A Phase 2B, randomized, double-blind, multicenter, placebo-controlled study to evaluate the efficacy of PB2452 in reversing the antiplatelet effects of ticagrelor in subjects aged 50 to 80 years old

PhaseBio Phase 2B ticagrelor reversal study

Investigational Product(s)	PB2452	
Protocol Number	PB2452-PT-CL-0003	
Clinical Trial Registry Identifiers	NCT04122170	
Version Number	Amendment 2 - version 2 dated 28May2021	
Amendment	Original Protocol - version 0 dated 16Aug2019 Amendment 1 - version 1 dated 29Oct2020	
Regulatory References	IND # 125267	
Principal/Site Investigator	Not applicable	
Sponsor	PhaseBio Pharmaceuticals, Inc. 1 Great Valley Parkway, Suite 30 Malvern, PA, USA 19355	
Medical Monitor	John Lee, MD, PhD PhaseBio Pharmaceuticals, Inc. 1 Great Valley Parkway, Suite 30 Malvern, PA, USA 19355	
Laboratories (or other Medical/Technical Institutions Involved in the Trial)	MLM Medical Labs 140 Collins St. Memphis, TN, USA 38112 Medpace Central Laboratories 5365 Medpace Way Cincinnati, OH, USA 45227	Frontage Labs 700 Pennsylvania Dr, Exton, PA, USA 19341

Confidentiality Statement

STATEMENT OF COMPLIANCE

The study will be conducted in compliance with this clinical study protocol, Good Clinical Practices (GCPs) as outlined by International Conference of Harmonization (ICH) E6(R2), and all applicable local and national regulatory requirements. Enrollment at any clinical study site may not begin prior to that site receiving approval from the ethics committee of record for the protocol and all materials provided to potential subjects.

Any amendments to the protocol or changes to the consent document will be approved before implementation of that amendment.

The Principal Investigator will ensure that changes to the study plan as defined by this protocol will not be made without prior agreement from the Sponsor and documented approval from the ethics committee of record, unless such a change is necessary to eliminate an immediate hazard to the study subjects.

All personnel involved in the conduct of this study should have completed Human Subjects Protection and GCP training as outlined by their governing institution.

SPONSOR'S APPROVAL

Title	**A Phase 2B, randomized, double-blind, multicenter, placebo-controlled study to evaluate the efficacy of PB2452 in reversing the antiplatelet effects of ticagrelor in subjects aged 50 to 80 years old**
Protocol Number	PB2452-PT-CL-0003
Version Number	Amendment 2 - version 2 dated 28May2021
Amendment	Original Protocol - version 0 dated 16Aug2019 Amendment 1 – version 1 dated 29Oct2020

The design of this study as outlined by this protocol has been reviewed and approved by the Sponsor's responsible personnel as indicated in the signature table below.

Name	**Title**	**Signature**
John Lee, MD, PhD	Chief Medical Officer	
Name	**Title**	**Signature**
Lauren Richardson	AVP Regulatory & Quality	
Name	**Title**	**Signature**
Lisa Hickey, PhD	Senior Director Biostatistics	
Name	**Title**	**Signature**
Susan Maloney	Global Head Clinical Research	
Name	**Title**	**Signature**
Susan Arnold, PhD	VP, Preclinical and CMC	

INVESTIGATOR'S AGREEMENT

I have read the protocol, appendices, and accessory materials (if applicable) related to this study and agree to the following:

- To conduct this study as described by the protocol and any accessory materials (if applicable)
- To conduct the study in accordance with all applicable local and national regulations, the requirements of the ethics committee of record for my clinical site, and Good Clinical Practices (GCPs) as outlined by ICH E6(R2)
- To obtain approval for the conduct of the protocol and all related amendments (if applicable) and all written materials provided to subjects prior to initiating the study at my site based on local requirements
- To obtain informed consent (IC) – and updated consent form where applicable and in the event of new information or amendments – from all subjects enrolled at my study site prior to initiating any study-specific procedures or administering investigational products to those subjects as outlined in the protocol
- To provide a completed and signed Food and Drug Administration (FDA) form 1572 (or equivalent where applicable) and a financial disclosure form

Name (Last Name, First Name)	**Site ID**	**Institution Name**

Signature	**Date**

Please note this page will be supplied separately to all sites. Please file the signed Investigator Agreement form in the study binder.

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1 SYNOPSIS

Title	**A Phase 2B, randomized, double-blind, multicenter, placebo-controlled study to evaluate the efficacy of PB2452 in reversing the antiplatelet effects of ticagrelor in subjects aged 50 to 80 years old**
Short Title	PhaseBio Phase 2B ticagrelor reversal study
Phase	2B
Study Design	Randomized, Double Blind, Multicentered, Placebo Controlled
Rationale	PB2452 is intended to reverse the antiplatelet effects of ticagrelor in patients who experience major or life-threatening bleeding or who require urgent surgery or invasive procedure
Population	Approximately 200 subjects between 50 and 80 years old who are in good general health or who have chronic, stable, and generally well-controlled medical conditions are eligible. This is the age group most typical of patients receiving ticagrelor. It is expected that approximately 20% of the study population will be ≥ 65 years old
Number of Subjects	Total: Approximately 200 Per treatment: The allocation ratio is 3:1 of active:placebo PB2452 arm: 150 Placebo arm: 50
Length of Participation	On treatment: Approximately 16-24 hours On study (including Screening and follow-up): up to 83 days compromised of up to 45 days of pre-screening and 35±3 days of follow up post study drug administration. Maximum total days involved will be 83 days The study will consist of a Screening period (Days –45 to –4), a Check-in period (Day –3 to Day -1), an on-site Randomization/Treatment day (Day 1), a 2-day on-site Follow-up period (Days 2 through 3), a Day 7 Follow-up visit, and a final Follow-up visit (Day 35±3) Note: If needed and at the discretion of the Investigator, a subject may remain in the study facility beyond the scheduled Day 3 discharge to accommodate Day 7 and/or Day 35±3 follow-up visits The estimated duration of the study for each subject, excluding screening, is approximately 35±3 days
Intervention	All subjects will be pretreated with both: 1. Aspirin 81 mg given once daily for a total of 8 doses, from Day -7 to Day 1 (2 hours prior to starting the study drug on Day 1)

	2. Ticagrelor 90 mg tablets for a total of 5 doses (180 mg loading dose followed by 90 mg twice daily) from Day -2 to morning of Day 1 (2 hours prior to starting the study drug on Day 1) The term "study drug" refers to PB2452 or placebo. Active: PB2452 is a ticagrelor-specific human monoclonal antibody fragment which binds to ticagrelor and ticagrelor active metabolite (TAM) with high affinity, thereby reversing the antiplatelet effects of ticagrelor. It has no known off-target effects PB2452 is formulated [redacted] For this study, the investigational product will be supplied either as a lyophilized powder requiring reconstitution with sterile water for injection, or as a high-concentration liquid. PB2452 18 g intravenous infusion will consist of 6 g infused over 10 minutes followed immediately by a 6 g loading dose infused over 4 hours, then a maintenance dose of 6 g infused over the next 12 hours immediately following completion of the loading period for a total infusion time of approximately 16 hours and 10 minutes. PB2452 is delivered via a standard IV bag(s) and IV pump, or syringe and syringe pump. If a subject is taking a moderate or strong CYP3A inhibitor, a 36 g alternative regimen of PB2452 will be administered consisting of 12 g infused over 10 minutes followed immediately by a 12 g loading dose infused over 6 hours, then a maintenance dose of 12 g infused over the next 18 hours immediately following completion of the loading period for a total infusion time of approximately 24 hours and 10 minutes. Placebo: 0.9% sodium chloride intravenous (IV) infusion, to be delivered as an infusion identical to the active drug regimens Ticagrelor: Ticagrelor 90 mg tablets for a total of 5 doses (180 mg loading dose followed by 90 mg twice daily) from Day -2 to morning of Day 1, and 2 hours prior to starting the study drug Aspirin: Enteric coated aspirin 81 mg oral tablet; administered daily between Day -7 to the morning of Day 1, two hours before receiving study drug, for a total of 8 tablets. Subject may resume aspirin after discharge from the study site on Day 3
Main Inclusion Criteria	Subjects must meet all the following criteria prior to randomization: 1. The subject provides written or verbal informed consent (in-person or remotely as applicable and per local requirements) and agrees to comply with all protocol requirements

	throughout study participation 2. The subject is male or female between ≥50 and ≤80 years of age 3. The subject has a body mass index between 18 and 35 kg/m^2 and a weight of ≥50 kg but ≤120 kg, inclusive, on first day of 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 and up to the time of randomization. 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 controlled with no more than two antihypertensive drugs • Hyperlipidemia (defined with a Screening LDL of <190 mg/dL) • Diabetes controlled with diet/exercise or treated with no more than 2 medications and/or Glycosylated Hemoglobin Hgb (HbA1c) ≤8% • Remote history of myocardial infarction (>3 years prior to screening) with no symptoms • Mild hepatic enzyme elevation (AST or ALT <1.5 x upper limit of normal (ULN) or total bilirubin <1.2 x ULN) 5. Specific inclusionary laboratory values at Screening and Check-in require the following: • Stable white blood cell (WBC) count, platelet count, haemoglobin level with no clinically significant abnormality within the normal range as assessed by the Investigator • Thyroid stimulating hormone (TSH) level within the normal range, as defined by the clinical laboratory at screening • Prothrombin time (PT) and/or international normalized ratio (INR) levels; plus partial thromboplastin time (PTT) and/or partial thromboplastin time (aPTT) levels less than or equal to the upper limit of normal 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 initiation of study drug 7. Subjects entering the study: i) **Who are not already taking daily aspirin** must be willing to start an 81 mg daily dose of aspirin on Day -7 and must document daily dosing until the final dose is administered on the morning of Day 1 ii) **Who are already taking daily aspirin** must be willing to document a daily 81 mg dose between Day -7 and Day 1 and must suspend further aspirin dosing until discharge from the study site on Day 3 8. Female subjects of childbearing potential must not be pregnant, lactating, or planning to become pregnant for 3 months after signing the informed consent, 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 for 3 months after signing the informed consent
Main Exclusion Criteria	Subjects will be excluded from the study if they meet any of the following criteria: 1. In the opinion of the Investigator there are concern(s) regarding the ability of the subject to comply with study procedures and/or follow-up, or, if 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 to an extent where the subject's study participation is affected 3. Any clinically significant acute illness, medical/surgical procedure, or trauma within 4 weeks of the administration of study drug or any planned surgical procedure that will occur during the study (from Screening through the Day 35±3 follow up visit) 4. Any clinically significant abnormal findings in physical examination, vital signs, laboratory assessments, and ECG parameters identified during Screening or Check-in. Note: abnormal results may be repeated (locally or centrally) 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 /Check-in or Day 1 are any of the following: • Prolonged Fridericia-corrected QT interval (QTcF) >450 milliseconds (msec), or pause >3 seconds, or family history of long QT syndrome 5. Any specific contraindication to ticagrelor as described in the Brilinta® prescribing information and as described below: • 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 • Having taken any oral or parenteral anticoagulant, including low molecular-weight heparin within 30 days of initiation of study drug • Severe hepatic impairment • Stool sample testing positive for occult blood within 3 months of Screening or at any time during the Screening period 6. Receiving treatment with nonsteroidal anti-inflammatory drugs [including aspirin (>100 mg daily), anticoagulants, or other antiplatelet agents, that cannot be discontinued between the date informed consent was signed and the end of the study period 7. First positive test result for any hepatitis B (unvaccinated), hepatitis C, or human immunodeficiency virus types 1 or 2 antigen or antibodies at screening 8. 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 9. History of severe or ongoing allergy/hypersensitivity to any biologic therapeutic agent

