2452.

1.1.3 Benefit/Risk Assessment

The first in human study of PB2452 in healthy volunteers (PB2452-PT-CL-0001) demonstrated that PB2452 appears to be generally safe and well tolerated when administered intravenously across a dose range of 0.1-18 g. The healthy volunteers who were 18-50 years in age were not expected to receive any benefit from administration of PB2452. Platelet function analyses showed that PB2452 delivered immediate and sustained reversal of ticagrelor, occurring as early as 5 minutes after initiation of PB2452 infusions and lasting for 20-24 hours. Rapid and sustained ticagrelor reversal by PB2452 may provide clinically significant benefit in patients taking ticagrelor who experience serious bleeding or require urgent surgical procedures by supporting rapid hemostasis or prevention of procedure-related bleeding.

Although treatment emergent adverse events associated with PB2452 in the Phase 1 study were mostly mild and infrequent with no infusion-related or hypersensitivity reactions observed, in the older and elderly subjects in this Phase 2A study, there remain potential risks of infusion-related reactions (IRRs), infusion site reactions, and hypersensitivity-type reactions which can result from exposure to recombinant protein drugs administered intravenously (IV). These risks may be mitigated by predefined exclusion criteria and by close monitoring during and after administration. Risks may also be mitigated by premedication prior to receiving PB2452 which will be implemented if a study subject develops a Grade ≥2 IRR.

The healthy subjects in Part B of this study will be administered a high-dose of ticagrelor (180 mg BID) which is expected to cause a dose-dependent increase in exposure compared to the 90 mg BID ticagrelor dose tested in Part A of this study and in the previous Phase 1 study of PB2452. Treatment with ticagrelor in any subject carries a risk of bleeding. However, in a ticagrelor study in atherosclerosis patients, the elevated exposures from 180 mg BID of ticagrelor demonstrated no apparent increase in bleeding compared to patients treated with ticagrelor 90 mg BID (Storey et al. DISPERSE-2 JACC 2007; 50: 1852-6). Based on the patient data and because the duration of high-dose ticagrelor treatment in Part B of this study is only 48 hours and will be administered without aspirin, the bleeding risk in study subjects is considered low.

Among those patients taking ticagrelor for therapeutic benefit, the potential risk of disease-related thrombosis upon reversal of the antiplatelet effect of ticagrelor will be evaluated in future clinical studies and by thorough monitoring of hemostasis parameters. In the current study, three platelet function assays and multiple platelet agonists will be used to monitor platelet function which will demonstrate both the reversal profile of PB2452 and also a potential prothrombotic rebound increase in platelet function. The risk of a platelet rebound effect is considered low and was not observed in the Phase 1 study.

Based on available information concerning the risks of PB2452 and the precautions included in this clinical study, the risks are considered acceptable.

1.2 RATIONALE FOR STUDY

Current recommendations for management of bleeding in patients treated with antiplatelet therapies are suboptimal; they are mostly supportive and non-specific. Platelet transfusion, while useful for some antiplatelet agents, exposes patients to the known risks of blood products. Further, the efficacy of transfused platelets may be limited by exposure to circulating antiplatelet drug or metabolites, if present. Moreover, it has been demonstrated that platelet transfusions do not reverse the effects of ticagrelor.(Dalen, 2013; Godier, 2015; Maillard, 2015; Teng, 2016)

An agent to rapidly reduce the anti-platelet aggregation (IPA) associated with effects of ticagrelor, and the metabolite TAM, would fulfill an important unmet clinical need for those patients:

- who have major bleeding with ticagrelor possibly contributing
- who are taking ticagrelor and require urgent surgery or intervention associated with a high risk of bleeding
- who are taking ticagrelor for conditions with a high risk of thrombosis, require major surgery, and/or need to minimize the time when they are not receiving ticagrelor

1.3 RATIONALE FOR DOSE SELECTION

In the first in human Phase 1 study of PB2452, 18 g administered as an initial 6 g bolus followed by a prolonged infusion of the remaining 12 g over 16 hours in healthy subjects aged 18-50 years old was considered generally safe and well tolerated. There were no PB2452-related adverse effects, ISRs, or DLTs observed as determined by the study investigator and SRC. The profile of rapid and sustained ticagrelor reversal delivered by the 18 g dose level is potentially clinically meaningful and considered ideal for patients on ticagrelor with acute major bleeding or who need urgent surgery.

The 18 g dose level and prolonged infusion regimen administered in the Phase 1 study will be repeated in the current study in older and elderly subjects who are more similar in age and background comorbidities to the actual patient population treated with ticagrelor. Potentially

longer infusions of PB2452 may be investigated in this study, using potentially high total doses of PB2452. To mitigate any risks related to dose escalation, a Safety Review Committee (SRC) will be assembled to review all emergent safety and tolerability data and available PK data after each cohort is completed to determine whether dose escalation and/or prolongation of infusion duration is warranted. PK/PD modeling will be used to simulate potential doses, infusion regimens, and C_{max} and AUC exposure profiles prior to dose-escalation or adjustment of infusion regimen to ensure that no dose or infusion regimen investigated in this study will exceed C_{max} or AUC exposures achieved at the no observed adverse effect level (NOAEL) in GLP toxicity study in rats.

In the rat GLP toxicity study, there were no adverse effects observed following single doses of PB2452 at the highest dose level tested of 2000 mg/kg given IV, alone or in combination with oral ticagrelor (20 mg/kg). Therefore, 2000 mg/kg was considered NOAEL with a maximum plasma concentration (C_{max}) of 18100 µg/mL and an area under the plasma concentration versus time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$) of 23100 µg*h/mL.

One or more doses and administration regimens of PB2452 will be tested in Part B to identify an approach to reverse a high oral dose of ticagrelor (180 mg BID). In a previous study of ticagrelor, co-administration of ticagrelor with CYP3A inhibitors resulted in higher exposure to ticagrelor and lower exposure to its active metabolite (Teng et al 2013). Similar increases in exposure were reported in ACS patients who were treated with oral 180 mg ticagrelor twice daily. In the patient population, the elevated exposures from this high dose of ticagrelor resulted in a dose-dependent increase in inhibition of platelet aggregation but no apparent increase in bleeding compared to patients treated with ticagrelor 90 mg BID (Cannon et al. 2007 and Storey et al. 2007).

2. STUDY OBJECTIVES AND METHODOLOGY

2.1 OBJECTIVES

Primary:

- To evaluate the safety and tolerability of intravenous (IV) doses of PB2452 vs matching placebo with a high dose of oral ticagrelor (180 mg BID) in healthy subjects
- To assess the efficacy/ pharmacodynamic (PD) of IV doses of PB2452 vs matching placebo in reversing a high dose of ticagrelor's antiplatelet activity by measuring $P2Y_{12}$ reaction units (PRU) with VerifyNow® $P2Y_{12}$ assay in healthy subjects

Secondary:

- To determine the pharmacokinetics (PK) of PB2452 in the presence of a high dose of ticagrelor
- To determine the PK of ticagrelor and TAM in the presence of PB2452
- To evaluate the effect of PB2452 on ticagrelor antiplatelet activity by measuring platelet aggregation with light transmittance aggregometry (LTA) and platelet reactivity index (PRI) with vasodilator-stimulated phosphoprotein (VASP) assay by enzyme-linked immunosorbent assay (ELISA)
- To evaluate the immunogenicity potential of PB2452

Exploratory:

- To evaluate the effect of PB2452 on the PK profile of unbound ticagrelor and unbound TAM plasma concentrations
- To investigate the effect of PB2452 vs matching placebo on circulating biomarkers of platelet activation, such as P-selectin, in subjects pretreated with high-dose ticagrelor
- To examine the correlation between estimated creatinine clearance (CrCl) and the PK of ticagrelor and TAM.

2.2 EVALUATION CRITERIA

2.2.1 Safety Endpoints

Safety and tolerability will be assessed by monitoring and recording of Adverse Events (AEs), clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), vital sign measurements (systolic blood pressure [SBP] and diastolic blood pressure [DBP], oral body temperature, respiratory rate [RR], and resting heart rate [HR]), 12-lead electrocardiogram (ECG), continuous 12-lead ECG (Holter monitoring), immunogenicity, and physical examination findings.

2.2.2 Pharmacodynamic Endpoints

VerifyNow® $P2Y_{12}$:

- Minimum %inhibition of PRU within 4 hours after the initiation of study drug. %inhibition of PRU is calculated as 100 * [(PRU_{bsl} – PRU_{trt})/PRU_{bsl}]. PRU_{bsl} refers to the PRU value measured before treatment with ticagrelor and PRU_{trt} refers to the PRU value measured posttreatment with the study drug.
- PRU AUC for the first 4 hours.
- Proportion of patients with normalized platelet reactivity units within 4 hours after the initiation of study drug. Normalized platelet reactivity is defined as PRU ≥ 180.
- Proportion of patients with ≥60%, ≥80%, and 100% of PRU response rate within 4 hours after the initiation of study drug. A PRU response rate is defined as the 100 * (PRU_{trt}/PRU_{bsl}).
- Time to 60%, 80%, 100% of PRU response rate within 4 hours after the initiation of study drug
- Duration of 80% and 100% of PRU response rate by PRU.

LTA:

- Minimum %inhibition of LTA within 4 hours after the initiation of study drug.
- LTA AUC for the first 4 hours.
- Proportion of patients with ≥60%, ≥80%, and 100% of LTA response rate within 4 hours after the initiation of study drug. LTA response rate is defined as the 100 * (LTA_{trt}/LTA_{bsl}).
- Time to 60%, 80%, 100% LTA response rate within 4 hours after the initiation of study drug.
- Duration of 80% and 100% of LTA response rate.

VASP by ELISA:

- Minimum %inhibition of PRI within 4 hours after the initiation of study drug.
- PRI AUC for the first 4 hours.
- Proportion of patients with ≥60%, ≥80%, and 100% of PRI response rate within 4 hours after the initiation of study drug. A PRI response is defined as the 100 * (PRI_{trt}/PRI_{bsl}).
- Time to 60%, 80%, 100% PRI response rate within 4 hours after the initiation of study drug
- Duration of 80% and 100% of PRI response rate

Additional PD parameters may be generated, if needed.

2.2.3 Pharmacokinetic Endpoints

Plasma PK
Plasma concentrations of total PB2452, unbound PB2452, total Ticagrelor, total TAM, unbound Ticagrelor, and unbound TAM, will be assessed at predetermined timepoints.

PK parameters for PB2452 include:

- Observed maximum plasma concentration (C_{max})

- Area under the plasma concentration versus time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC_{0-t})
- Time to reach the observed maximum plasma concentration (T_{max})
- AUC from time zero to 24 hours post-dose (AUC_{0-24})
- AUC from time zero to 48 hours post-dose (AUC_{0-48})
- Area under the plasma concentration versus time curve (AUC) from time zero to the time of the end of the dosing period(AUC_{0-tau})
- AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$; if data permit)
- Terminal elimination half-life ($t_{½}$; if data permit)
- Clearance (CL; if data permit)
- Volume of distribution (Vd)

PK parameters for Ticagrelor/TAM include:

- C_{max}
- AUC_{0-t}
- T_{max}
- AUC_{0-24}
- AUC_{0-48}
- AUC_{0-tau}
- $AUC_{0-\infty}$; if data permit
- $t_{½}$; if data permit

Urine PK

Pooled urine samples to assess urine PB2452, ticagrelor, and TAM concentrations will be collected over these intervals: before dosing (within 60 minutes prior to the first ticagrelor dose on Day -2) and 0 to 6, 6 to 12, and 12 to 24 hours.

Pharmacokinetics parameters for PB2452, ticagrelor, and TAM concentrations in urine for all subjects in the PK population to be calculated are:

- Total amount of drug excreted in urine at 24 hours after dosing (Ae_{24}) and at 48 hours after dosing (Ae_{48})
- Ae from time t1 to t2 hours when the values of t1 to t2 are 0 to 6, 6 to 12, 12 to 24 and 24 to 48 hours (Ae_{t1-t2})
- Fraction excreted in urine from 1 to 24 hours after dosing (Fe_{24}) and from 1 to 48 hours after dosing (Fe_{48})
- Renal clearance (CLr) for 24 hours after dosing

Additional PK parameters may be generated, if needed. Details will be provided in a separate document, the SAP.

3. INVESTIGATION PLAN

3.1 STUDY DESIGN AND METHODOLOGY

This is Part B of a Phase 2A, randomized, double-blind, placebo-controlled, single dose, sequential group study to evaluate the safety, tolerability, PK, and PD of PB2452 vs matching placebo with ticagrelor pretreatment. Various dose levels and/or administration regimens of PB2452 may be administered to healthy male and female subjects 18-50 years old. All references to study drug within the content of the protocol apply to PB2452 or matching placebo.

In Part B up to 3 dose levels and/or administration regimens of PB2452 will be evaluated in up to 3 cohorts. Each cohort will include up to 12 subjects randomized in a 3:1 ratio (PB2452:placebo).

This initial cohort of Part B (Cohort 3) will pretreat subjects with 180 mg of oral ticagrelor twice daily for 48 hours prior to randomization to a dose and regimen of PB2452 or matching placebo described in a cohort-specific Dosing Memo. The written Dosing Memo provided by the Sponsor to the clinical site will describe details of the dosing regimen, cohort size, sampling schedules, and other cohort-specific study activities prior to initiation of each cohort. The dose level of the initial regimen in Part B will not exceed twice the total dose level (36 g) shown to be safe and well tolerated in older and elderly subjects (50-80 years) in Part A of this Phase 2A study and in the Phase 1 study of PB2452 in healthy subjects (PB2452-PT-CL-0001).

Following completion of Cohort 3, subsequent cohort(s) may test the same, higher or lower dose levels, and/or different infusion regimens of PB2452 or matching placebo in the same population as in Cohort 3, or in different populations such as elderly subjects (65 to 80 years old), as determined by the Sponsor after examination of available PD and safety data from the prior cohort(s) and described in a subsequent Dosing Memo. Duration of study drug infusions will not exceed 48 hours.

A Safety Review Committee (SRC) will review all available safety data from ongoing or completed cohorts and will document their review and assessment in written SRC minutes prior to initiation of a subsequent cohort. Dose escalation may occur only if the SRC affirms the dose and regimen from the previously completed cohorts were safe and well tolerated and no dose-limiting toxicities (DLTs) were observed.

The study will consist of a Screening period (Days –45 to –4), a Check-in day (Day -3), a 48 hour Pretreatment Period starting on Day -2, an on-site Randomization/Treatment day (Day 1), 3 days on-site for treatment and safety monitoring, a Follow-up Visit (Day 7), and a Final Follow-up visit (Day 28 [±2 days]). Two days prior to Randomization (Day -2), subjects will be administered ticagrelor 180 mg orally twice daily (BID) until the final dose on the morning of Day 1 before receiving study drug. The first ticagrelor 180 mg oral dose will be

administered on the morning of Day -2 followed by 180 mg every 12 hours until the 5th dose has been administered on the morning of Day 1.

Subjects will check in to the clinical site (PPD) on Day -3. In the morning on Day -2, subjects will begin pretreatment with ticagrelor as described in the preceding paragraph. On Day 1, subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomized in a ratio 3:1 (PB2452:placebo), to receive an IV dose of PB2452 or placebo 2 hours following the 5th ticagrelor dose. Subjects may be discharged from the clinical site between Days 3 and 7 inclusive and will return for a Follow-up visit on Day 7, if already discharged, and on Day 28 (±2 days).

Serum and plasma sampling times for PB2452, ticagrelor, and TAM PK and PD assessments will be described in the detailed Dosing Memo for each cohort. Hour 0 will be the time for initiation of study drug infusion (2 hours following administration of the 5th ticagrelor dose). PK and PD time points for subsequent cohorts may be adjusted as needed based on available PK, PD, and safety data from prior cohorts. In any cohort subsequent to Cohort 3, there will be no more than 6 additional sampling time points. The written Dosing Memo provided by the Sponsor prior to initiation of each cohort will include the following instructions:

- Number of subjects to be randomized
- Total PB2452 dose and administration regimen
- The PK and PD sampling schedule
- Safety ECG schedule
- Biomarkers schedule

Safety and tolerability will be carefully monitored throughout the study. Immunogenicity samples will be collected from all subjects at Day -3, Randomization , Days 7 and 28 (±2 days) following administration of study drug.

3.2 SELECTION OF STUDY POPULATION

Male or female subjects will be evaluated in up to 3 cohorts in the US, North America. To ensure the study clinic has sufficient subjects available for dosing for any cohort, additional subjects may be asked to present to the clinic for check in. The number of subjects brought in for check-in and pre-dosed with ticagrelor will be at the discretion of the study clinic personnel/principal investigator to ensure there is a sufficient number of subjects available for dosing with study drug for a given cohort. Subjects who check in to the clinic may be dosed with ticagrelor in preparation for dosing with the study drug according to the Schedule of Events (Appendix 7.1). Extra subjects may be dosed with ticagrelor, so on the day of randomization there is a sufficient number of subjects available to fill the cohort.

3.2.1 Inclusion Criteria

Subjects must meet ALL the following criteria to be eligible for inclusion in the study:

1. The subject provides written informed consent and agrees to comply with all protocol requirements.
2. The subject is male or female between 18 and 50 years of age, inclusive.
3. The subject has a body mass index (BMI) between 18 and 35 kg/m^2 and a weight of ≥50 kg but ≤120 kg, inclusive, at Screening.
4. The subject is considered by the investigator to be in good general health, as determined by medical history, clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings at Screening.
5. Specific inclusionary laboratory values at Screening and Check-in require:
   - White blood cell (WBC) count, platelet count, hemoglobin (Hgb) level within normal range, as, defined by the clinical laboratory
   - Thyroid stimulating hormone (TSH) level within normal range, as defined by the clinical laboratory at Screening
   - Prothrombin time (PT) and partial thromboplastin time (PTT) level within normal range, as defined by the clinical laboratory
6. Female subjects of childbearing potential must not be pregnant, lactating, or planning to become pregnant for 3 months after the last dose of study drug, and have a negative serum pregnancy test at Screening and Check-in. Female subjects of childbearing potential must use 2 effective methods of birth control from 30 days before study drug administration through to the end of the study.
   - Effective birth control methods include oral, implantable, patch, or injectable contraceptive hormone treatment, hormone-containing intrauterine device that has been in place ≥2 months prior to Screening, sponge, diaphragm, or cervical cap with spermicidal gel or cream for female subjects or condom or vasectomy for male subjects.
   - Women are considered to not be of childbearing potential if they have fulfilled one of these criteria: documentation of irreversible surgical sterilization (i.e., hysterectomy or bilateral oophorectomy [not tubal ligation]) or are postmenopausal (defined as amenorrhea for 12 consecutive months following cessation of all exogenous hormonal treatments, and documented plasma follicle-stimulating hormone (FSH) level >40 IU/mL) or amenorrhea for 24 consecutive months.
   - Male subjects with partners of childbearing potential must agree to use appropriate and effective measures of contraception (e.g., condom plus diaphragm with spermicide, condom plus spermicide) during the study and for 30 days after the last dose of study drug, and refrain from donating sperm for ≥90 days following the last dose of study drug.