	10. Involvement with any PhaseBio or study site employee or their close relatives (e.g., spouse, parents, siblings, or children whether biological or legally adopted) 11. Previously received PB2452
Primary Objective and Primary Endpoint	Primary Objective: To demonstrate reversal of the antiplatelet effects of ticagrelor with intravenous PB2452 vs. placebo Primary Endpoint: The primary study endpoint is the minimum % inhibition of $P2Y_{12}$ reaction units (PRU) assessed by VerifyNow™ PRUTest™ (VerifyNow™, 2016) within 4 hours after the initiation of study drug. Percent inhibition of PRU is calculated as 100 * [(PRU_{bsl} – PRU_{trt})/PRU_{bsl}] where PRU_{bsl} refers to the PRU value measured before treatment with ticagrelor and PRU_{trt} refers to the PRU value measured post treatment with the study drug
Secondary Objective(s) and Corresponding Endpoint(s)	Secondary Objectives: 1. To evaluate the safety, tolerability, and immunogenicity of PB2452 in subjects treated with ticagrelor 2. To evaluate the pharmacokinetic (PK) profile of intravenous PB2452, ticagrelor, and its active metabolite (TAM) in blood and urine 3. To evaluate additional parameters of PB2452-mediated ticagrelor reversal by assessment of PRU using the VerifyNow™ PRUTest™ (VerifyNow™, 2016) $P2Y_{12}$ assay and assessment of the platelet reactivity index (PRI) using the Vasodilator-stimulated phosphoprotein (VASP) assay Secondary Endpoints: 1. Safety, tolerability and immunogenicity will be assessed by monitoring and recording of adverse events (AEs), including infusion site and systemic infusion reactions, clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, body temperature, respiratory rate, and heart rate), 12-lead electrocardiogram (ECG) results, physical examination findings, and immunogenicity 2. 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-last} • T_{max} • AUC_{0-24} • AUC_{0-48} • AUC_{0-tau} • $AUC_{0-\infty}$; if data permit • $t_{½}$; if data permit <u>Urine PK endpoints:</u> Pooled urine samples to assess urine PB2452, ticagrelor, and TAM concentrations will be collected according to predefined intervals. PK 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 over 24 hours (Ae_{24}) and over 48 hours (Ae_{48}) • Ae from time t1 to t2 hours including 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 (Fe_{24}) and from 1 to 48 hours (Fe_{48}) • Renal clearance (CLr) for 24 hours 3. Additional reversal endpoints: • Minimum %inhibition of PRI assessed by VASP within 4 hours after the initiation of study drug. %inhibition of PRI is calculated as $100 * [(PRI_{bsl} – PRI_{trt})/PRI_{bsl}]$. PRI_{bsl} refers to the PRI value measured before treatment with ticagrelor

	and PRI_{trt} refers to the PRI value measured posttreatment with the study drug • PRU AUC for the first 4 hours • Proportion of subjects with normalized platelet reactivity units within 4 hours after the initiation of study drug Normalized platelet reactivity is defined as PRU ≥ 180. • Proportion of subjects with ≥60%, ≥80%, and 100% of PRU response rate within 4 hours after the initiation of study drug. A PRU response 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% response rate by PRU • PRI AUC for the first 4 hours • Proportion of subjects 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% response rate by PRI • Percent reversal of PRU within 4 hours after the initiation of study drug. Percent reversal is calculated as 100 *[($PRU_{trt} - PRU_{pre\text{-}trt}$)/($PRU_{bsl} - PRU_{pre\text{-}reversal}$)]. $PRU_{pre\text{-}trt}$ is defined as the PRU value prior to administration of study drug • Percent reversal of PRI within 4 hours after the initiation of study drug. Percent reversal is calculated as 100 * [($PRI_{trt} - PRI_{pre\text{-}trt}$)/($PRI_{bsl} - PRI_{pre\text{-}trt}$)]. $PRI_{pre\text{-}reversal}$ is defined as the PRU value prior to administration of study drug
Other Prespecified Objective and Corresponding Endpoints	Other Prespecified Objective: • Assessment of platelet function related biomarkers Other Prespecified Endpoints: • Circulating levels of P-selectin and other platelet function-related biomarkers at baseline and post-initiation of PB2452 • Proportion of subjects with known single-nucleotide polymorphisms related to $P2Y_{12}$ receptor function

Number of Sites	Approximately 5-15 sites in the United States and other countries at the discretion of the Sponsor
Study Duration	Estimated start date: Q42019 Projected stop date: Q42021 Estimated duration: Timelines may be altered based on recruitment
Committee(s)	Not applicable

1.1 Schedule of Events

The schedule of events (SOE) is also presented in Appendix 3.

Table 1 Schedule of Events

	Outpatient		Outpatient/In-Clinic			Treatment (In-Clinic)			Outpatient[s]	
Procedure	**Screening[a]**		**Check-in/ Pretreatment**			**Rand**		**Subject DC**	**FUP**	**FUP EOS**
Study Day(s)	**–45 to –4**	**-7**	**–3**	**-2**	**–1**	**1**	**2**	**3**	**7**	**35±3**
Informed consent[b]	X									
Inclusion/exclusion criteria	X		X		X	X				
Demographics	X									
Medical history	X									
Urine drug screen	X		X							
Urine alcohol screen	X		X							
Serum pregnancy test[c]	X		X							X
Serology testing	X									
Stool for occult blood[d]	X							X[d]		
Admission to study clinic			X	X	X	X	X	X		
Physical examination[e,f]	X[e]		X[e]					X[f]	X[f]	X[e]
Vital signs[g]	X		X			X	X	X	X	X
12-lead ECG[h]	X				X	X	X		X	X
Clinical laboratory testing[i]	X		X		X[i]		X		X	X
Randomization[j]						**X**				
Drug administration										
ASA 81 mg QD[k]	X	X	X	X	X	X				
Ticagrelor administration[l]				X	X	X				
Administration PB2452 or placebo[m]						X				
PK sampling[n]: - Plasma PB2452 - Plasma ticagrelor/TAM - Unbound plasma ticagrelor/TAM				X[n]		X	X	X	X	X
PK urine sampling[o,p]				X[p]		X	X	X		

	Outpatient		Outpatient/In-Clinic			Treatment (In-Clinic)			Outpatient[s]	
Procedure	**Screening[a]**		**Check-in/ Pretreatment**			**Rand**		**Subject DC**	**FUP**	**FUP EOS**
Study Day(s)	**–45 to –4**	**-7**	**–3**	**-2**	**–1**	**1**	**2**	**3**	**7**	**35±3**
PD sampling (PRU/VASP)[q]				X		X	X	X		
Platelet function biomarkers[r]					X		X		X	X
Serum immunogenicity (ADA testing)[s]			X			X[s]			X	X[s]
Infusions site assessment[t]						X	X	X	X	X
AEs/SAEs[u]	X	X	X	X	X	X	X	X	X	X
Concomitant medications[v,w]	X[v]	X[v]	X[v]	X[v]	X[v]	X[w]	X[w]	X[w]	X[w]	X[w]
Discharge from clinic[x]								X	X[x]	X[x]

Abbreviations: AE=adverse event; ADA=anti-drug antibody; ASA= aspirin; BMI=body mass index; DBP=diastolic blood pressure; DC = discharged; ECG=electrocardiogram; EDC=electronic data capture; EOS=end of study; FUP=follow-up; HR=heart rate; PD=pharmacodynamics; PK=pharmacokinetics; PRU=$P2Y_{12}$ reaction units; QD=once daily; Rand=Randomization; RR=respiratory rate; SAE=serious adverse event; SBP=systolic blood pressure; TAM=ticagrelor active metabolite AR-C124910XX; VASP=vasodilator-stimulated phosphoprotein

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

b If verbal consent is obtained, it must be witnessed by an impartial witness. The details and full process to be fully documented in source documents

Note: Any changes to site-specific processes due to COVID-19 pandemic must be fully documented and identified within source documents and eCRF

c Serum pregnancy test for women of childbearing potential only. May utilize central or local laboratory as needed

d Stool for occult blood test may be conducted at either the central or local laboratory as needed. The Day 3 stool occult sample may be collected on Day 2 if needed

e A full physical examination is conducted at Screening, Day -3 and Day 35±3

Height and weight collected at Screening and Day 35±3 only

BMI is calculated within the electronic data capture system

f Brief physical examination and querying the subject concerning any changes from baseline. A brief physical examination will include assessment of heart, skin, lungs, cardiovascular system, and abdomen, and extremities

g Vital sign measurements (SBP and DBP, body temp, RR, and HR) will be collected at screening, check-in (Day -3), before dosing (30 to 60 minutes prior to the initiation of the study drug

infusion) and at 15±5, 30±10, 45±10, 60±15 min, 24 hours±15 min and 48 hours±15 min following initiation of study drug

Vital Signs are also collected on Day 7 and 35±3. Vital signs at 15, 30, 45, and 60 minutes following infusion require only SBP and DBP, and HR

h 12-lead ECGs will be obtained at Screening before initiation of PB2452/placebo, pre-treatment Day -1, and on treatment Days 1, 2, 7 and 35±3. The specific time points for 12-lead ECG on Day 1 and 2 will be pre-dose, 10 minutes after bolus, end of infusion, and after 24 hours (± 30 minutes) from initiation of infusion. ECGs will be collected anytime on Days 7 and 35±3

i All scheduled clinical laboratory tests will be performed centrally with the exception of Day -1 clinical laboratory testing which should be performed locally to provide results prior to randomization

Note: There is no scheduled clinical laboratory test o Day 3. However, if required the clinical laboratory tests (hematology, chemistry, coagulation, and urinalysis) may be repeated if considered clinically significant by the Investigator based on Day 2 lab results

j Local/Central laboratory results must be confirmed to ensure continued eligibility prior to randomization

k ASA 81 mg will be taken on Days -7, -6, -5, -4, -3, -2, -1, and on Day 1 no less than 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. Subjects will receive daily ASA 81 mg between Day -3 (or Day -2 if the subject 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 on Day 3

l 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 (or BID) for 4 additional doses through to Day 1. The final dose of ticagrelor should occur 2 hours±15 min before study drug is initiated)

m PB2452/placebo will be administered at Hour 0 of Day 1

Infusion of PB2452/placebo is initiated on Hour 0 of Day 1 and will continue for approximately 16 hours for a total of 18 g (180 mL), as described in the protocol and pharmacy manual.

In subjects with known or reported concomitant use of moderate or strong CYP3A inhibitors (Appendix 4), an alternative 36 g (360 mL) regimen of PB2452 infused for approximately 24 hours will be administered as directed by the pharmacy manual

n A pre-ticagrelor blood sample will be collected on Day -2, within 60 mins prior to the dose of ticagrelor. Blood samples for determination of plasma PB2452, plasma ticagrelor/TAM and unbound plasma ticagrelor/TAM will be collected on Days 1 to 3 within 10 minutes prior to the initiation of PB2452/placebo infusion (Hour 0) and at 5, 10, 30 minutes and 1, 2, 4, 8, 12, 20, 24, 36, and 48 hours after initiation of study drug infusion

Plasma PK samples will also be collected on Day 7, and Day 35±3 after initiation of study drug infusion

o Urine samples for PK ticagrelor/AR-C124910XX to be collected at i) 0 to 6 hours; ii) 6 to 12 hours and iii) 12 to 24 hours and iv) 24 to 48 hours after the initiation of the study drug infusion

p Collection of Day -2 urine PK sample is a single sample collected within 60 minutes prior to the first ticagrelor dose

q Blood samples for PD analysis (PRU/VASP testing) will be collected at the following timepoints: Day -2 and Day 1 (within 60 minutes prior to first ticagrelor dose) and Hour 0 (up to 10 minutes prior to PB2452/placebo infusion), 5, 10, 30 minutes, 1, 2, 4, 8, 12, 20, 24, 36 and 48 hours after initiation of PB2452/placebo infusion

If there is sufficient material leftover from PK and/or PD blood samples, additional platelet function-related biomarker testing, such as P-selectin, may be performed

r One sample for platelet biomarker testing will be collected into a plasma tube (3.2% Na Citrate) at the indicated timepoints. A single Qiagen PAXgene DNA tube per subject is collected at any convenient sampling timepoint throughout the study. Detailed instructions are provided in the laboratory manual

s Subjects may be required to return to the site for collection of additional follow-up samples, if the sample collected at Day 35±3 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