3.2.2 Exclusion Criteria

Subjects will be excluded from this study if they meet ANY of the following criteria:

1. Concern the subject may be unable to comply with study procedures and/or follow-up, or, in the opinion of the investigator, the subject is not suitable for entry into the study
2. History of any acute or chronic medical disorder expected to decrease the life expectancy of the subject
3. History or presence of gastrointestinal (GI), hepatic (with the exception of Gilbert's syndrome), or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs
4. Significant renal insufficiency, as indicated by estimated glomerular filtration rate (eGFR) <30 mL/min/1.73m^2 according to the Modification of Diet in Renal Disease (MDRD) equation
5. Any CS acute illness, medical/surgical procedure, or trauma within 4 weeks of administration of study drug or any planned surgical procedure that will occur during the study (from Screening through the Day 28 [±2 days] Follow-up visit).
6. Any CS abnormal findings in physical examination, vital signs, laboratory assessments, and ECG parameters identified during Screening or Check-in. Note: abnormal results may be repeated for confirmation immediately after the first out of range measurement. Abnormal vital signs may be repeated twice if needed, immediately after the first abnormal result and/or after the subject has rested for at least 10 minutes.

   Specific vital sign exclusionary criteria occurring after 10 minutes of supine rest are any of the following:

   - SBP <100 or >160 mm Hg
   - DBP <40 or >95 mm Hg
   - Resting HR <50 or >100 beats per minute (bpm)

   Specific exclusionary criteria for ECG parameters at Screening or Check-in include any of the following:

   - Prolonged Fridericia-corrected QT interval (QTcF) >450 milliseconds (msec), shortened QTcF <340 msec, or pause >3 seconds, or family history of long QT syndrome
7. Any specific contraindication to Brilinta® as described in the Brilinta prescribing information and:
   - History of intracranial hemorrhage, active bleeding, or hypersensitivity or allergic reaction to ticagrelor or any component of the product
   - Any history of severe head trauma, intracranial neoplasm, arteriovenous malformation, aneurysm, or proliferative retinopathy
   - Any history of intraocular, retroperitoneal, or spinal bleeding
   - Have taken, within 30 days of Screening, any oral or parenteral anticoagulant, including low molecular-weight heparin
   - Stool sample testing positive for occult blood within 3 months of Screening or at any time during the Screening Period.
8. Receiving chronic treatment with nonsteroidal anti-inflammatory drugs (NSAIDS; including ASA [>100 mg daily]), anticoagulants, or other antiplatelet agents that cannot

be discontinued 14 days prior to randomization (including clopidogrel, prasugrel, ticlopidine, dipyridamole, or cilostazol).

9. Positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody, or human immunodeficiency virus (HIV) types 1 or 2 antibodies at Screening.
10. Concomitant oral or IV therapy with strong or moderate cytochrome P450 3A4 (CYP3A) inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers, which cannot be stopped within at least 5 half-lives, but not fewer than 10 days, before randomization (a list of examples may be found in Appendix 7.2).
11. Consumption of grapefruit or grapefruit juice, Seville orange or Seville orange-containing products (e.g., marmalade), or xanthine-containing products within 48 hours before dosing with study drug.
12. Prescription or over-the-counter (OTC) medications within 14 days before the first dose of study drug unless specifically allowed by protocol. (Permitted medications include multivitamins, paracetamol [up to 2g per day], and/or treatments for chronic stable diseases provided the drug and dose have been stable for ≥30 days prior to administration of study drug)
13. Has received another investigational drug (defined as a small molecule or biologic compound which has not been approved for marketing) within 30 days of the administration of study drug in this study or within 5 half-lives of the experimental medication, whichever is longer.
14. Positive test result for alcohol or drugs of abuse at Screening or Check-in.
15. Participated in strenuous activity or contact sports within 24 hours before the infusion of study drug or while confined in the clinical site.
16. History of severe or ongoing allergy/hypersensitivity to any drug or biologic therapeutic agent.
17. Involvement with any PhaseBio or study site employee or their close relatives (e.g., spouse, parents, siblings, or children whether biological or legally adopted).
18. Previously received PB2452 or had been randomized to receive study drug in an earlier cohort for this study.

3.2.3 Subject Restrictions During the Study

If a subject is unable to comply with any of the following restrictions before study drug dosing on Day 1, the subject's participation in the study will be re-evaluated by the investigator in consultation with the Sponsor and/or medical monitor on behalf of the Sponsor; the subject may not be eligible to participate in the study:

- Subjects must be willing to remain at the study site from Day -3 through 48 hours following study drug dosing on Day 3.
- Subjects must be willing to return to the clinic for Follow-up visits on Day 7 and Day 28 (±2 days).
- Subjects must refrain from smoking or using nicotine or nicotine-containing products and from drinking alcohol-containing products

- Subjects must refrain from strenuous exercise for 24 hours prior to Check-in and for 7 days after discharge from the study
- Subjects must be willing to maintain their usual caloric intake and to consume only food and beverages provided by the clinical site while confined to the study site.

3.3 WITHDRAWAL OF SUBJECTS FROM THE STUDY

3.3.1 Reasons for Withdrawal

Subjects may withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the Sponsor. The investigator may also withdraw a subject at the request of the Sponsor or if the Sponsor terminates the study.

The investigator may withdraw a subject from the study if the subject:

- Is non-compliant with the protocol;
- Experiences a serious adverse event (SAE) or intolerable adverse event (AE) that, in the investigator's opinion, requires withdrawal from the study;
- Has laboratory safety assessments that reveal CS hematological or biochemical changes from Baseline values;
- During the course of the study and through the end of study (EOS) develops symptoms or conditions listed in the exclusion criteria;
- Requires a medication prohibited by the protocol; or
- Requests an early discontinuation for any reason.

If a subject experiences an SAE or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an AE, the event will be followed until it is resolved or until it is stable.

3.3.2 Handling of Withdrawals

When a subject withdraws from the study, the reason(s) for withdrawal will be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, any subject who withdraws from the study if willing, should continue to be followed according to the protocol. For example, if termination occurs earlier than planned (i.e., after a subject has received all or partial study drug infusion) all efforts should be made to ensure the remaining protocol visits are completed. If a subject refuses to return for the Follow-up visits, the Day 28 (±2 days) visit procedures should be completed. Any subject who fails to return for final assessments will be contacted by the site in an attempt to obtain compliance with the protocol. The status of subjects who fail to complete final assessments will be documented in the eCRF.

3.3.3 Replacement of Subjects

At the discretion of the investigator after consultation with the Sponsor, any subject who withdraws before completing the study, for reasons other than a DLT, may be replaced. Any replacement subject will be assigned to receive the same treatment as the subject he or she is replacing.

3.4 STUDY TREATMENTS

3.4.1 Method of Assigning Subjects to Treatment Groups

On Study Day 1 eligible subjects will be randomly assigned to treatment with either PB2452 or matching placebo in a 3:1 ratio, PB2452:placebo.

3.4.2 Treatments Administered

PB2452:

PB2452 IV infusion, prepared according to the Pharmacy Manual, will be administered on Day 1 for up to 48 hours. For each cohort, the dose, infusion rate, and duration will be communicated from the Sponsor to the study site, PPD, in a Dosing Memo issued prior to initiation of each treatment cohort.

Matching Placebo:

0.9% sodium chloride single IV infusion, administered on Day 1, will be delivered at a rate and volume matching the active infusion.

Ticagrelor:

Ticagrelor 90 mg oral tablets (immediate release) administered as 180 mg (2 × 90 mg tablets) every 12 hours for 5 total doses.

3.4.2.1 Dose Escalation

The SRC will conduct a blinded review of all safety and tolerability data from a cohort at least through Day 3 (e.g., clinical laboratory results, AEs, ECGs, Holter monitoring reports if available, vital signs, and available PK data) and available data for each completed dose cohort and will document their review and assessment in written SRC minutes prior to initiation of a subsequent cohort. Dose escalation may occur only if the SRC affirms the dose and regimen from the previously completed cohorts were safe and well tolerated and no DLTs were observed.

The SRC will be minimally composed of the on-site PPD investigator/medical monitor, PhaseBio medical monitor, and PhaseBio clinical operations lead. Changes to the administration regimen (rate and duration) without escalation of the total dose or without

increases in the infusion rate will not require formal SRC approval. Similarly, reductions in the total dose or the infusion rate will not require SRC approval.

The investigator may make a recommendation concerning whether the safety profile is sufficient to proceed to a higher dose level, whether a pause in dosing for review of additional safety and/or PK data is needed, or whether adjustment of the dose of the next dose cohort is needed. The decision to adjust or pause the dose or proceed to the next cohort will be made by the SRC.

3.4.2.2 Infusion-related or Allergic Reactions

The administration of study drug infusion must be performed under supervision of trained medical staff and where facilities to handle allergic reactions are available. Should a subject experience symptoms typical of IRRs seen with some recombinant protein drugs e.g., lightheadedness, nausea, chills, fever(Doessegger 2015) the study drug infusion must be immediately and permanently discontinued. Should a subject experience symptoms typical of an allergic reaction (e.g., shortness of breath, anaphylaxis, urticaria, angioedema), the study drug administration must be immediately and permanently discontinued. Suspected IRRs will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.(NCI CTCAE, v5, 2017) Should any one subject develop a ≥Grade 2 IRR to study drug, all subsequent subjects in the study, inclusive of all dose cohorts, must be administered premedication (diphenhydramine 25 mg by mouth [PO] + acetaminophen 650 mg PO) 30 to 60 minutes prior to receiving study drug to mitigate the risk of IRR. If any recipient of PB2452 (after unblinding) develops a ≥Grade 2 IRR in the absence of premedication, the entire dose level must be repeated as an additional cohort in which all subjects must be premedicated (as described above) 30 to 60 minutes prior to administration of study drug.

To monitor for potential IRRs, vital signs, including BP, HR, Temp, RR, will be assessed at Baseline (prior to study drug infusion), every 10 minutes during the first 30 minutes of the infusion, and every 15 minutes thereafter for the first hour after initiation of the infusion. The remaining assessments of vital signs will be performed as described in the Schedule of Events (Appendix 7.1). Suspected allergic (hypersensitivity) reactions and anaphylaxis will be assessed according to the clinical diagnostic criteria outlined by the National Institute of Allergy and Infectious Diseases provided in the CTCAE v5 in Appendix 0 (Definition and Management of Anaphylaxis) and Appendix 7.4 (Clinical Criteria for Diagnosing Anaphylaxis). Subjects will receive appropriate medical treatment for these and other medical concerns at the discretion of the investigator.

3.4.2.3 Dose-limiting Toxicities

The SRC will review all AEs and all laboratory and ECG Holter monitoring abnormalities according to CTCAE v5 to determine whether DLT has been identified in a subject who is confirmed to have received PB2452. If the SRC determines an AE is related to administration of ticagrelor or another confirmed cause, the AE will not be considered a DLT. Definitions of DLT are:

- Any AE assessed as ≥Grade 2 based on the CTCAE v5 grading scale and occurred in a subject confirmed to have received PB2452.
- Any ≥Grade 2 laboratory abnormality (outside the clinical laboratory normal reference range) that occurs in a subject confirmed to have received PB2452.
- Note: For a Grade 2 electrolyte abnormality that spontaneously resolves to ≤Grade 1 without intervention within 24 hours, the SRC may decide to exempt the laboratory abnormality from being considered a DLT.
- Any treatment-emergent adverse event (TEAE) that leads to study withdrawal of a subject confirmed to have received PB2452.

3.4.2.4 Stopping Criteria

Dose escalation or ongoing infusions will be suspended, pending investigation by the SRC, if any of the following occur after confirmation the subject has received PB2452:

- Any preclinical or clinical events that, in the opinion of the SRC, contraindicate further dosing of additional subjects with PB2452
- Any serious AE (SAE) occurring prior to discharge from the clinical site
- Data from previous cohorts indicate safety concerns for dosing at a higher level, such as unanticipated adverse responses (e.g., CS changes in clinical laboratory test data, ECGs Holter monitoring results, vital signs, physical examinations)
- Two or more subjects in a cohort experience any DLT, or 1 subject experiences a ≥Grade 2 AE (DLT) that, in the opinion of the SRC, warrants suspension of dose escalation
- Two or more subjects have >3 x ULN of either alanine aminotransferase (ALT) or aspartate aminotransferase (AST), or >2 x ULN of bilirubin or alkaline phosphatase (ALP) when no other reason can be found to explain the increases
- One or more subjects experiences a ≥Grade 2 IRR despite having been premedicated for IRRs.

Continuation of dosing following suspension will be determined by the SRC and documented in an ad hoc SRC Safety Report. Dosing may also be suspended if, in the opinion of the SRC or Sponsor, any new or unexpected significant safety or tolerability issues related to ticagrelor or PB2452 are identified that warrant further evaluation before additional subjects are dosed. This may include emerging nonclinical data, clinically relevant AEs, or relevant data from other sources indicating safety concerns, even if the event(s) per se does not meet the protocol-specified definition of a DLT.

Dose-limiting toxicities identified during the study will be assessed as potential indicators of cumulative toxicity and provide rationale for defining the maximum tolerated dose (MTD). Although this study is not designed to dose to a MTD, the MTD may be reached if ≥2 subjects in a dose cohort experience a DLT, as defined in Section 3.4.2.3. There will be no further dosing above the MTD.

3.4.3 Identity of Investigational Product

Study drug PB2452 is supplied as a sterile white to off-white lyophilized cake, free from visible foreign particles in a 20R glass vial at a nominal fill volume of 7.5 mL. PB2452 in the reconstituted state is formulated at 100 mg/mL in 25 mM histidine/histidine hydrochloride buffer, 290 mM sucrose, and 0.05% (w/v) polysorbate-80, pH 6.0.

Matching placebo is a sterile, nonpyrogenic liquid product intended for IV administration composed of 0.9% sodium chloride in water for injection, USP. Separate instructions will be provided to the clinic for dose dilution, preparation, storage, and administration.

3.4.4 Management of Clinical Supplies

3.4.4.1 Packaging and Storage

PhaseBio Pharmaceuticals, Inc will provide the investigator and clinical site with adequate quantities of PB2452, and matching placebo. The study site will purchase commercially available ticagrelor 90 mg tablets.

PB2452 will be supplied in a 20R glass vial at a nominal fill volume of 7.5 mL, stoppered with siliconized 20 mm chlorobutyl elastomer, flurotec-coated, single vent lyophilization stopper, and sealed with flip-off cap overseal. Following reconstitution with water for injection, PB2452 is further diluted into 0.9% saline for IV infusion.

The clinical site pharmacy will prepare a single dose for each subject based on the dosing cohort and randomization assignment. The concentration will vary between 0.4 mg/mL up to 72 mg/mL. Separate instructions will be provided to the clinic for dose dilution, preparation, storage, and administration.

PB2452 must be stored in a secure area (e.g., a locked, temperature-controlled unit) at 2°C to 8°C (36°F to 46°F) protected from moisture and light with access restricted to necessary clinic personnel. with access restricted to necessary clinic personnel. The clinical site will be required to keep a temperature log to establish a record of compliance with these storage conditions.

3.4.4.2 Drug Accountability

The investigator will maintain accurate records of receipt of all drug supplies used in this study including lot numbers (if applicable) and dates of receipt. In addition, accurate records

will be kept regarding when and how much drug is dispensed and used by each subject in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all drugs will be reconciled and retained or destroyed according to applicable regulations.

3.4.5 Blinding

This is a double-blind study. Neither the subjects nor the investigator will be aware of the treatment assignment. Blinding will be maintained throughout the study by use of active and placebo dose forms prepared to be similar in appearance. To maintain the blind, only designated pharmacy staff at the study site will have access to the randomization code and will prepare each dose for each subject. In order to prepare preliminary summaries of safety, PK, and/or PD data, as needed, to make timely decisions concerning adjustment of study procedures, dosing regimens, or potentially early termination of the study, certain designated staff at PhaseBio (e.g. study director, a single biostatistician, and bioanalytical scientist[s]) study drug accountability monitor, will receive unblinded data after each cohort completes Day 3 assessments. Except as noted above, all other members of PhaseBio will remain blinded. Access to the randomization code will be strictly controlled according to PPD SOPs.

3.4.6 Treatment Compliance

All doses of study drug, matching placebo, and ticagrelor will be administered at the clinical site under direct observation of clinic personnel and recorded in the eCRF.

The date, time, and actual dose received of study drug and matching placebo infusion and ticagrelor dosing will be recorded on the appropriate pages of the eCRF. If a subject was scheduled to receive any of these drugs and did not, the reason for the missed or partial dose will be recorded in the eCRF pages.

3.4.7 Breaking the Blind

A subject may be unblinded in the event of a DLT, an SAE, or if there is a medical emergency when the identity of the drug must be known to properly treat a subject. A cohort may be unblinded to determine if dose escalation to the next dose level will or will not proceed. In the event of a medical emergency requiring identification of the study drug administered to an individual subject, the investigator will make every attempt to contact the medical monitor to explain the need for opening the code within 24 hours of performing that task. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

3.4.8 Prior and Concomitant Medication

Prior medications are defined as medications taken prior to the first dose of study medication, regardless of whether they are continued or not after the first dose of study medication. Concomitant medications are defined as medications taken on or after the first dose date of study medication, including those started before the first dose and continued into the treatment period.

3.4.8.1 Prior Medication and Therapies

Information about prior medications taken by the subject within 30 days before he or she provides informed consent will be recorded in the subject's eCRF.

3.4.8.2 Concomitant Medication and Therapies

Subjects are prohibited from taking any additional prescription or OTC medications or nutritional supplements during their participation in the study (with the exception of protocol allowed medications, hormonal birth control and/or chronic medications). Paracetamol/acetaminophen or other medications may be administered at the discretion of the investigator at doses of up to 2 g/day.

Subjects are prohibited from therapy with strong or moderate CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers. A list of example inhibitors and inducers of CYP3A4 is presented in Appendix 7.2.

Subjects are prohibited from taking NSAIDs (within 14 days of screening), anticoagulants, or other antiplatelet agents within 30 days of screening.

Concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD). With the exception of drug therapy specified in the protocol, if drug therapy is taken, a joint decision will be made by the investigator and the Sponsor whether to continue or discontinue the subject based on the time the medication was administered, its pharmacology and PK, and whether the use of the medication will compromise the subject's safety or interpretation of the data. It is the investigator's responsibility to ensure that details regarding the medication are accurately recorded in the eCRF.

3.5 STUDY PROCEDURES

After signing the ICF, subjects will have study procedures at the time points specified in the Schedule of Events (Appendix 7.1).