Note: serum immunogenicity sample on Day 1 must be collected prior to initiation of study drug infusion

t Infusion site assessments will be performed for all subjects within 15 minutes before initiation of PB2452/placebo infusion at Hour 0, 1, 3, 24, and 48 hours after initiation of PB2452/placebo infusion, and on Days 7 and 35±3

u All AEs/SAEs from the time of consent to Day 35±3 are to be reported, regardless of subject being within or outside the facility/study site

v All concomitant medications (prescription, over the counter and supplements) to be collected -45 days from the date informed consent is signed until Day 35±3. Subjects must be on a stable dose (meaning no changes in dose) of their medications for at least 30 days prior to initiation of study drug (time of randomization)

w New medications and changes to dosing of existing medications can occur post Day 1 (randomization) and are to be captured at schedule visit up to Day 35±3

x Subjects are discharged from the clinic on Day 3. However, if needed and at the discretion of the Investigator, a subject may remain in the study facility beyond the scheduled Day 3 discharge to accommodate Day 7 and Day 35±3 follow-up visits. All applicable study-related assessments for Day 7 and Day 35±3 will occur as outlined in the protocol

2 INTRODUCTION

PB2452 is an intravenously delivered monoclonal antibody fragment (Fab) intended to reverse the antiplatelet effects of ticagrelor in patients who experience uncontrolled major or life-threatening bleeding or who require urgent surgery or invasive procedure. PB2452 (molecular weight 47.4 kDa) is a specific and selective recombinant human neutralizing antibody IgG1λ monoclonal fragment antigen-binding (Fab) antibody that binds with high affinity to ticagrelor and selectively to circulating ticagrelor and its major active metabolite AR-C124910XX (TAM). It is expressed and manufactured from *Escherichia coli* cells (Buchanan, 2015).

Ticagrelor is an orally available inhibitor of platelet activity that in combination with low-dose acetylsalicylic acid (ASA, aspirin) has been shown to prevent recurrent thrombotic events, e.g., myocardial infarction (MI), stroke, and cardiovascular death, 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. Ticagrelor is a direct-acting cyclopentyltriazolopyrimidine inhibitor of platelet function that selectively and reversibly binds and antagonizes the platelet $P2Y_{12}$ receptor (Teng, 2016; van Giezen, 2009). A ticagrelor active metabolite (TAM) achieves a 30% to 40% plasma exposure relative to the circulating ticagrelor exposure in humans, (Storey R. H., 2007) and has potency similar to ticagrelor in inhibiting the $P2Y_{12}$ receptor.

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, if continued, the prescribed dosage is decreased to 60 mg bid. Ticagrelor is administered in combination with low-dose ASA (aspirin) as part of a regimen called dual antiplatelet therapy (DAPT). Although DAPT is strongly recommended in the management of patients experiencing an ACS event, it is also known to increase the risk of major or life-threating bleeding (Storey, 2011).

In the event of major bleeding in a patient on DAPT, there are limited treatment options. There are no approved drugs or biological agents capable of reversing the $P2Y_{12}$ inhibition produced by ticagrelor or other $P2Y_{12}$ inhibitors. Although platelet transfusion may restore platelet function in patients on ASA (Taylor G, 2013), it is not expected to reverse the antiplatelet effect of ticagrelor in patients with bleeding because of the reversibility of the ticagrelor $P2Y_{12}$ receptor interaction. (Teng, 2016). Accordingly, the current lack of a reliable effective therapy to mitigate ticagrelor-induced platelet inhibition in patients who have major bleeding or who have elevated bleeding risk due to a requirement for urgent surgery or intervention represents a significant unmet need.

2.1 Background

2.1.1 Target Indication and Population

The target indication for PB2452 is to reverse the antiplatelet effects of ticagrelor in adult ticagrelor-treated patients with major bleeding or prior to an urgent surgery or intervention.

2.1.2 Description of PB2452

PB2452 (molecular weight 47.4 kDa) is a recombinant human IgG1λ monoclonal fragment antigen-binding (Fab) antibody that binds specifically to ticagrelor and TAM. It is produced in *E.*

coli cells. PB2452 is [redacted]. It is presented as either a ready to use liquid formulation or as a lyophilized product that is reconstituted with sterile water for injection prior to use or as a high-concentration liquid.

2.1.2.1 Administration Regimen

Approximately 200 subjects ≥50 to ≤80 years old will be administered aspirin 81 mg daily for at least 7 days prior to initiation of ticagrelor pretreatment with a 180 mg oral loading dose of ticagrelor, followed by 90 mg bid for a total of 5 doses of ticagrelor.

The peak plasma concentration of ticagrelor occurs approximately 2 hours after the last oral dose. Therefore, in this study, subjects will be randomized to receive PB2452 or placebo 2 hours after the 5th dose of ticagrelor to ensure that the initial assessment of reversal occurs at peak ticagrelor plasma concentrations.

PB2452 will be administered as a 16-hour and 10 minutes intravenous infusion in subjects who have been pretreated with a combination of oral ticagrelor plus low-dose aspirin (DAPT).

Dual antiplatelet therapy (DAPT) pretreatment includes oral doses of aspirin 81 mg will be administered daily for at least 7 days prior to study drug infusion and ticagrelor which will be administered as an initial 180 mg oral loading dose followed by 4 additional doses of 90 mg tablets prior to randomization.

PB2452/placebo infusion will be administered intravenously as follows starting at 2 hours after the final dose of ticagrelor:

- An initial 6 g bolus of PB2452 infused over 10 minutes followed immediately by an additional 6 g loading infusion of PB2452 over 4 hours
- A 6 g maintenance infusion of PB2452 administered over 12 hours will immediately follow completion of the loading regimen for a total infusion time of 16 hours and 10 minutes

If a subject is taking a moderate or strong CYP3A inhibitor, a 36 g alternative regimen of PB2452 will be administered intravenously starting at 2 hours after the final dose of ticagrelor:

- An initial 12 g bolus of PB2452 infused over 10 minutes followed immediately by an additional 12 g loading infusion of PB2452 over 6 hours
- A 12 g maintenance infusion of PB2452 administered over 18 hours will follow completion of the loading regimen for a total infusion time of 24 hours and 10 minutes

2.1.2.2 Justification for Dosing Strategy

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 provided immediate and sustained reversal of the antiplatelet effects of ticagrelor and was considered generally safe and well tolerated. Significant reversal was observed by 5 minutes after initiation of infusion and was sustained for 20-24 hours. This profile of rapid and sustained ticagrelor reversal delivered by the 18 g infusion of PB2452 is considered ideal for patients on ticagrelor with uncontrolled major or life-threating major bleeding or who need urgent or invasive surgery. Importantly, there were no PB2452-related adverse effects, infusion-related

reactions (IRRs), or dose-limiting toxicities (DLTs) observed as determined by the study Investigator and safety review committee (SRC) of the Phase 1 study. The 18 g dose level and 16-hour infusion regimen administered in the Phase 1 study was repeated in a Phase 2A (PB2452-PT-CL-0002) clinical study of PB2452 in older (50-64 years old) and elderly (65-80 years old) subjects pretreated with DAPT for 48 hours. This population is similar in age and background comorbidities to the target patient population treated with ticagrelor as part of DAPT for prior heart attack or recent coronary stent placement. Preliminary data indicate that the reversal and safety profiles in the Phase 2A population pretreated with DAPT was similar to the results observed in the Phase 1 study.

PB2452 provided immediate and sustained reversal of the antiplatelet effects of ticagrelor with significant reversal observed as early as 5 min after initiation of infusion that was sustained for 20-24 hours. These data support the 18g regimen of PB2452 infused over 16 hours and 10 min. In the last cohort of the Phase 2A study, healthy volunteers aged 18-50 years old were pretreated with a supratherapeutic 180 mg PO BID doses of ticagrelor for 48 hours. A regimen of PB2452 consisting of a 12g bolus infused over 10 min followed immediately by 12g infused over 6 hours and then 12g infused over 18 hours for a total of 36g infused over a total of 24 hours and 10 min was found to provide immediate and sustained reversal of supratherapeutic levels of ticagrelor. Because this regimen of ticagrelor (180 mg BID) was found to produce circulating ticagrelor levels similar to ticagrelor levels occurring in the presence of ticagrelor 90 mg BID administered concomitantly with moderate CYP3A inhibitors (Teng R, 2013). This 36g regimen is expected to be appropriate for patients treated with ticagrelor who are currently taking moderate CYP3A inhibitors, such as, diltiazem or verapamil, and require urgent reversal of the antiplatelet effects of ticagrelor.

In the current study, a larger population of older and elderly subjects (N=200), PB2452 will be investigated to confirm the rapid and sustained reversal profile and overall safety, tolerability, and immunogenicity profile of the IV regimen of 18 g infused over 16 hours.

2.1.3 Supportive Nonclinical Data

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 administration prior to a tail cut had reduced bleeding to a degree comparable and not statistically different from the observation in mice not treated with ticagrelor (Buchanan, 2015).

The non-clinical pharmacology profile of PB2452 supported further exploration of the use of this compound as a novel ticagrelor antidote therapy. Detailed descriptions of the non-clinical pharmacology of PB2452 may be found in the Investigators' Brochure (IB) for PB2452.

2.1.3.1 Pharmacology

The key non-clinical pharmacology study findings for PB2452 are as follows:

- PB2452 binds free ticagrelor and its active metabolite, TAM, selectively and with a high affinity (equilibrium dissociation constant [KD] 20 pmol/L)
- PB2452 rapidly neutralizes the unbound plasma fraction of ticagrelor and TAM and thereby reverses ticagrelor- and TAM-mediated inhibition of 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)

The non-clinical pharmacology profile of PB2452 supports further exploration of the use of this compound as a novel ticagrelor antidote therapy. For further details please refer to the current IB.

2.1.3.2 Toxicology

Because PB2452 is directed at a non-endogenous target (i.e., ticagrelor and its metabolite TAM), one species was selected for the toxicology program, in accordance with ICH S6 guidelines (ICH, S6 (R1), 2011). The rat was selected as the relevant species, as ticagrelor and TAM exert similar toxicology profiles across species, metabolite profiles are comparable to those in humans, and the rat was a pharmacologically relevant species for ticagrelor.

In the rat Good Laboratory Practice (GLP) toxicity study, single doses of PB2452 were administered intravenously to groups of rats at doses up to 2000 mg/kg. Toxicity was assessed either 24 hours after dosing or following 14 days of extended monitoring. Additional groups of animals received ticagrelor pretreatment via oral gavage at 20 mg/kg for 2 days prior to initiation of single IV doses of PB2452 at 0, 500, or 2000 mg/kg, approximately 4 hours (C_{max}) after administration of ticagrelor. In this study, 2000 mg/kg PB2452 (± 20 mg/kg oral ticagrelor) was considered to be the no adverse effect level (NOAEL) (systemic exposures of PB2452 for the combined sexes; C_{max}: 18100 µg/mL, AUC from zero to ∞ ($AUC_{0-\infty}$): 23100 µg.h/mL). Overall, 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. The results of this GLP toxicity study support assessment of PB2452 in human studies (ICH, M3 (R2), 2009).

To determine whether PB2452 would be expected to cross react with human tissues, a human tissue cross-reactivity study was performed using PB2452 that was tagged with a fluorescent marker PB2452-FITC. In this study, no staining was seen with the test article, designated PB2452-FITC, in any of the organ systems present in the human tissue panel. Lack of PB2452-FITC staining of human tissues was expected as ticagrelor, the target of PB2452, is not expected to be present in, or expressed by, normal human tissues and because PB2452 binds ticagrelor with high specificity and affinity.