Screening (Days -45 to -4)

- Subjects sign informed consent
- Inclusion/Exclusion criteria

- Demographics
- Medical history
- Urine screen, including cotinine
- Urine alcohol screen
- Serum pregnancy test for women of childbearing potential
- Serology test
- Stool occult blood test
- Physical examination, full, including height, weight, and BMI calculation
- Vital signs measured including SBP and DBP, oral body temperature, respiration rate (RR), and HR
- 12-lead ECG
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis

Check-in/Pretreatment - Baseline (Day -3)

- Inclusion/Exclusion criteria
- Urine drug screen, including cotinine
- Urine alcohol screen
- Serum pregnancy test for women of childbearing potential
- Admission to study site
- Physical examination, full, including weight,
- Vital signs measured including SBP and DBP, oral body temperature, RR, and HR
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- Blood sampling for PD (LTA/PRU/VASP)
- Serum immunogenicity
- AEs collected

Pretreatment - Baseline (Day -2)

- Administration of high-dose ticagrelor begins in the morning, single dose oral ticagrelor 180 mg (2 x 90 mg), followed by oral ticagrelor 180 mg every 12 hours for 4 additional doses through to Day 1 (2 hours before study drug is initiated; for a total of 5 doses of ticagrelor)
- Urine sampling, PK
- Blood sampling for PD (LTA/PRU/VASP)
- AEs collected

Pretreatment - Baseline (Day -1)

- Inclusion/Exclusion criteria
- 12-lead ECG
- Biomarkers
- Ticagrelor administered
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis

- AEs collected

On-site Treatment – Randomization (Day 1)

- Administration of ticagrelor 2 hours prior to study drug administration
- 12-lead ECG *before* study drug is administered
- Continuous 12-lead Holter monitor placed 2 hours b*efore* administration of study drug will remain in place for 24 hours *after* initiation of study drug. Subjects should be resting in the supine or semi-recumbent position depending upon Dosing Memo.
- Vital signs (SBP, DBP, oral body temperature, RR, HR) measured 30 to 60 minutes prior to and during infusion of study drug according to Schedule of Events (Appendix 7.1)
- Randomization
- Administration of PB2452 or matching placebo at Hour 0
- Blood sampling for PK: plasma PB2452, ticagrelor, and TAM PK, collected within 10 minutes *before* initiation of PB2452 infusion at Hour 0
- Blood sampling for PK: plasma PB2452, ticagrelor, and TAM PK, collected according to the cohort-specific Dosing Memo
- Blood sampling for PD: LTA/PRU/VASP according to the cohort-specific Dosing Memo
- Urine sampling (PK)
- Infusion site assessment
- Serum immunogenicity prior to dosing
- AEs collected

On-site Treatment (Day 2)

- Vital signs measured
- 12-lead ECG
- Continuous ECG recording (Holter) for ECG evaluation to remain in place for 24 hours *after* initiation of study drug on Day 1
- Blood sampling for plasma PB2452, ticagrelor, and TAM PK, collected according to the cohort-specific Dosing Memo
- PK Urine sampling
- Blood sampling for PD: LTA/PRU/VASP according to the cohort-specific Dosing Memo
- Biomarkers
- Infusion site assessment
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- AEs collected

On-site Treatment (Day 3)

- Physical examination, brief, includes querying the subject concerning any changes from Baseline
- 12-lead ECG
- Vital signs measured
- Blood sampling for PK: plasma PB2452, ticagrelor, and TAM PK collected according to the cohort-specific Dosing Memo
- Urine sampling (PK)
- Blood sampling for PD: LTA/PRU/VASP according to the cohort-specific Dosing Memo
- Infusion site assessment
- AEs collected
- Subjects discharged from site

Out-patient, Return to Study Site, Follow-up (Day 7)

- Physical examination, brief, includes querying the subject concerning any changes from Baseline
- Vital signs measured
- 12-lead ECG
- Blood sampling for PK: plasma PB2452, ticagrelor, and TAM PK, collected according to the cohort-specific Dosing Memo
- Biomarkers
- Serum immunogenicity
- Infusion site assessment
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- AEs collected

Out-patient, Return to Study Site, Follow-up, End of Study (Day 28 ±2 Days)

- Serum pregnancy test
- Physical examination, full, including height, weight, and BMI calculation
- Vital signs measured
- 12-lead ECG
- Blood sampling for PK: plasma PB2452, ticagrelor, and TAM PK, collected according to the cohort-specific Dosing Memo
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- Biomarkers
- Serum immunogenicity
- AEs collected

3.5.1 Pharmacokinetic Sample Collection

Samples for PK analyses should be collected after subjects has been resting supine for ≥10 minutes. Additional details concerning the collection, preparation, and handling of PK

blood and urine samples and sample shipping instructions will be provided to the clinical site. The clinical site will store all urine and plasma samples at the designated temperatures until shipped to the appropriate laboratories for analysis. Back-up samples will be maintained by the clinical site under the same conditions or at a designated storage facility until the Sponsor indicates the back-up samples should be shipped to the Sponsor.

PB2452 PK and immunogenicity analysis will be performed by:

PhaseBio Pharmaceuticals, Inc.
1 Great Valley Parkway, Suite 30
Malvern, PA 19355
Telephone: 610-981-6500

Ticagrelor and TAM concentration analysis will be performed by:

Covance
1121 East 3900 South, Suite C-110
Salt Lake City, UT 84124
Telephone: 801-313-6450

3.5.1.1 Bioanalytical Methods

Pharmacokinetic samples for total and free ticagrelor and the metabolite TAM will be analyzed using a validated liquid chromatography coupled with tandem mass spectrometry assay in human plasma. Pharmacokinetic samples for PB2452 will be analyzed using an immunoassay. The methods will be validated according to ICH standards and fit for purpose. Details of the bioanalytical methods and validation will be available in a separate bioanalytical report.

3.5.1.2 Pharmacodynamic Sample Collection

Blood samples for PD analysis will be collected at the following times: Day -3, -2, Day 1 (within 10 minutes prior to the initiation of study drug infusion [Hour 0] and per Dosing Memo), Day 2, and Day 3 if needed.

Collection time points for each cohort will be specified in a Dosing Memo from the Sponsor to PPD prior to initiation of each cohort.

Blood samples will be collected in collection tubes specific for each of the 3 PD assays. Specific instructions referring to the collection, processing, testing and, when applicable, the shipment of PD samples to CirQuest Labs, will be in the laboratory manual provided by CirQuest Labs and must be followed. If there is a discrepancy between the protocol and the lab manual, the lab manual should be followed.

- LTA: 3.2% sodium citrate (blue-top)
- VerifyNow® $P2Y_{12}$: Greiner Bio-One Vacuette® partial fill blood collection tube containing 3.2% sodium citrate

- VASP: 3.2% sodium citrate (blue-top)

3.5.2 Adverse Events

3.5.2.1 Adverse Event Definitions

The investigator is responsible for reporting all AEs observed or reported during the study, regardless of their relationship to study drug or their clinical significance. If there is any doubt whether a clinical observation is an AE, the event should be reported. For the purposes of AE recording when relationship to study drug is assessed, study drug refers to PB2452 or placebo. A separate line on the eCRF is for assessing whether or not an AE is related to the administration of ticagrelor.

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related. Subjects will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A TEAE is defined as any AE not present before exposure to study drug or any AE already present that worsens in intensity or frequency after exposure to study drug.

A suspected adverse reaction is any AE for which there is a reasonable possibility the study drug caused the AE. For the purposes of investigational new drug (IND) safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the study drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction," which means any AE caused by a study drug.

An adverse reaction is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions when there are reasons to conclude the drug caused the event.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the IB or at the specificity or severity that has been observed with the study drug; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions mentioned in the IB that occur with a certain class of drugs or as anticipated based on the pharmacological properties of the drug but are not specifically mentioned as having occurred with the specific drug under investigation.

An AE or suspected adverse reaction is considered an SAE/suspected unexpected serious adverse reaction if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect

Important medical events that may not result in death, may not be life threatening, or may not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE or suspected adverse reaction is considered "life threatening" if, in the opinion of either the investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Special attention will be given to DLTs and the MTD, if applicable. DLT is defined in Section 3.4.2.3. The overall safety profile, including but not limited to DLTs and MTDs will be used in the selection of the starting dose(s) in future studies of PB2452 administered by infusion.

3.5.2.2 Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to PhaseBio Pharmaceuticals, Inc. From the time informed consent is signed through to completion of all study procedures and assessments at the Day 28 (±2 days) visit, all AEs will be assessed.

Subjects may spontaneously report and/or will be asked a standard question to elicit any medically related changes in their well-being. They will also be asked if they have used any new medications or changed concomitant medication regimens (both prescription and OTC medications).

In addition to subject observations, AEs will be documented from any data collected on the AE page of the eCRF (e.g., laboratory values, physical examination findings, ECG, Holter monitoring changes) or other documents relevant to subject safety.

3.5.2.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, type of event, time of onset, dosage,

investigator-specified assessment of severity and relationship to study drug, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant (NCS). The current version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all AEs.

Any medical condition present at the time the subject is screened but does not deteriorate should not be reported as an AE. However, if the condition deteriorates at any time during the study, it should be recorded as an AE.

Any AE considered serious by the investigator or that meets SAE criteria (Section 3.5.2.1) must be reported to the Sponsor immediately (after the investigator has confirmed the occurrence of the SAE). The investigator will assess whether there is a reasonable possibility the study drug caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE, as outlined in the US Title 21 Code of Federal Regulations (CFR) Parts 312 and 320. The investigator is responsible for notifying the Institutional Review Board (IRB) directly.

The following contact information is to be used for SAE reporting:

PPD Medical Monitor: Rahul Bhatnagar, MD
PPD 7551 Metro Center Drive, Suite 300
Austin, TX 78744
Telephone (24 hour): 888-483-7729
Fax: 888-529-3580
email: rtpsafety@ppdi.com

3.5.2.4 Assessment of Severity

The severity (or intensity) of an AE will be determined by the investigator and refers to the extent to which it affects the subject's daily activities. Severity will be classified as mild, moderate, or severe using the following criteria:

- *Mild:* These events require minimal to no treatment and do not interfere with the subject's daily activities.
- *Moderate:* These events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with normal functioning.
- *Severe:* These events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually incapacitating.

Changes in the severity of an AE should be documented to allow assessment of the duration of the event at each level of intensity. An AE characterized as intermittent requires

documentation of onset and duration of each episode. The CTCAE v5 grading scale will be used by the SRC to assess all IRRs to determine whether premedication is required to mitigate future potential IRRs for subsequent study subjects. Additionally, CTCAE v5 will be used by the SRC to assess all AEs and laboratory abnormalities to determine whether a DLT and/or stopping criteria have been reached.

3.5.2.5 Assessment of Causality

The investigator's assessment of the relationship between an AE and study drug or ticagrelor is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality of all AEs and SAEs (i.e., whether there is a reasonable certainty the study drug caused the event). The relationship between an AE and an SAE to study drug (and ticagrelor) will be characterized using the following classifications:

- *Unrelated:* This relationship suggests there is no association between study drug (or ticagrelor) and the reported event.
- *Possible:* This relationship is based on evidence suggesting a causal relationship between the study drug (or ticagrelor) and the AE (i.e., there is a reasonable possibility the drug caused the event). The event follows a reasonable temporal sequence from the time of drug administration or the event follows a known response pattern to study drug (or ticagrelor) but could also have been caused by other factors.
- *Probable:* This relationship suggests a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with study drug (or ticagrelor) seems likely.
- *Definite:* This relationship suggests that a definite causal relationship exists between study drug (or ticagrelor) administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event.

3.5.2.6 Follow-up of Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed until it is resolved or stable or judged by the investigator to be NCS.

3.5.3 Clinical Laboratory Testing

Clinical laboratory tests will be performed by PPD Central Laboratory. Blood will be collected at the time points indicated in the Schedule of Events (Appendix 7.1) and will be prepared using standard procedures. Repeat clinical laboratory tests may be performed at the discretion of the investigator, if necessary, to evaluate inclusion and exclusion criteria or

clinical laboratory abnormalities. The clinical laboratory performing the tests will provide the reference ranges for all clinical laboratory parameters.

The following clinical laboratory assessments will be performed:

Hematology	Complete blood count (CBC) with differential hematocrit (hct) hemoglobin (Hgb) mean corpuscular hemoglobin (MCH) mean corpuscular hemoglobin concentration (MCHC) mean corpuscular volume (MCV) mean platelet volume (MPV) platelet count erythrocyte (red blood cell [RBC]) count total and differential leukocyte (white blood cell [WBC]) count
Serum Chemistry	alanine aminotransferase (ALT) albumin alkaline phosphatase (ALP) aspartate aminotransferase (AST) bicarbonate bilirubin (total and direct) blood urea nitrogen (BUN) calcium chloride cholesterol total high-density lipoprotein (HDL) calculated low-density lipoprotein (LDL) creatine phosphokinase creatinine gamma-glutamyl transferase (GGT) glucose Hgb A1C lactate dehydrogenase (LDH) magnesium phosphorus potassium sodium thyroid stimulating hormone (TSH; Screening only) total protein triglycerides (repeat fasting triglyceride if TG >500) uric acid
Coagulation	activated partial thromboplastin time (aPTT) international normalized ratio (INR) partial thromboplastin time (PTT) prothrombin time (PT)
Urinalysis (should be aligned to PPD urinalysis)	appearance bilirubin color glucose ketones leukocyte esterase reflex microscopy (at Screening and Check-in only, if dipstick is positive for protein or blood value ≥1+); includes

	bacteria crystals RBCs nitrites pH specific gravity (SpGr) urobilinogen casts epithelial cells WBCs occult blood protein turbidity
Serology	hepatitis B surface antigen (HBsAg) hepatitis C virus (HCV) antibody human immunodeficiency virus (HIV) types 1 and 2 antibodies (Screening only)
Other analyses	urine drug screen (Screening and Check-in only): amphetamines barbiturates benzodiazepines cannabinoids cocaine cotinine methylenedioxymethamphetamine (MDMA) opiates phencyclidine propoxyphene tetrahydrocannabinol urine alcohol (Screening and Check-in only) female subjects: follicle-stimulating hormone (FSH; Screening only) serum pregnancy test (human chorionic gonadotropin [Screening, Check-in, and Day 28 (±2 days) only])

Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter. The investigator will determine whether any of the abnormally high or low results are CS or NCS. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, therapeutic measures). If a CS change from the Screening value is noted, the CS value and etiology or reason for clinical significance will be documented on the AE page of the eCRF. The investigator will continue to monitor the subject with additional assessments until the values have reached either the reference range or the values at Screening or until the investigator determines that follow-up is no longer medically necessary.

When schedule procedures overlap at the same time point (see Schedule of Events (Appendix 7.1). there must be planning to collect the specific information within the designated time window. Accordingly, the importance of these procedures is:

1. *Blood collection* (whether for PD, PK, immunology, or safety) should always be collected at the designated time point (if possible). However, multiple collections (PD, PK, immunology, and safety) may be required at the same time point. Therefore, the

recommendation is for blood to be drawn in this order: PD, PK, immunology, and safety (see lab collection manual from CirQuest for additional information related to collection of PD samples).

2. The *12-lead ECG Holter monitoring* has a ±10-minute window (unless otherwise designated in the Schedule of Events, [Appendix 7.1]) when this may be done, either before or after blood collection.
3. If time permits, *vital sign measurements* should be completed just prior to or just after blood collection; this may be still be done within the designated window in the Schedule of Events (Appendix 7.1).

3.5.4 Vital Signs Measurements

Vital signs will be measured at the time points indicated in the Schedule of Events (Appendix 7.1).

Vital sign measurements will include SBP, DBP, oral body temperature, RR, and HR. The subject will have rested in a supine position for ≥10 minutes before all measurements are taken. *Note:* Vital signs collected during the initial 30 minutes of infusion of study drug require only the BP and HR.

The investigator will determine whether any of the vital sign measurements are CS or NCS. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, therapeutic measures). If a CS change from Screening values is noted, the CS value and reason for clinical significance will be documented on the AE page of the eCRF. The investigator will continue to monitor the subject with additional assessments until the value has reached either the reference range or the value at Screening or until the investigator determines follow-up is no longer medically necessary.

3.5.5 Twelve-lead Electrocardiogram

Twelve-lead ECGs will be obtained after the subject has rested in the supine position for ≥10 minutes or as clinically indicated based on reported AEs or laboratory findings, as necessary. The investigator should review and sign the ECG for any immediate issues. Electrocardiogram assessments will include comments concerning whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, and any evidence of MI, or ST-segment, T-Wave, and U-Wave abnormalities. In addition, measurements of these intervals will be reported: RR interval, PR interval, QRS width, and and QTcF

The investigator will determine whether any of the 12-lead ECG results are CS or NCS. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, therapeutic measures). If a CS change from Screening is noted, the CS value and reason for

CS will be documented on the AE page of the eCRF. The investigator will continue to monitor the subject with additional assessments until either the values have reached either reference range or the values at Screening or until the investigator determines follow-up is no longer medically necessary.

3.5.6 Holter Monitoring (Continuous Twelve-lead ECG)

Holter monitoring (continuous 12-lead ECG recording) for 24 hours will be performed at the time points indicated in the Schedule of Events (Appendix 7.1) to monitor HR and rhythm activity as standard safety measurements. The clinical research site will be responsible for providing trained study personnel for setting up and managing the Holter monitoring system to ensure that reports of Holter findings for each subject will be available for review at the safety review meeting for each cohort. The continuous ECG waveform data recorded by the Holter device will be stored for optional exposure-response QTc analysis. The Holter monitoring system used will be maintained in accordance with the clinical research site SOPs.

The SRC will determine if any of the Holter findings are CS at the safety review meetings. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, therapeutic measures).

If a CS finding from the Holter report is noted, the CS findings and etiology or reason for clinical significance will be documented in the AE page of the eCRF. The SRC may recommend repeat Holter monitoring during the 28-day safety period if clinically indicated.

3.5.7 Physical Examinations

A physical examination will be performed at the time points indicated in the Schedule of Events (Appendix 7.1).

A full physical examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities.

A brief physical examination will include assessment of skin (including any signs of cutaneous erythema), lungs, cardiovascular system, and abdomen (liver, spleen). Interim physical examinations will be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities. Height and weight will be measured, and BMI will be calculated at Screening and at Day 28 (±2 days).

3.5.8 Infusion Site Assessments

The infusion site will be examined by the investigator or designée concerning pain, tenderness, erythema/redness, and induration/swelling, as indicated in the Schedule of Events (Appendix 7.1). Infusion site reactions will be assessed according to the CTCAE v5 grading scale and will be recorded as AEs; these should be followed until resolution.

3.5.9 Immunogenicity Assessments

Immunogenicity (antibody) samples will be screened for the presence of binding anti-drug antibodies (ADA) at the time points indicated in the Schedule of Events (Appendix 7.1).

Results of immunogenicity samples taken prior to administering study drug do not need to be available prior to dosing nor to confirm subject eligibility. A subject who tests positive for ADAs at the final scheduled visit (Day 28 ±2 days) will be asked to return for follow-up sampling approximately 3 months after the final visit and approximately every 6 months thereafter until ADAs no longer test positive or until levels return to a predose state.