2.1.3.3 Toxicokinetics

The toxicity and PK of PB2452 were investigated following a single IV administration of 500 or 2000 mg/kg to the rat, alone and in combination with 20 mg/kg of oral ticagrelor. An assessment of delayed onset toxicity and/or reversibility of toxicity was made following a 2-week extended monitoring phase. The key PK results were as follows:

- Following IV infusion dosing, PB2452 was rapidly distributed before being cleared with an estimated terminal half-life ($T_{1/2}$) of 5.26 to 7.40 hours. Clearance (CL) was consistent between doses, ranging from 86.4 to 105 mL/hr/kg. The presence of ticagrelor did not affect the PK profile of PB2452, which was linear within the dose range tested, with dose proportional increases in maximum plasma concentration (C_{max}) and area under the curve (AUC) for plasma concentration versus time
- Concentrations of total ticagrelor and TAM increased from pre-dose concentrations following dosing with PB2452. While C_{max} was consistent between the 500 mg/kg PB2452 plus 20 mg/kg ticagrelor-dosed group and 2000 mg/kg PB2452 plus 20 mg/kg ticagrelor-dosed group, the AUC from zero to 30 hours (AUC_{0-30}) was greater in the 2000 mg/kg PB2452 plus 20 mg/kg ticagrelor-dosed group, indicating that the ticagrelor and TAM may be cleared at a slower rate than in the 500 mg/kg PB2452 plus 20 mg/kg ticagrelor-dosed group. The decrease in clearance for total ticagrelor and TAM at the highest dose is likely to be associated with higher concentrations of circulating PB2452 and a subsequent higher rate of complex formation. Total ticagrelor and TAM concentrations at follow-up ($C_{follow-up}$), 14 days after PB2452 administration, were below the assay limit of quantification (BLQ). Additionally, total ticagrelor and TAM systemic concentrations increased immediately following dosing of PB2452 by approximately 15- and 20-fold, respectively, indicating that PB2452:ticagrelor and TAM complexes formation leads to redistribution of extravascular ticagrelor into the circulation (Buchanan, 2015; ICH, S6 (R1), 2011)
- The PK of free ticagrelor and TAM as measured in the rat toxicology study were inconsistent, with variable pre-dose concentrations and quantifiable concentrations at $C_{follow-up}$. There were no differences between groups treated with 500 mg/kg PB2452 plus 20 mg/kg ticagrelor, 2000 mg/kg PB2452 plus 20 mg/kg ticagrelor, or the ticagrelor only group, and there was no identifiable trend in the data over time. This is likely to be associated to the limitation of the assay, as ticagrelor and TAM are highly protein bound. (Of note, a different research assay with a lower limit of quantification was used in the pharmacology studies summarized in Section 2.1.3.1, where the concentrations of free ticagrelor and TAM were reduced in a dose-dependent manner.) However, that the total ticagrelor and TAM systemic concentrations increased immediately following dosing of PB2452 by approximately 15- and 20-fold, respectively, demonstrates the pharmacodynamic (PD) effect of PB2452 binding to both ticagrelor and TAM

The absorption, distribution, metabolism, and excretion (ADME) of PB2452 have not been formally assessed. However, in a pharmacology study in which pigs were dosed to a supra-therapeutic ticagrelor exposure on a background of ASA before PB2452 administration, urine was collected and total ticagrelor and TAM measured as an exploratory assessment of ticagrelor elimination in the presence of PB2452. The addition of PB2452 resulted in marked increases in mean concentrations of total ticagrelor and TAM in the urine. Because ticagrelor is mainly excreted in the feces, with renal excretion playing only a minor role; accordingly, in 10 animals treated with ticagrelor on a background of ASA, the concentrations of total ticagrelor and TAM in the urine were BLQ. The addition of PB2452 resulted in marked increases in mean concentrations of total ticagrelor and TAM in the urine, supporting the idea that PB2452 complexation changes the ticagrelor elimination route from hepatic to renal (Buchanan, 2015).

2.1.4 Supportive Clinical 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. PB2452 was found to provide rapid, dose- and infusion duration-dependent reversal of the antiplatelet effects of ticagrelor. Detailed descriptions of the clinical safety, PK, and PD profiles of PB2452 may be found in the 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 toxic effects or infusion-related reactions (IRRs). There were no deaths or adverse events that led to discontinuation of the trial drug. 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 (Bhatt DL, 2019).

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. At this stage of development, other than the reversal of ticagrelor effect described above, there are no known drug-drug interaction between PB2452 and other approved or investigational drugs. There have been no formal drug-drug interaction studies performed to date.

2.1.4.1 Clinical Pharmacology and Pharmacokinetics

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) values of total PB2452 from time zero extrapolated to infinity ($AUC_{0-\infty}$) 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 produced an increase in the mean total plasma concentrations of ticagrelor and TAM compared to placebo, and this effect was dependent upon the dose of PB2452. Among volunteers who received placebo and ticagrelor pretreatment, the mean $AUC_{0–48}$ for ticagrelor ranged from 4730 to 6750 hours times nanograms per milliliter. Among volunteers who received 30-minute infusions of PB2452 and ticagrelor pretreatment, there was a dose-dependent increase in mean $AUC_{0–48}$ for ticagrelor by a factor of 2.0 to 5.6. Among volunteers who received 18 g of PB2452 with longer infusions and ticagrelor pretreatment, the mean $AUC_{0–48}$ for ticagrelor was increased by a factor of 5.6. This increased ticagrelor exposure probably reflected tight binding between PB2452 and ticagrelor and redistribution of extravascular ticagrelor into the vascular compartment.

Ticagrelor and TAM are known to be primarily metabolized hepatically with less than 1% of the dose cleared renally (BRILINTA (ticagrelor), 2021). As expected, PB2452 increased the renal clearance of ticagrelor and TAM in a dose-dependent manner presumably reflecting the clearance of PB2452 complexed with ticagrelor and TAM via the kidney. This is consistent with the preclinical PK data (Section 2.1.3.3) and is also consistent with the prediction that PB2452 changes the primary route of ticagrelor elimination from hepatic to renal.

2.1.5 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 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 (CS) 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 have been mostly mild and infrequent with no infusion-related or hypersensitivity reactions observed in the Phase 1 study in healthy volunteers and in the ongoing Phase 2A study (PB2452-PT-CL-0002) in subjects 50-80 years old, there remain potential risks related to PB2452. Infusion-related reactions (IRRs), infusion site reactions, and hypersensitivity-type reactions can result from exposure to recombinant protein drugs like PB2452 administered intravenously (IV). These risks are considered low and have not been observed to date and 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 any study subject develops a Grade ≥2 IRR. Development of antibodies to PB2452 might pose issues with a subsequent dose of PB2452, either an amnestic immunological reaction or, in the case of neutralizing antibodies, reduced efficacy. However, it is considered unlikely that re-administration will occur. The risk of other rare unexpected adverse reactions to PB2452 is considered very low but cannot be excluded.

As in previous studies with PB2452, the Phase 2B (Protocol PB2452-PT-CL-0003) study population will be administered low-dose ASA and ticagrelor which carries a risk of bleeding. The bleeding risk in study subjects is considered very low because the total duration of dual antiplatelet therapy is only 48 hours and subjects with a prior history of clinically significant

bleeding will be excluded from participation in the study. Among patients who take ticagrelor for therapeutic benefit, there is a potential risk of disease-related thrombosis upon reversal of the antiplatelet effect of ticagrelor. The safety profile of PB2452 in this patient population 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 has not been observed in the Phase 1 (PB2452-PT-CL-0001) study and Protocol Phase 2A (PB2452-PT-CL-0002) study.

Based on all available information concerning the risks of PB2452 and the precautions included in this clinical study, the risks are considered acceptable to enroll subjects 50-80 years old for investigation of ticagrelor reversal by PB2452.

2.1.5.1 Additional Risks

PB2452 lacks an endogenous target, and in a human tissue panel cross-reactivity study utilizing PB2452-FITC, no staining was observed in any of the human tissues on the panel. Therefore, due to high binding specificity, the risk of off-target effects is considered low.

The 14-day extended single-dose non-clinical GLP toxicology study conducted in rats with PB2452 doses up to 2000 mg/kg did not identify a clinically relevant safety concern. The maximum human dose proposed for Phase 1 was approximately 250 mg/kg.

Potential risks based on class effects

- **Infusion site reactions:**
  Possible risks associated with IV administration are redness, swelling, pain, induration, and sometimes infection at the administration site
- **Anaphylactic-type and infusion reactions:**

  Although anaphylactic-type reactions are considered of importance due to their serious nature, they are rare. Acute anaphylactic reactions may include cardio-respiratory distress, chest pain, hypotension, dyspnea, bronchospasm, respiratory failure, urticaria, pruritus, angioedema, nausea, vomiting, diarrhea, hypotonia, and collapse
- **Immunogenicity:**

  Development of antibodies to PB2452 might pose issues with a subsequent dose of PB2452, either an amnestic immunological reaction or, in the case of neutralizing antibodies, reduced efficacy. However, it is considered very unlikely that readministration will be required
- **Thrombosis:**

  There is a risk of thrombosis following reversal of ticagrelor's therapeutic antiplatelet effect in patients with clinical conditions at very high risk of thrombosis, such as recent ACS or recent placement of a coronary stent
- **Bleeding (aspirin and/or ticagrelor only):**

  Volunteers receiving pre-treatment with both aspirin and ticagrelor have a risk of bleeding during the clinical study

2.1.5.2 Benefits

Other than frequent assessments of overall health occurring during the screening, treatment, and follow-up periods of this study, there are no expected benefits from participation in this study.

2.2 Study Rationale

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 M, 2013; Godier A, 2015; Maillard J, 2015; Teng, 2016).

An agent to rapidly reverse the anti-platelet effects of ticagrelor, and its active metabolite TAM, would fulfill an important unmet clinical need for those ticagrelor-treated patients:

- who have major or life-threatening bleeding
- who require urgent surgery or intervention associated with a high risk of bleeding

3 OBJECTIVES AND ENDPOINTS

The primary hypothesis for this trial is to evaluate whether intravenous PB2452 will result in reversal of the antiplatelet effects of ticagrelor.

3.1 Primary Objective and Endpoint

Primary Objective:

To demonstrate reversal of the antiplatelet effects of ticagrelor with intravenous PB2452 vs. placebo.

Primary Endpoint:

The primary study endpoint is the minimum % inhibition of platelet reactivity unit (PRU) assessed by VerifyNow™ PRUTest™ (VerifyNow™, 2016) within 4 hours after the initiation of study drug. Percent inhibition of PRU is calculated as 100 * [(PRU_{bsl} – PRU_{trt})/PRU_{bsl}] where 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.

Primary Endpoint Justification:

VerifyNow™ PRUTest™ is an effective and widely used clinical assay for assessment of ticagrelor's suppression of platelet function. It is a point-of-care assay that quantitatively assesses $P2Y_{12}$ dependent platelet aggregation. Degree of aggregation is reported on a PRU scale of 0-350. The lower limit of normal (LLN) platelet function is 180 PRU based on the assay's labeling.

Primary Endpoint Analysis:

Please refer to Section 9 of this protocol for further details.

3.2 Secondary Objectives and Endpoints

3.2.1 Secondary Objectives:

1. To evaluate the safety, tolerability, and immunogenicity of PB2452 in subjects treated with ticagrelor
2. To evaluate the pharmacokinetic (PK) profile of intravenous PB2452, ticagrelor, and its active metabolite (TAM) in blood and urine
3. To evaluate additional parameters of PB2452-mediated ticagrelor reversal by assessment of PRU using the VerifyNow™ PRUTest™ (VerifyNow™, 2016) $P2Y_{12}$ assay and assessment of the platelet reactivity index (PRI) using the Vasodilator-stimulated phosphoprotein (VASP) assay

3.2.2 Secondary Endpoints:

1. Safety, tolerability and immunogenicity will be assessed by monitoring and recording of adverse events (AEs), including infusion site and systemic infusion reactions, clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, body temperature, respiratory rate, and heart rate), 12-lead electrocardiogram (ECG) results, physical examination findings, and immunogenicity

2. 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-last}
- T_{max}
- AUC_{0-24}
- AUC_{0-48}
- AUC_{0-tau}
- $AUC_{0-\infty}$; if data permit
- $t_{½}$; if data permit

Urine PK endpoints:

Pooled urine samples to assess urine PB2452, ticagrelor, and TAM concentrations will be collected according to predefined intervals.

PK 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 (Ae_{24}) and at 48 hours (Ae_{48})
- ae from time t1 to t2 hours including 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 (Fe_{24}) and from 1 to 48 hours (Fe_{48})
- Renal clearance (CLr) for 24 hours

3. Additional reversal endpoints:

- Minimum %inhibition of PRI assessed by VASP within 4 hours after the initiation of study drug. %inhibition of PRI is calculated as 100 * [(PRI_{bsl} – PRI_{trt})/PRI_{bsl}]. PRI_{bsl} refers to the PRI value measured before treatment with ticagrelor and PRI_{trt} refers to the PRI value measured posttreatment with the study drug
- PRU AUC for the first 4 hours
- Proportion of subjects with normalized platelet reactivity units within 4 hours after the initiation of study drug Normalized platelet reactivity is defined as PRU ≥ 180.
- Proportion of subjects with ≥60%, ≥80%, and 100% of PRU response rate within 4 hours after the initiation of study drug. A PRU response 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% response rate by PRU
- PRI AUC for the first 4 hours
- Proportion of subjects 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% response rate by PRI
- Percent reversal of PRU within 4 hours after the initiation of study drug. Percent reversal is calculated as 100 *[(PRU_{trt} – $PRU_{pre\text{-}trt}$)/(PRU_{bsl} – $PRU_{pre\text{-}reversal}$)]. $PRU_{pre\text{-}trt}$ is defined as the PRU value prior to administration of study drug
- Percent reversal of PRI within 4 hours after the initiation of study drug. Percent reversal is calculated as 100 * [(PRI_{trt} – $PRI_{pre\text{-}trt}$)/(PRI_{bsl} – $PRI_{pre\text{-}trt}$)]. $PRI_{pre\text{-}reversal}$ is defined as the PRU value prior to administration of study drug

3.3 Other Prespecified Objectives Endpoints

3.3.1 Other Prespecified Objectives:

- Assessment of platelet function related biomarkers

3.3.2 Other Prespecified Endpoints

- Circulating levels of P-selectin and other platelet function-related biomarkers at baseline and post-initiation of PB2452
- Proportion of subjects with known single-nucleotide polymorphisms related to $P2Y_{12}$ receptor function

4 STUDY PLAN

4.1 Study Design

This phase 2B study is a multi-center, randomized, double-blind, multicenter, placebo-controlled study. The study is designed to evaluate the efficacy of PB2452 in reversing the anti-platelet effects of ticagrelor as part of a dual antiplatelet regimen and to evaluate the safety and tolerability of PB2452 in subjects aged 50-80 years old.

Approximately 200 subjects between 50-80 years old will be enrolled in the US and other countries at the discretion of the Sponsor across 5-15 sites. The subjects will be randomized at a ratio of 3:1 receiving either the PB2452 investigational study drug or placebo. Hence, a total of approximately 150 subjects will be receiving PB2452 and approximately 50 subjects will be receiving placebo.

All subjects will be administered enteric coated aspirin 81 mg daily for at least 7 days prior to initiation of study drug for a total of 8 doses. Ticagrelor tablets will be administered prior to initiation of study drug with a 180 mg oral loading dose, followed by 90 mg bid for a total of 5 doses of ticagrelor. Two hours following the last dose of ticagrelor on morning of Day 1, subjects will receive either PB2452 or a placebo administered intravenously (IV) to assess reversal at peak ticagrelor plasma concentrations.

The infusion regimen is as follows:

- An initial intravenous (IV) bolus infusion consisting of a 6 g of study drug infused over 10 minutes followed immediately by an additional 6 g loading regimen of PB2452 infused over 4 hours
- A maintenance regimen of 6 g infused over 12 hours will immediately follow completion of the loading regimen for a total infusion time of approximately 16 hours

If a subject is taking a moderate or strong CYP3A inhibitor, a 36 g alternative regimen of PB2452 will be administered intravenously starting at 2 hours after the final dose of ticagrelor:

- An initial 12 g bolus of PB2452 infused over 10 minutes followed immediately by an additional 12 g loading infusion of PB2452 over 6 hours
- A 12 g maintenance infusion of PB2452 administered over 18 hours will immediately follow completion of the loading regimen for a total infusion time of 24 hours and 10 minutes

No interim analysis or subsequent long-term extensions are planned.

4.2 Design Rationale

This study uses a placebo-control to estimate the effect relative to the placebo response that would occur due to the decrease of ticagrelor over time. The double-blind nature of the design will allow for unbiased safety assessment. The use of subjects pre-treated with ASA and ticagrelor allows for assessment of suppressed platelet function prior to study-drug treatment which is required to calculate reversal.

5 POPULATION

Approximately 200 male or female subjects between 50 and 80 years old who are in good general health or who have chronic, stable, and generally well-controlled medical conditions will be evaluated across centers in the United States (US) and Canada. The Sponsor reserves the right to include sites in other countries if deemed necessary.

If a subject is unable to comply with any of the study procedures 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; the subject may not be eligible to participate in the study.

1. Subjects must be willing to remain at the study site at a minimum from Day 1 through Day 3 i.e. 48 hours following study drug dosing on Day 1
2. Subjects must be willing to return to the clinic for Follow-up visits on Day 7 and Day 35±3

   Note: If needed and at the discretion of the Investigator, a subject may remain in the study facility beyond the scheduled Day 3 discharge to accommodate Day 7 and Day 35±3 follow-up visits
3. Subjects must refrain from smoking or using nicotine or nicotine-containing products and drinking alcohol-containing products, while confined to study site
4. 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

Approximately 250-300 subjects may be screened to meet the target enrollment number of 200 subjects. Additional countries may be added at discretion of the Sponsor.

5.1 Definitions

Subjects officially enter the Screening Period following provision of signing an informed consent (written or verbal).

A screen failure is a consented subject who has been deemed ineligible based on 1 or more eligibility criteria or who has withdrawn consent prior to treatment assignment.

Screen failures may be rescreened upon confirmation with Sponsor. Screen failures may be rescreened once, upon review and confirmation from the Sponsor. For examples, subjects that have out of range laboratory results and vital sign measurements may have repeat assessment(s) during the Screening period.

An enrolled subject is one who has provided written or verbal informed consent.

A randomized subject is one who has been randomized to a treatment group on Day 1.

5.2 Inclusion Criteria

Subjects must meet all the following criteria prior to randomization:

1. The subject provides written or verbal informed consent (in-person or remotely as applicable and per local requirements) and agrees to comply with all protocol requirements throughout study participation
2. The subject is male or female between ≥50 and ≤80 years of age

3. The subject has a body mass index between 18 and 35 kg/m^2 and a weight of ≥ 50 kg but ≤ 120 kg, inclusive, on first day of 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 and up to the time of randomization. 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 controlled with no more than two antihypertensive drugs
    - Hyperlipidemia (defined with a Screening LDL of <190 mg/dL)
    - Diabetes controlled with diet/exercise or treated with no more than 2 medications and/or a Glycosylated Hemoglobin Hgb (HbA1c) ≤8%
    - Remote history of myocardial infarction (> 3 years prior to screening) with no symptoms
    - Mild hepatic enzyme elevation (AST or ALT <1.5 x upper limit of normal (ULN) or total bilirubin <1.2 x ULN)
5. Specific inclusionary laboratory values at Screening and Check-in require the following:
    - Stable white blood cell (WBC) count, platelet count, haemoglobin level with no clinically significant abnormality within the normal range as defined by the Investigator
    - Thyroid stimulating hormone (TSH) level within the normal range, as defined by the clinical laboratory at screening
    - Prothrombin time (PT) and/or international normalized ratio (INR) levels, plus partial thromboplastin time (PTT) and/or activated partial thromboplastin time (aPTT) level less than or equal to the upper limit of normal 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 initiation of study drug
7. Subjects entering the study:
    i. **Who are not already taking daily aspirin** must be willing to start an 81 mg daily dose of aspirin on Day -7 and must document daily dosing until the final dose is administered on the morning of Day 1
    ii. **Who are already taking daily aspirin** must be willing to document a daily 81 mg dose between Day -7 and Day 1 and must suspend further aspirin dosing until discharge from the study on Day 3
8. Female subjects of childbearing potential must not be pregnant, lactating, or planning to become pregnant for 3 months after signing the informed consent, 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 for 3 months after signing the informed consent

5.3 Exclusion Criteria

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

1. In the opinion of the Investigator there are concern(s) regarding the ability of the subject to comply with study procedures and/or follow-up, or, if 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 to an extent where the subject's study participation is affected
3. Any clinically significant acute illness, medical/surgical procedure, or trauma within 4 weeks of the administration of study drug or any planned surgical procedure that will occur during the study (from Screening through the Day 35±3 follow up visit)
4. Any clinically significant abnormal findings in physical examination, vital signs, laboratory assessments, and ECG parameters identified during Screening or Check-in

   Note: abnormal results may be repeated (locally or centrally) 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/Check-in or Day 1 are any of the following:
     - Prolonged Fridericia-corrected QT interval (QTcF) >450 milliseconds (msec), or pause >3 seconds, or family history of long QT syndrome
5. Any specific contraindication to ticagrelor as described in the Brilinta® prescribing information and as described below:
   - 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
   - Having taken any oral or parenteral anticoagulant, including low molecular-weight heparin within 30 days of initiation of study drug
   - Severe hepatic impairment
   - Stool sample testing positive for occult blood within 3 months of Screening or at any time during the Screening period
6. Receiving chronic treatment with nonsteroidal anti-inflammatory drugs including aspirin (>100 mg daily), anticoagulants, or other antiplatelet agents that cannot be discontinued between the date the informed consent form was signed and the end of the study period

7. First positive test result for any hepatitis B (unvaccinated), hepatitis C, or human immunodeficiency virus types 1 or 2 antigen or antibodies at screening
8. 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
9. History of severe or ongoing allergy/hypersensitivity to any biologic therapeutic agent
10. Involvement with any PhaseBio or study site employee or their close relatives (e.g., spouse, parents, siblings, or children whether biological or legally adopted)
11. Previously received PB2452

5.4 Exceptions to Eligibility Criteria

Approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

6 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.

This Phase 2B study will consist of:

- A Screening period (Days –45 to –4)
- Pretreatment with ASA 81mg daily (Day -7 to Day 1)
- Check-in Day–admission to study clinic (Day -3 to Day 3)
- Pretreatment and ticagrelor treatment (Day -2 to Day 1)
- On-site Randomization/Treatment (Day 1)
- 2-Day on-site Follow-up period (Day 1 to Day 3)
- Day 7 Follow-up visit (Day 7)
- Final Follow-up visit on (Day 35±3)

Plasma samples for PD and PK analysis of PB2452, ticagrelor and its active metabolite, (TAM) will be collected at Day -2, pre-dose (within 10 minutes prior to start of infusion), Day 1 and Day 2 at 5, 10 and 30 minutes and 1, 2, 4, 8, 12, 20, 24, 36, 48 hours following initiation of the study drug infusion. Plasma PK samples will also be collected on Day 7, and Day 35±3 after initiation of study drug infusion.

Safety and tolerability will be carefully monitored through the study. The existence of anti-drug-antibodies will be assessed in all subjects at Day -3, Day 1 (randomization), Day 7 and 35±3 following administration of study drug at 3 months and then every 6 months until return to baseline.

The estimated duration of the study for each subject, excluding screening, is approximately 35±3 days.

6.1 Study Procedures

After signing the ICF, subjects will have study procedures at the time points specified in the Schedule of Events (Appendix 3).