3.6 STATISTICAL CONSIDERATIONS

3.6.1 Sample Size Calculations

The sample size (N) of up to 3 cohorts of up to 12 subjects for Part B of this study is based on clinical and practical considerations rather than on formal statistical power calculation. The sample size will provide preliminary safety, efficacy and PK information in a dose/regimen finding fashion.

3.6.2 Analysis Populations

The *Safety Population* will include all subjects who receive any amount of study drug.

The *PK Population* will include subjects in the safety population who have ≥1 measurable PK concentration.

The *PD Population* will include subjects in the safety population who receive ≥1 dose of ticagrelor and have ≥1 measurable post dose PRU value.

3.6.3 Statistical Analysis

Details concerning all statistical analyses will be described in a separate Statistical Analysis Plan (SAP). All data collected during the study will be presented in Data Listings.

Data from subjects excluded from an analysis population will be presented in the Data Listings but will not be included in the calculation of summary statistics.

Data from subjects who receive placebo will be pooled across cohorts for all presentations.

For categorical variables, frequencies and percentages will be presented. Continuous variables will be summarized using descriptive statistics (number of subjects, mean, median, standard deviation [SD], minimum, and maximum).

Demographic and baseline characteristics will be summarized. The number of subjects who enroll in the study and the number and percentage of subjects who complete the study will be presented. Frequency and percentage of subjects who withdraw or discontinue from the study, and the reason for withdrawal or discontinuation, will also be summarized.

3.6.3.1 Pharmacokinetic Analyses

Plasma concentrations will be listed and summarized descriptively (number of subjects, arithmetic mean, SD, coefficient of variation [CV], median, minimum, and maximum). Plasma concentration versus time profiles for each subject will be presented graphically. The mean plasma concentration versus scheduled time profiles will be presented graphically by dose.

Pharmacokinetic parameters will be summarized by time point for each dose level using descriptive statistics (number of subjects, mean, standard deviation (SD), CV, median, minimum, and maximum). Geometric means will be reported for AUCs and C_{max}.

The PK parameters of PB2452, ticagrelor, and TAM will be determined with noncompartmental methods using Phoenix® WinNonlin® (Certara, L.P., Princeton, NJ) Version 6.4 or higher or SAS® Version 9.3 or higher (SAS Institute Inc., Cary, NC). Actual sampling times, rather than scheduled sampling times, will be used in all calculations of PK parameters. However, for ease of presentation, scheduled sampling times will be used to present results in tables, listings, and figures.

3.6.3.2 Pharmacodynamic Analyses

Pharmacodynamic data will be summarized for each time point using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum) for each treatment group or by cohort at each time point. Pharmacodynamic parameters will also be summarized . Inferential analysis maybe carried out to compare the % inhibition of PRU, LTA, PRI between PB2452 vs Placebo individually. However due to the limited sample size, efficacy analysis results will be considered descriptive.

3.6.3.3 Safety Analyses

Adverse events will be coded by preferred term and system-organ-class (SOC) using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). All AE data will be presented in Data Listings. Treatment-emergent AEs (TEAEs) will be summarized by

treatment and overall, as well as by severity and relationship to study drug. All SAEs and AEs leading to discontinuation of study drug will be presented in the Data Listings.

Actual values and changes from Baseline in clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, standard deviation [SD], median, minimum, and maximum). Clinical laboratory test results, vital sign measurements, 12-lead ECG results, Holter monitor results, immunogenicity results, and physical examination findings will be presented in Data Listings.

3.6.4 Handling of Missing Data

Missing PD data will not be imputed. Missing safety data will not be imputed except for the sake of determining TEAE and prior/concomitant medicine.

For PK data, concentrations below the limit of quantification (BLQ) will be treated as zero for descriptive statistics. Mean BLQ concentrations will be presented as BLQ, and the SD and CV will be reported as not applicable. Missing concentrations will be excluded from the calculations.

For the PK analysis, BLQ values will be treated as zero with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing. Missing concentrations will be treated as missing from the PK parameter calculations. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing.

3.6.5 Interim Analyses

There is no interim analysis planned for this study.

3.7 DATA QUALITY ASSURANCE

This study will be conducted using quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with current ICH guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current GCP, the protocol, and SOPs. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documents, and discussion of the conduct of the study with the investigator and staff.

Electronic CRFs and electronic data capture will be used. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that provides record

traceability. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

4. INVESTIGATOR OBLIGATIONS

Administrative items provided in this section are meant to guide the investigator in the conduct of the study and may be subject to change based on industry and government SOPs, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

4.1 CONFIDENTIALITY

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without written permission of the subject (or the subject's legal guardian), except as necessary for monitoring and auditing by the Sponsor, designee, the US Food and Drug Administration, or the IRB.

The investigator and all employees and coworkers involved in this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or designee must be obtained for the disclosure of any said confidential information to other parties.

4.2 INSTITUTIONAL REVIEW

Federal regulations and ICH guidelines require approval to be obtained from an IRB before human subjects participate in research studies. Before study onset, the protocol, ICF, advertisements to be used for recruitment of study subjects, and any other written information concerning this study must be provided to the subject must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH E6(R2): GCP will be maintained by the site and will be available for review by the Sponsor or designee. All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

4.3 SUBJECT CONSENT

Written informed consent in compliance with US Title 21 CFR Part 50 will be obtained from each subject before he or she enters the study or before any unusual or non-routine procedure is performed that involves risk to the subject. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the Sponsor or designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

Before recruitment and enrollment, each prospective subject will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured the subject understands the implications of participating in the study, the subject will be asked to give his/her consent to participate in the study by signing the ICF. A copy of the ICF will be provided to the subject/legal guardian.

4.4 STUDY REPORTING REQUIREMENTS

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his/her IRB, as appropriate.

4.5 FINANCIAL DISCLOSURE AND OBLIGATIONS

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigator must provide the Sponsor with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for
1 year following completion of the study.

Neither the Sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor PPD is financially responsible for further treatment of the disease under study.

4.6 INVESTIGATOR DOCUMENTATION

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R2) Section 8.2 and US Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB approval
- The original signed investigator agreement page of the protocol
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the principal investigator and each sub-investigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. CVs will be signed and dated by the principal investigators and sub-investigators at study start-up, indicating they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study to be provided to the subject or legal guardians
- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with US Title 42 CFR Part 493.

4.7 STUDY CONDUCT

The investigator will agree to perform all aspects of this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH E6(R2): GCP, the protocol, and all national, state, and local laws or regulations.

4.8 DATA COLLECTION

4.8.1 Case Report Forms and Source Documents

Site personnel will maintain source documentation and enter subject data into the eCRF as accurately as possible and will rapidly respond to any reported discrepancies.

Electronic CRFs and electronic data capture will be used. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved in the study will have an individual identification code and password that provides record traceability. Therefore, the system, and subsequently any investigative reviews, can identify coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

Each eCRF is presented as an electronic copy, allowing data entry by site personnel, who can add and edit data, add new subjects, identify and resolve discrepancies, and view records. This system provides immediate direct data transfer to the database, as well as immediate detection of discrepancies, enabling site coordinators to resolve and manage discrepancies in a timely manner.

Paper copies of the eCRFs and other database reports may be printed and signed by the investigator. This system provides site personnel, monitors, and reviewers with access to hardcopy audits, discrepancy reviews, and investigator comment information.

4.9 ADHERENCE TO PROTOCOL

The investigator will agree to conduct the study as outlined in this protocol, in accordance with ICH E6(R2) and all applicable guidelines and regulations.

4.10 REPORTING ADVERSE EVENTS

By participating in this study, the investigator agrees to submit reports of SAEs according to the time line and method outlined in this protocol. In addition, the investigator agrees to

submit annual reports to his/her IRB, as appropriate. The investigator also agrees to provide the Sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

4.11 INVESTIGATOR'S FINAL REPORT

Upon completion of the study, the investigator, when applicable, should inform the institution; the investigator/institution should provide the IRB with a summary of the study outcome and provide the Sponsor and regulatory authority(ies) with any reports required.

4.12 RECORD RETENTION

Essential documents should be retained until ≥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 ≥2 years have elapsed since the formal discontinuation of clinical development of PB2452. 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 Sponsor's responsibility to inform the investigator/institution when these documents no longer need to be retained.

4.13 PUBLICATIONS

After completion of the study, the study data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the Sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publications to which it will be submitted, and any other related issues. The Sponsor has final approval authority over all such issues.

Data from this study are the property of the Sponsor and cannot be published without their prior authorization; however, data and any publication thereof will not be unduly withheld.

5. ETHICS

5.1 ETHICAL CONDUCT OF THE STUDY

PhaseBio Pharmaceuticals, Inc and designées carried out all aspects of this study in accordance with the US Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), IRBs (21 CFR 56), and the obligations of clinical investigators (21 CFR 312). U.S. Title 21 CFR on Good Clinical Practice (GCP) is consistent with principles set forth by the Declaration of Helsinki and the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use. The study will be registered on Clinicaltrials.gov in accordance with Section 801 of the FDA Amendments Act of 2007 (FDAAA).

All Investigators were required to review and sign a Food and Drug Administration (FDA) Form 1572 and Sponsor-provided Study Operations Manual which described the Investigator's responsibility according to ICH/GCP guidelines.

5.2 INSTITUTIONAL REVIEW BOARD

The study protocol and amendments, ICFs, advertisements, and other information given to study subjects and/or their guardians will be reviewed and approved by the Institutional Review Board (IRB) of each study center prior to use. Each investigator will be responsible for informing the IRB of the progress of the study and submitting annual reports. This study will be conducted in the US, North America.