Screening (Days -45 to -4)

- Subjects sign informed consent
- Inclusion/Exclusion criteria
- Demographics
- Medical history
- Urine drug screen
- Urine alcohol screen
- Serum pregnancy test for women of childbearing potential

- Serology tests
- Stool occult blood test
- Full physical examination, including height and weight
- Vital signs measured including SBP and DBP, body temperature, respiration rate (RR), and heart rate (HR)
- 12-lead Electrocardiogram (ECG)
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- Adverse Events (AEs)/serious adverse events (SAEs) collected
- Concomitant medications within -45 Days before subject provides informed consent. To include all prescription, over the counter (OTC) and supplements

  Note: For subjects who are already taking aspirin they must be willing to document a daily 81 mg dose between Day -7 and Day 1 and must suspend further aspirin dosing from Day 1 until discharge from the clinical facility on Day 3

Screening (Day -7)

- Start ASA 81mg (enteric coated) daily (QD)
  - Subjects who enter the study already taking ASA 81 mg daily will document a daily ASA 81 mg dose)
- AEs/SAEs collected
- Concomitant medications

Screening (Day -6)

- ASA 81mg QD

Screening (Day -5)

- ASA 81mg QD

Screening (Day -4)

- ASA 81mg QD

Check-in/Pretreatment – Admission to Study Clinic - Baseline – Outpatient (Day -3)

- ASA 81mg QD
- Inclusion/Exclusion criteria
- Urine drug screen
- Urine alcohol screen
- Serum pregnancy test for women of childbearing potential
- Admission to study clinic
- Full physical examination and querying the subject for changes from baseline

- Vital signs measured including SBP and DBP, body temperature, RR, and HR
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- Serum immunogenicity
- AEs/SAEs collected
- Concomitant medications

Pretreatment - Baseline (Day -2) – May involve admission to study clinic as per study site's policy

- ASA 81mg QD
- Urine sample for PK ticagrelor/AR-C124910XX within 60 minutes prior to the first ticagrelor dose
- Ticagrelor administration
  - Single dose oral 180 mg (a.m.)
  - Single dose oral 90 mg 12 hours later (p.m.)
- Blood sampling for PK plasma (Plasma PB2452/Plasma ticagrelor/TAM/Unbound plasma ticagrelor/TAM) within 60 minutes prior to the first ticagrelor dosing
- Blood sampling for PD (PRU/VASP) within 60 minutes prior to the first ticagrelor dose
- AEs/SAEs collected
- Concomitant medications

Pretreatment - Baseline (Day -1) – May involve admission to study clinic as per study site's policy

- ASA 81mg QD
  - No less than 2 hours before study drug is started
- Inclusion/Exclusion criteria reconfirmed
- 12-lead ECG
- Local clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- Ticagrelor administration
  - Single dose oral 90 mg (a.m.)
  - Single dose oral 90 mg (p.m.)
- Platelet biomarker sample collection (3.2% Na Citrate plasma tube)

  Note: a single Qiagen PAXgene DNA tube per subject may be collected at any convenient sampling timepoint throughout the study
- AEs/SAEs collected

- Concomitant medications

In-House Treatment – Randomization (Day 1) – Admission to study clinic

- ASA 81mg QD
    - Approximately **2 hours prior** to study drug administration (PB2452/placebo)
- Vital signs measurements SBP, DBP, body temperature, RR, HR measured 30 to 60 minutes prior to initiation of study drug (PB2452/placebo) and at 15+5 minutes, 30+10 minutes, 45+10 minutes, 60+15 minutes and 24 hours±15 minutes, 48 hours±15 minutes hours following initiation of study drug infusion
- 12-lead ECG within **one hour before** study drug (PB2452/placebo), after bolus, (10 minutes), end of infusion (16 hours and 10 minutes) post initiation of the study drug (PB2452/placebo)
- Serum immunogenicity blood sample
- Ticagrelor administration
    - Single dose oral 90 mg (a.m.)
        - 2 **hours±15 minutes prior** to study drug administration (PB2452/placebo)
- Review of lab results of Day -1 and the vital sign assessments of Day 1 prior to randomization to confirm eligibility
- **Randomization**
- Administration of PB2452 or placebo at Hour 0
- Blood sampling for PK plasma (Plasma PB2452/Plasma ticagrelor/TAM/Unbound plasma ticagrelor/TAM) within 10 minutes prior to initiation of PB2452/placebo infusion (Hour 0), and 5, 10, 30 minutes, 1, 2, 4, 8, 12, 20, and 24 hours after initiation of study drug infusion
- Blood sampling for PD sampling (PRU/VASP) within 10 minutes prior to study drug (PB2452/placebo) infusion at hour 0 and at 5, 10, 30 minutes and 1, 2, 4, 8, 12, 20, and 24 hours after initiation of study drug (PB2452/placebo)
- Pooled urine sample for PK ticagrelor/AR-C124910XX at 0 to 6, 6 to 12 and 12 to 24 hours after the initiation of the study drug infusion
- Infusion site assessment to be done within 15 minutes prior to the initiation of the PB2452/placebo infusion at Hour 0 and at 1, 3, and 24 hours after initiation of PB2452/placebo infusion
- AEs/SAEs collected
- Concomitant medications (new medications and changes in dosing of previously reported medications)

In-House Treatment (Day 2)

- Vital signs measurements at 48 hours±15 minutes following initiation of study drug infusion as per Schedule of Events (Appendix 3)
- 12-lead ECG at 24 hours (±30 minutes) post initiation of study drug (PB2452/placebo) infusion
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- Blood sampling for PK plasma (Plasma PB2452/Plasma ticagrelor/TAM/Unbound plasma ticagrelor/TAM) 36 and 48 hours after initiation of study drug (PB2452/placebo)
- Blood sampling for PD sampling (PRU/VASP) 36 and 48 hours after initiation of study drug (PB2452/placebo)
- Pooled urine sample for PK ticagrelor/AR-C124910XX at 24 to 48 hours after the initiation of the study drug infusion
- Platelet biomarker sample collection (3.2% NaCitrate plasma tube)

  Note: a single Qiagen PAXgene DNA tube per subject may be collected at any convenient sampling timepoint throughout the study
- Infusion site assessment at 48 hours after initiation of PB2452/placebo infusion
- AEs/SAEs collected
- Concomitant medications (new medications and changes in dosing of previously reported medications only)

In-House Treatment (Day 3)

- Brief physical examination and querying the subject for changes from baseline
- Vital signs measurements (SBP, DBP, RR and HR)
- Stool occult test (local or central laboratory) which may be completed on Day 2 if needed
- Blood sampling for PK plasma (Plasma PB2452/Plasma ticagrelor/TAM/Unbound plasma ticagrelor/TAM)
- Blood sampling for PD sampling (PRU/VASP) 48 hours after initiation of study drug (PB2452/placebo)
- Pooled urine sample for PK ticagrelor/AR-C124910XX at 24 to 48 hours after the initiation of the study drug infusion
- Infusion site assessment
- May repeat clinical laboratory tests (hematology, chemistry, coagulation, and urinalysis) if considered clinically significant by the Investigator based on Day 2 lab results
- AEs/SAEs collected
- Concomitant medications (new medications and changes in dosing of previously reported medications)
- Subjects discharged from study site/clinic

- If needed and at the discretion of the Investigator, a subject may remain in the study facility beyond the scheduled Day 3 discharge to accommodate Day 7 and Day 35±3 follow-up visits

Out-patient, Return to Study Site, Follow-up (Day 7) OR In-House if the Subject Remained at the Study Site until Day 7

- Brief physical examination and querying the subject for changes from baseline
- Vital signs measurements (SBP, DBP, RR, temperature and HR)
- 12-lead ECG
- Blood sampling for PK plasma (Plasma PB2452/Plasma ticagrelor/TAM/Unbound plasma ticagrelor/TAM)
- Platelet biomarker sample collection (3.2% Na Citrate plasma tube)

  Note: a single Qiagen PAXgene DNA tube per subject may be collected at any convenient sampling timepoint throughout the study
- Serum immunogenicity
- Infusion site assessment
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- AEs/SAEs collected
- Concomitant medications (new medications and changes in dosing of previously reported medications only)

Out-patient, Return to Study Site, Follow-up, End of Study (Day 35±3) OR In-House if the Subject Remained at the Study Site until Day 35±3

- Serum pregnancy test for women of childbearing potential only
- Full physical examination, including height and weight
- Vital signs measurements (SBP, DBP, temperature, RR and HR)
- 12-lead ECG
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- Blood sampling for PK plasma (Plasma PB2452/Plasma ticagrelor/TAM/Unbound plasma ticagrelor/TAM)
- Platelet biomarker sample collection (3.2% Na Citrate plasma tube)

  Note: a single Qiagen PAXgene DNA tube per subject may be collected at any convenient sampling timepoint throughout the study
- Serum immunogenicity
  - If anti-drug antibodies are detected, then a follow up visit 3 months post end of study (i.e. Day 35±3) is required. These samples are to be taken every 6 months until anti-drug antibodies no longer are present or until levels return to pre-dose state

- Infusion site assessment
- AEs/SAEs collected
- Concomitant medications (new medications and changes in dosing)

Out-patient, Return to Study Site, Follow-up, 3 months post EOS (Month 4) – If ADA Positive

- Serum immunogenicity
  - If anti-drug antibodies are detected at EOS visit, then a follow up visit 3 months post end of study (i.e. Day 35±3) must be collected

Out-patient, Return to Study Site, Follow-up, 6 months post last visit (Month 10) – If ADA Positive

- Serum immunogenicity
  - If anti-drug antibodies are detected at the follow up month 4 visit, blood samples are to be taken every 6 months until anti-drug antibodies are no longer present or until levels return to pre-dose state

6.1.1 Screening Period

6.1.1.1 Informed Consent Form

All subjects must provide written or witnessed verbal informed consent prior to participating in any Screening evaluations or any other study activities.

The Investigator or his/her approved designee must explain the nature of the study protocol and associated risks to the potential study subject. The potential subject must be allowed sufficient time to review the information and to ask questions. The date that the informed consent form is signed, a brief description of the consent process (i.e., questions asked by the subject) and the name of the individual who obtained the consent will be recorded in the subject's source documentation. A copy of the signed informed consent form will be provided to each subject. The date and confirmation that informed consent was obtained will be recorded in the electronic case report from (eCRF).

6.1.1.2 Demographics and General Medical and Social History

Subject demographic information and medical history will be recorded at Screening Days (-45 to -4). Demographic information will include date of birth, gender, race, and ethnicity. Medical history will include medical diagnoses, major surgical procedures within the last 3 years, and social history (tobacco, drug, and alcohol use). Findings will be documented in the source documentation and eCRF.

6.1.1.3 Physical Examination

A general physical examination completed by trained staff will include at minimum an examination of general appearance, skin, eyes, ears, nose, throat, neck/thyroid, lungs, heart, upper/lower extremities, lymph nodes, abdomen, musculoskeletal system and neurological system. Additional systems will be evaluated as needed.

hysical exam findings must be recorded in the source documentation and include the date and name of the individual conducting the examination. Physical exam findings will be recorded in the eCRF.

A brief physical examination will include assessment of heart, skin, lungs, cardiovascular system, and abdomen, and extremities. 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, at Screening and at Day 35±3.

6.1.1.4 Height/Weight and Calculation of Body Mass Index

Height and weight will be measured at Screening and Day 35±3 during the physical examination for calculation of body mass index (BMI). BMI will be calculated within the EDC system.

6.1.1.5 Standard Vital Signs

Vital signs will be measured at the time points indicated in the Schedule of Events (Appendix 3). Vital sign measurements will include SBP, DBP, 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 60 minutes of infusion of study drug require only the SBP, DBP and HR.

The Investigator will determine whether any of the vital sign measurements are clinically significant (CS) or not clinically significant (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.

6.1.1.6 12 Lead Electrocardiogram

Twelve-lead ECGs will be obtained after the subject has rested in the supine position for ≥10 minutes at scheduled timepoints 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 uncorrected QT, QTcB, 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.

The study site will provide a calibrated ECG machine for use during the study unless otherwise provided by the Sponsor. Site personnel must assess the quality of the ECG to ensure that the test was collected appropriately and to repeat the ECG if necessary (i.e., if artifact(s) are present).

6.1.1.7 Laboratory Testing

All scheduled clinical laboratory tests will be performed by Medpace with the exception of Day -1 clinical laboratory testing which should be performed locally to provide results prior to randomization. Pharmacokinetic and immunogenicity testing will be performed by Frontage Labs, Exton, Pennsylvania. Blood will be collected at the time points indicated in the Schedule of Events (Appendix 3) and will be prepared using standard procedures defined in the laboratory manual. Repeat clinical laboratory tests of scheduled Medpace tests may be performed locally or centrally at the discretion of the Investigator, if deemed necessary, to evaluate inclusion and exclusion criteria, for urgent safety assessments, or to follow-up on clinical laboratory abnormalities. The local clinical laboratory used to perform tests must provide laboratory certification and the reference ranges for all clinical laboratory parameters.

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 abnormal 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 scheduled procedures overlap at the same time point (see Schedule of Events - Appendix 3), there must be planning to collect the specific information within the designated time window. Accordingly, the importance of these procedures are:

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 relevant lab collection manual(s) from Medpace or MLM Medical Labs for additional information related to collection of PD samples).
2. 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 3).

All clinical laboratory data will be evaluated by the Investigator (Principal or physician Sub-Investigator) and clinical relevance will be assessed for abnormal values and the assessment will be documented on the laboratory report. A copy of the reports will be maintained as part of the source documentation. Additionally, a copy of the report may be included with the eCRF.

Standard rapid urine drug Screening test kits will be supplied for local testing. The test kit may check (but not limited to) for drugs such as cocaine, cannabinoids, opiates, benzodiazepines, PCPs, amphetamines, methamphetamines, barbiturates, methadone, alcohol or additional drugs not listed.

6.1.1.7.1 Serology for HIV, Hepatitis B, and Hepatitis C

All subjects will be screened for human immune deficiency virus (HIV) type I and II antigen or antibodies, hepatitis B, and hepatitis C at screening. Evaluation for HIV seropositivity will consist of enzyme-linked immunosorbent assay (ELISA) and, if positive, will be confirmed by Western blot analysis. Appropriate counseling will be made available to the subject in the event of a positive finding. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator.

6.1.1.7.2 Pregnancy Test

A blood pregnancy test result from either the local or central laboratory is required for female subjects of childbearing potential. Results must be negative in order for subjects to be randomized in the study.

6.1.1.7.3 Follicle-Stimulating Hormone (FSH) Level

Follicle stimulating hormone level may be performed at Screening using local or central laboratory, for confirmation of postmenopausal status as directed by the Investigator.

6.1.1.7.4 Lipid Profile

A lipid profile includes (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein-cholesterol [LDL-C], low-density lipoprotein/high-density lipoprotein (LDL/HDL) ratio, and triglycerides [TG]).

6.1.1.7.5 General Safety Laboratory Testing and Confirmation of Eligibility

Refer to laboratory manual for processing requirements. Any laboratory result including alcohol and drug test results may be repeated or performed locally for clinical follow-up as needed by Investigator.

The following clinical laboratory assessments will be performed:

Table 2 List of Clinical Laboratory Assessments

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 HgbA1C 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	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 (Screening only)	hepatitis B hepatitis C human immunodeficiency virus (HIV) types 1 and 2 antigen or antibodies

Other analyses	stool for occult blood urine drug screen may include (not limited to and may vary based on the testing kits provided): amphetamines and methamphetamines barbiturates benzodiazepines cannabinoids cocaine PCPs opiates methadone urine alcohol female subjects: follicle-stimulating hormone (FSH; Screening only) serum pregnancy test (human chorionic gonadotropin)

6.1.1.7.6 Calculation of Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate (eGFR) will be calculated by the central laboratory from serum creatinine using the IDMS-Traceable MDRD formula and reported on the eCRF as follows.

Estimated glomerular filtration rate will be calculated by the central laboratory from serum creatinine using the IDMS-Traceable MDRD formula as follows.
Conventional units
GFR (mL/min/1.73 m^2) = 175 x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)
SI units
GFR (mL/min/1.73 m^2) = 175 x $(S_{cr}/88.4)^{-1.154}$ x $(Age)^{-0.203}$ x (0.742 if female) x (1.212 if African American)

6.1.2 Randomization

This is a double-blind placebo controlled trial. For further details on randomization please refer to section 7.2.2.

6.1.3 Active Treatment Period

Throughout the study protocol visits are noted by Days.

All subjects will be pretreated with enteric coated aspirin (81 mg QD for at least 7 days prior to randomization), and ticagrelor (180 mg loading dose, followed by 90 mg bid for a total of 5 doses of ticagrelor). The term “study drug” refers to PB2452/placebo.

Active: PB2452 is a ticagrelor-specific human monoclonal antibody fragment which binds to ticagrelor and TAM with high affinity, thereby reversing the antiplatelet effects of ticagrelor. It has no known off-target effects.

For this study, the investigational product will be supplied either as a lyophilized powder requiring reconstitution with sterile water for injection, or as a high-concentration liquid.

PB2452 18 g intravenous infusion will consist of 6 g infused over 10 minutes followed by a 6 g loading dose infused over 4 hours, then a maintenance dose of 6 g infused over the next 12 hours immediately following completion of the loading period for a total infusion time of approximately 16 hours and 10 minutes.

Note that if a subject is taking a moderate or strong CYP3A inhibitor, a 36 g alternative regimen of PB2452 will be administered consisting of 12 g infused over 10 minutes followed by a 12 g loading dose infused over 6 hours, then a maintenance dose of 12 g infused over the next 18 hours immediately following completion of the loading period for a total infusion time of approximately 24 hours and 10 minutes.

Placebo: 0.9% sodium chloride IV infusion, to be delivered as an infusion identical to the active drug regimens.

Ticagrelor: Ticagrelor 90-mg oral tablet (immediate release); administered as 180 mg (2 × 90-mg tablet) loading dose plus 90 mg every 12 hours for 4 additional doses.

Aspirin: Enteric costed aspirin 81 mg oral tablet administered daily between Day -7 to the morning on Day 1, for a total of 8 tablets given prior to dosing with study medication.

Subjects may resume aspirin after discharge from the study on Day 3.

6.1.4 Safety Follow-up Period

All AEs must be reported in detail on the appropriate page of the eCRF from the time of consent through the date of the EOS Day 35±3. Adverse events must be followed until resolved or stable or judged by the Investigator that further follow-up is not required.

6.1.5 Unscheduled Visits

Unscheduled visits will be performed as necessary at the discretion of the Principal Investigator to follow-up on Adverse Events and safety issues. All details must be captured in source documents and eCRF as applicable.

6.1.6 End of Study

All subjects will return to the clinic at Day 35±3 to complete the end of study (EOS) visit. The following procedures and assessments will be performed:

- Serum pregnancy test
- Physical examination, full, including height and weight
- Vital signs measured (SBP, DBP, RR, temperature and HR)
- 12-lead ECG
- Clinical laboratory tests including hematology, chemistry, coagulation, and urinalysis
- Blood sampling for PK: plasma PB2452, ticagrelor, and TAM PK
- Platelet biomarker sample collection (3.2% Na Citrate plasma tube)

  Note: a single Qiagen PAXgene DNA tube per subject may be collected at any convenient sampling timepoint throughout the study
- Serum immunogenicity
- AEs/SAEs collected
- Concomitant medication(s)

6.1.7 Long-term Extension

There is no long-term extension. The trial concludes at the EOS (Day 35±3) visit.

6.2 Discontinuation or Withdrawal

6.2.1 Individual Subjects

6.2.1.1 Treatment Discontinuation

A subject 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, or if the study is terminated.

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 develops symptoms or conditions listed in the exclusion criteria
- Requires a medication prohibited by the protocol
- Requests an early discontinuation for any reason

If a subject experiences a SAE or an intolerable adverse event (AE) that requires discontinuation in the opinion of the Investigator or as reported by the subject, then the Investigator may confer with the Sponsor regarding disposition of the subject. If a subject is discontinued from treatment because of an AE, the event will be followed until it is resolved or until the AE is stable in the opinion of the Investigator.

When a subject withdraws or is withdrawn 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 35±3 visit procedures should be completed to the extent possible, and the site should try contacting the subject at least 3 times by letter, certified letter, phone call, email or other reasonable methods. All attempts to contact subjects and the final status of subjects who fail to complete final assessments will be documented in the source documents.

At the discretion of the Sponsor any subject who withdraws before completing the study, may potentially be replaced. Any replacement subject will be assigned to receive the same treatment as the subject he or she is replacing.

6.2.1.1.1 Temporary Treatment Discontinuation

Though not expected, treatment may be discontinued temporarily at the discretion of the Investigator.

6.2.1.1.2 Permanent Discontinuation of Treatment

Treatment may be permanently discontinued at the discretion and based on clinical judgment of the Investigator. The Investigator is required to inform the Sponsor.

6.2.1.2 Withdrawal from Study

Subjects may withdraw from the study at any time at their own request or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The Investigator should inquire about the reason for withdrawal and request that the subject return for the EOS follow-up visit (complete procedures at final safety visit) and follow up with the subject regarding any unresolved adverse events.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.2.1.3 Replacement of Subjects

Subjects who withdraw from the study and who do not have adequate collection of safety, hemodynamic and pharmacokinetic samples for evaluation of safety, PK, and PD profiles may be replaced at the discretion of the Sponsor. Any replacement subject will be assigned to receive the same treatment as the subject he or she is replacing.

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) (ICH, E3, 2015).

7 STUDY INTERVENTIONS

All subjects will be pretreated with aspirin (81 mg QD for at least 7 days prior to randomization), and ticagrelor (180 mg loading dose, followed by 90 mg bid for a total of 5 doses of ticagrelor). The term "study drug" refers to PB2452 or placebo.

Aspirin: Aspirin 81 mg oral tablet (enteric coated); administered daily between Day -7 to the morning of Day 1, for a total of 8 tablets. Subject may resume aspirin after discharge from the clinical site on Day 3.

Ticagrelor: Ticagrelor 90-mg oral tablet (immediate release); administered as 180 mg (2 × 90-mg tablet) loading dose plus 90 mg every 12 hours for 4 additional doses.

Active: PB2452 is a ticagrelor-specific human monoclonal antibody fragment which binds to ticagrelor and TAM with high affinity, thereby reversing the antiplatelet effects of ticagrelor. It has no known off-target effects.

For this study, the investigational product will be supplied either as a lyophilized powder requiring reconstitution with sterile water for injection, or as a high-concentration liquid.

- PB2452: 18 g intravenous infusion will consist of 6 g infused over 10 minutes followed by a 6 g loading dose infused over 4 hours, then a maintenance dose of 6 g infused over the next 12 hours immediately following completion of the loading period for a total infusion time of approximately 16 hours and 10 minutes
- Placebo: 0.9% sodium chloride IV infusion, to be delivered as an infusion identical to the active drug regimens

If a subject is taking a moderate or strong CYP3A inhibitor, a 36 g alternative regimen of PB2452 will be administered consisting of 12 g infused over 10 minutes followed by a 12 g loading dose infused over 6 hours, then a maintenance dose of 12 g infused over the next 18 hours immediately following completion of the loading period for a total infusion time of approximately 24 hours and 10 minutes.

7.1.1 Active Intervention

7.1.1.1 Formulation, Storage, Preparation, and Handling

PB2452 i [redacted].

For this study, the investigational product will be supplied either as a lyophilized powder requiring reconstitution with sterile water for injection, or as a high-concentration liquid. PB2452 is delivered via a standard IV bag(s) and IV pump or a standard syringe and syringe pump.

Placebo is formulated as 0.9% sodium chloride IV infusion, to be delivered as an infusion identical to the active drug regimens.

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

Lyophilized 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. Lyophilized PB2452 is reconstituted to 100 mg/mL with sterile water for injection. Concentrated PB2452 liquid is supplied in a 100R glass vial at a concentration of 100 mg/mL using a similar container closure system.