6. STUDY MANAGEMENT

6.1 MONITORING

6.1.1 Monitoring the Study

The clinical monitor, as a representative of the Sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documents, and discussion of the conduct of the study with the investigator and staff. All aspects of the study will be carefully monitored by the Sponsor or designee in compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and SOPs.

6.1.2 Inspection of Records

The investigator and institution involved in the study will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the Sponsor, their representatives, the FDA, or other regulatory agency access to all study records.

The investigator should promptly notify the Sponsor and study site(s) of any audits scheduled by any regulatory authorities and promptly forward to the Sponsor copies of any audit reports received.

6.2 MANAGEMENT OF PROTOCOL AMENDMENTS AND DEVIATIONS

6.2.1 Modification of the Protocol

Any changes in this clinical study, except those necessary to remove an apparent immediate hazard to a subject, must be reviewed and approved by the Sponsor or designee. Amendments to the protocol must be submitted in writing to the investigator's IRB and approved before subjects are enrolled into an amended protocol.

6.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a deviation from or a change to the protocol without prior IRB approval to eliminate an immediate hazard to study subjects. As soon as possible after such an event, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be

submitted to the IRB for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. An important protocol deviation (sometimes referred to as a protocol violation or a major protocol deviation) is a subset of protocol deviations that might significantly affect the reliability of study data or might significantly affect subject safety. An important deviation can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH E6(R2) guidelines.

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. The investigator will be notified by the monitor of deviations in writing. The IRB should be notified of protocol deviations, if appropriate, in a timely manner.

6.3 STUDY TERMINATION

Although the Sponsor has every intention of completing the study, the Sponsor reserves the right to discontinue at any time for clinical or administrative reasons.

The EOS is defined as the date on which the last subject completes the last visit; this includes the EOS visit and any additional long-term follow-up required for monitoring the resolution of an AE; the finding may be appended to the Clinical Study Report CSR.

6.4 FINAL REPORT

Whether the study is completed or prematurely terminated, the Sponsor will ensure CSRs are prepared and provided to regulatory agency(ies) according to the applicable regulatory requirement(s). The Sponsor will also ensure CSRs in marketing applications meet the standards of the ICH E3: Structure and Content of Clinical Study Reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for approval of the CSR. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have an opportunity to review complete study results.

Upon completion of the CSR, the investigator(s) will be provided with the final approved CSR, as appropriate.

7. APPENDICES

This section presents the following:

Appendix 7.1 Schedule of Events

Appendix 7.2 Examples of Inhibitors and Inducers of CYP3A4

Appendix 7.3 Definition and Management of Anaphylaxis Summary Report

Appendix 7.4 Clinical Criteria for Diagnosing Anaphylaxis

7.1 PART B SCHEDULE OF EVENTS

Procedure	Screening[a]	Check-in/ Pretreatment			Rand		Subjects Discharged	FUP	FUP/End of Study (EOS)
Study Day(s)	**–45 to –4**	**–3**	**-2**	**–1**	**1**	**2**	**3**	**7**	**28 (±2)**
Sign informed consent	X								
Inclusion/exclusion criteria	X	X		X					
Demographics	X								
Medical history	X								
Urine drug screen	X	X							
Urine alcohol screen	X	X							
Serum pregnancy test[b]	X	X							X
Serology testing	X								
Stool occult blood test	X								
Admission to study site clinic		X							
Physical examination[c,d]	X[c]	X[c]					X[d]	X[d]	X[c]
Vital sign measurements[e]	X	X			X	X	X	X	X
12-lead ECG[f]	X			X	X	X	X	X	X
Continuous ECG recording (Holter)					X	X[i]			
Clinical laboratory testing	X	X		X		X		X	X
Randomization					X				
Drug administration									
Ticagrelor[g]			X	X	X				
PB2452/Placebo[h]					X				
PK blood sampling*									
Plasma PB2452					X	X	X	X	X
Plasma ticagrelor/TAM					X	X	X	X	X
Free plasma ticagrelor/TAM					X	X	X	X	X
PK urine sampling**			X		X	X	X		
PD sampling (LTA/PRU/VASP)[j]		X	X		X	X	X		
Biomarkers*				X		X		X	X
Infusion site assessment[k]					X	X	X	X	
Serum immunogenicity		X			X[l]			X	X[l]
Adverse events		X	X	X	X	X	X	X	X
Discharge from clinical site							X[m]		

Abbreviations: ADA=anti-drug antibody; BMI=body mass index; DBP=diastolic blood pressure; ECG=electrocardiogram; EOS=end of study; FUP=follow-up; HR=heart rate; LTA=light transmittance aggregometry; PD=pharmacodynamics; PK=pharmacokinetics; PRU=$P2Y_{12}$ reaction units; QD=once daily; Rand=Randomization; RR=respiratory rate; SBP=systolic blood pressure; TAM=ticagrelor active metabolite AR-C124910XX; VASP=vasodilator-stimulated phosphoprotein

(Continued)

Schedule of Events (Cohort 1) ***(continued)***

* Modifications to this schedule may be made in a Dosing Memo from Sponsor to site prior to initiation of each cohort.

** Modifications to this schedule may be made in a Dosing Memo from Sponsor to site prior to initiation of each cohort.

a=Screening Period=Days -45 to -4

b=Serum pregnancy test for women of childbearing potential

c=A full physical examination is conducted at Screening, Day -3 and Day 28. Height and BMI calculation are completed at Screening and Day 28 only. Weight is collected at Screening, Day -3 and Day 28.

d=Brief physical examination (querying the subject concerning any changes from Baseline)

e=Vital sign measurements (SBP and DBP, oral body temp, RR, and HR) will be collected at screening, check-in, before dosing (30 to 60 minutes prior to the initiation of the study drug infusion) and at 10, 20, 30, 45, 60 min, 24 and 48 hours following initiation of study drug. Vital Signs are also collected on Day 7 and 28. Vital signs at 10, 20 and 30 minutes following infusion require only SBP and DBP, and HR.

f=12-lead ECGs will be obtained at Screening before initiation of PB2452 (or placebo), pre-treatment Day -1, and on treatment Days 1, 2, 3, 7 and 28. The specific time points for 12-lead ECG on Day 1 and 2 will be pre-dose, after bolus, end of infusion, and after 24 hours. If there is change to this schedule it will be communicated in a Dosing Memo. ECGs will be collected anytime on Day 3, 7, and 28.

g=Beginning in the morning on Day –2, a dose of oral ticagrelor 180 mg will be given, followed by oral ticagrelor 180 mg every 12 hours for 4 additional doses through to Day 1 (2 hours before study drug is initiated; this will be 5 total doses of ticagrelor).

h=PB2452 (or placebo) will be administered at Hour 0 of Day 1.

i=Continuous 12-lead Holter monitor placed 2 hours *before* administration of study drug will remain in place for 24 hours *after* initiation of study drug (to Day 2). The resting schedule for Holter monitors will be aligned with PK draws

j=PD samples may be tested for additional hematologic biomarkers, such as P-selectin.

k=Infusion site assessments will be performed for all subjects within 15 minutes before initiation of PB2452 (or placebo) infusion at Hour 0, and at 1, 3, 24, and 48hours after initiation of PB2452 (or placebo) infusion, and on Day 7.

l=Subjects may be required to return to the site for collection of additional follow-up samples, if the sample collected at Day 28 tests positive for treatment-emergent ADAs. These visits may occur approximately 3 months after the final study visit and approximately every 6 months thereafter or until antibody levels return to Baseline level..

Schedule of Events (Cohort 1) ***(continued)***

m=Subjects are discharged from the clinic on Day 3. Subjects are permitted, if necessary/convenient to the subject to remain housed at PPD following discharge through Day 7 visit. There are no study assessments to be completed on Days 4, 5, and 6.

7.2 EXAMPLES OF INHIBITORS AND INDUCERS OF CYP3A4

Strong Inhibitors (≥5-fold increase in AUC or >80% decrease in oral clearance):
Boceprevir
Clarithromycin
Conivaptan
Grapefruit juice
Indinavir
Itraconazole
Ketoconazole
Lopinavir/ritonavir
Mibefradil
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Voriconazole

Moderate Inhibitors (>2-fold and <5-fold increase in AUC)
aprepitant
cimetidine
ciprofloxacin,
clotrimazole
crizotinib
cyclosporine
dronedarone
erythromycin
fluconazole
fluvoxamine
imatinib
tofisopam
verapamil
diltiazem

Strong Inducers (≥80% decrease in AUC):
Avasimibe
Carbamazepine
Phenytoin
Rifampin
St John's wort

Note: This list is not all-inclusive. Please refer to the following website for further guidance: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

7.3 COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

Summary Report – Second National Institute of Allergy and Infectious Disease/Food Allergy, and Anaphylaxis Network Symposium

The common terminology criteria for adverse events, V5, can be found at the following link:

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Clinical criteria for diagnosing anaphylaxis are presented in Appendix 7.4

7.4 CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis is highly likely when any ONE of the following 3 criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
    b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
    d. Persistent gastrointestinal (GI) symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
    a. Infants and children: low systolic blood pressure (SBP; age specific) or >30% decrease in SBP*
    b. Adults: SBP <90 mm Hg or >30% decrease from that person's Baseline

* Low SBP for children from 1 month to 1 year is defined as <70 mm Hg (<70 mmHg + [2 x age]); <70 mmHg + [2 x age] from 1 to 10 years; and <90 mm Hg from 11 to 17 years.

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