PB2452 must be stored in a secure area (e.g., a locked, secure, 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. The clinical site will be required to keep a temperature log to establish a record of compliance with these storage conditions.

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.

7.1.1.2 Dosing and Administration

As mentioned in Section 7, dosing for the investigational product will be as follows:

- PB2452: 18 g intravenous infusion will consist of 6 g (60 mL)infused over 10 minutes followed by a 6 g (60 mL) loading dose infused over 4 hours, then a maintenance dose of 6 g (60 mL) infused over the next 12 hours immediately following completion of the loading period for a total dose of 18 g (180 mL) and total infusion time of approximately 16 hours and 10 minutes.

  If a subject is taking a moderate or strong CYP3A inhibitor, a 36 g alternative regimen of PB2452 will be administered consisting of 12 g infused over 10 minutes followed by a 12 g loading dose infused over 6 hours, then a maintenance dose of 12 g infused over the next 18 hours immediately following completion of the loading period for a total infusion time of approximately 24 hours and 10 minutes

- Placebo: 0.9% sodium chloride IV infusion, to be delivered as an infusion identical to the active drug regimens

For short term stability information for PB2452 please refer to the pharmacy manual.

7.2 Treatment Assignment and Bias Minimization

Subjects will be randomized to active and placebo treatment in a blinded fashion in order to minimize bias with respect to safety assessments, as well as any decisions in exclusions from the per-protocol population due to protocol deviations.

7.2.1 Treatment Allocation

Approximately 200 subjects will be randomized to PB2452 and Placebo with an allocation ratio of 3:1 resulting in a sample-size of 150 for the PB2452 and 50 for the Placebo arm.

7.2.2 Randomization Strategy and Procedure

This study employs a simple randomization procedure without any stratification. The randomization will be employed via a Randomization & Trial Supply Management (RTSM) system.

7.2.3 Extent and Maintenance of Blinding

The treatment assignment will not be known to Investigators, research staff, or study subjects. The following study procedures will be in place to ensure double-blind administration of study treatments.

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 an opaque covering over the prepared dosage form to maintain blinding.

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. Except as noted above, all members of PhaseBio will remain blinded, except the unblinded Sponsor representative(s) who may be contacted in case of emergencies and if it is required to break the blind.

The study blind will be broken on completion of the clinical study and after the study database has been locked. If necessary (e.g., information required for enrolment in a subsequent study), a request may be submitted to the Sponsor to receive study treatment assignment for a subject.

7.2.4 Unblinding Procedures

7.2.4.1 Planned Unblinding

A subject may be unblinded in the a SAE, or if there is a medical emergency when the identity of the drug must be known to properly treat a subject. 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 inform the unblinded Sponsor contact and/or the Medical Monitor to explain the need for breaking 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.

7.2.4.2 Unplanned or Unintentional Unblinding

During the study, the blind may be broken only in emergencies when knowledge of the subject's treatment group is necessary for further medical management. It is preferred (but not required) that the Investigator first contacts the medical monitor or PhaseBio study personnel to discuss options before unblinding the subject's treatment assignment

Unblinding of individual subjects may occur to ensure appropriate clinical management of a subject, for example if an SAE is considered by the Investigator as being causally related to study treatment OR in the event of a serious medical condition when knowledge of the study treatment is essential for the welfare of the subject as judged by the Investigator.

All unplanned, emergency unblinding will be considered as a protocol deviation. The date and reason for the unblinding must be fully documented.

A subject may continue in the study if that subject's treatment assignment is unblinded if it remains appropriate for them to do so and at the Sponsor's discretion.

PhaseBio's clinical or regulatory staff may request unblinding of thetreatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one

or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to Investigators in accordance with local regulations.

7.3 Assessment and Verification of Compliance

Study drug will be received, dispensed and returned to the Sponsor (unused study drug at the end of the study) by pharmacist or designee as applicable. Study drug will be accounted for by the USDD on a study drug inventory/accountability log and will include:

- Subject ID
- Number/time vials removed from storage
- Date/time dose prepared
- Amount remaining in inventory

Inventory records will not be reviewed by the study monitor during routine monitoring visits in order to maintain the study blind. In order to ensure accuracy on the drug accountability logs a designated individual from the Sponsor will assume this task and will periodically request the pharmacist (designee) at the site to provide documentation to PhaseBio Pharmaceuticals, Inc.

All doses of study drug, placebo, ticagrelor and ASA from the date of site check-in will be administered at the clinical site under direct observation of clinic personnel and recorded in the eCRF. Subjects will be required to document ASA use from Day -7 to Day 1 and provide the diary to the study staff upon check-in.

The date, time, and actual dose received of study drug or placebo infusion, ticagrelor and ASA 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.

7.4 Concomitant Therapies

Concomitant medications are defined as all medications taken from -45 days prior to date of informed consent, to Day 35±3. This is to include all medication including prescription, supplements, over the counter (OTC). New and changes to medications are captured at every visit until Day 35±3.

Concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary (WHO-DD).

7.4.1 Prohibited Therapies

Subjects are prohibited from taking any new prescription or over the counter (OTC) medications or nutritional supplements from Day -30 thru Day 3. Acetaminophen up to 2 g/day may be taken as needed.).

7.4.2 Permitted Therapies

In addition to study-required medications specified in the protocol, subjects may take medications to treat chronic baseline conditions, hormonal birth control and/or acetaminophen up to 2 g/day. If new prescription drug therapy is indicated due to an AE, a joint decision will be made by the Investigator and the Sponsor whether to continue or discontinue the subject in the

study based on the time the new medication is to be 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.

8 SAFETY MONITORING

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to the study drug will be reported as described in the following sections.

For all adverse events, the Investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to PhaseBio Pharmaceuticals, Inc. For all adverse events, sufficient information should be obtained by the Investigator to determine the causality of the adverse event. The Investigator (Principal or physician Sub-Investigator) is required to assess causality. For all adverse events follow-up by the Investigator (delegate) is required until the event or its sequelae resolve or stabilize or judged by the Investigator to be not clinically significant (NCS).

8.1 Definitions

Adverse event – An AE is any untoward medical occurrence associated with the use of an intervention in humans whether or not it is considered intervention-related. This may include worsening of a pre-existing medical condition (e.g., diabetes, congestive heart failure, rheumatoid arthritis, psoriasis) that occurs at any time after signing of the informed consent (IC). Examples of adverse events include, but are not limited to:

- Clinically significant abnormal test findings
- Clinically significant signs and symptoms
- Clinically relevant changes in physical examination findings
- Hypersensitivity
- Progression/worsening of an underlying disease

Additionally, AE reporting may also include signs or symptoms resulting from:

- Drug overdose
- Drug abuse
- Drug dependency
- Drug withdrawal
- Drug misuse
- Drug interactions
- Exposure during pregnancy
- Exposure via breast-feeding
- Medication error

Serious adverse event (SAE) – An event is considered “serious” if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death

- A life-threatening AE (An event is considered **"**life-threatening**"** if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction (AR) that, had it occurred in a more severe form, might have caused death.)
- Inpatient hospitalization or prolongation of existing hospitalization
  - NOTE: Any hospital admission will be considered an inpatient hospitalization, regardless of duration. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness
  - Admission to the hospital for a pre-planned procedure or social or situational reasons (i.e., no place to stay, lives too far away to come for hospital visits) will not be considered inpatient hospitalizations
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or 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

All AEs and SAEs must be documented and recorded on eCRF upon signing of the informed consent form.

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.

Causality or relatedness – The relationship of an adverse event to the administration of the study drug is to be assessed according to the following definitions:

No – (unrelated, not related, no relation) – The time course between the administration of study drug and the occurrence or worsening of the adverse event rules out a causal relationship and another cause (concomitant drugs, therapies, complications, etc.) is suspected.

Yes – The time course between the administration of study drug and the occurrence or worsening of the adverse event is consistent with a causal relationship and no other cause (concomitant drugs, therapies, complications, etc.) can be identified.

The following factors should also be considered:

The temporal sequence from study medication administration: The event should occur after the study medication is given. The length of time from study medication exposure to event should be evaluated in the clinical context of the event.

Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

Concomitant medication: The other medications the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be recognized to cause the event in question.

Known response pattern for this class of study medication: Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.

Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and explanation for the event.

The pharmacology and pharmacokinetics of the study medication: The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study medication should be considered.

Adverse reaction (AR): An AR is any AE caused by a drug.

Suspected adverse reaction (SAR): An SAR is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of regulatory safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. SAR implies a lesser degree of certainty about causality than AR.

Unexpected: An event is considered unexpected if it is not listed in the IB, is not listed at the specificity or severity that has been observed, 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 IND. Unexpected also refers to events that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

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.

8.1.1 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 35±3 visit (i.e. EOS), 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 over-the-counter (OTC) medications).

Changes in laboratory values, physical examination findings, ECG monitoring changes or other events relevant to subject safety are to be assessed and reported as an AE on the eCRF and captured in source documents.

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 of medications used (if any), 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 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 8.1) must be reported to the Sponsor immediately and within 24 hours (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 and applicable ICH and local guidelines and requirements. The Investigator is responsible for notifying the IRB/IEC directly.

The following information is to be used for SAE reporting:

PhaseBio Pharmaceuticals Inc.
1 Great Valley Parkway, Suite 30
Malvern, PA 19355
[redacted]

8.1.2 Timeframe for Collection

Serious adverse events require immediate notification to PhaseBio Pharmaceuticals, Inc. within 24 hours of awareness beginning from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving study drug (investigational product), through and including 35±3 days after the last dose of study drug. Any serious adverse event (SAE) occurring any time within the reporting period must promptly (within 24 hours) be reported .

- Adverse events (serious and non-serious) should be recorded on the eCRF from the time the subject has signed informed consent form (written or verbal) through last study visit, unless otherwise specified
- Any clinically significant adverse changes in the subject's baseline status between enrollment (signing informed consent form or documentation of verbal consent) up to the time of study drug administration will be recorded as an adverse event and severity assessed

8.1.3 Classification of Events

8.1.3.1 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, life-threatening or fatal

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 Sponsor to assess all AEs and laboratory abnormalities.

8.2 Reporting Adverse Events

8.2.1 Reporting to the Sponsor

If a serious adverse event occurs, the Sponsor is to be notified within 24 hours of awareness of the event by the Investigator. In particular, if the SAE is fatal or life-threatening, notification to PhaseBio Pharmaceuticals, Inc. must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously forwarded serious adverse event reports as well as to the initial and follow-up reporting of Exposure in-utero cases.

In the rare event that the Investigator does not become aware of the occurrence of a serious adverse event immediately (e.g., if an outpatient trial subject initially seeks treatment elsewhere), the Investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the adverse event.

Serious adverse events are reported by either:

a) SAEs should be reported to PhaseBio as early as possible and within 24 hours after occurrence of the event by scanning and emailing the completed SAE [redacted]

OR

b) Entering the adverse event (or updates) in eCRF within 24 hours after initial reporting by selecting "Serious" as the Severity which will automatically notify appropriate PhaseBio personnel of the SAE

For all SAEs, the Investigator is obligated to pursue and provide information to PhaseBio Pharmaceuticals, Inc. in accordance with the timeframes for reporting specified above.

In addition, an Investigator may be requested by PhaseBio Pharmaceuticals, Inc. to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality.

Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to PhaseBio Pharmaceuticals, Inc. or its designated representative. The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form and submit to PhaseBio.

8.2.2 Sponsor Regulatory Reporting of Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information e.g. summary or listing of SAE from the Sponsor will review and then file it along with the Investigators' Brochure (IB) and will notify the IRB/IEC, if appropriate according to local requirements. Investigational sites will be responsible for notifying and reporting SAEs to their respective IRBs.

8.3 Adverse Events of Special Interest

There are no adverse events of special interest.

8.4 Clinical Laboratory Findings

Clinical laboratory tests will be performed by MedPace Central Laboratory or local laboratory where applicable (i.e. Day -1). Blood and urine will be collected at the time points indicated in the Schedule of Events (Appendix 3) and will be prepared using standard procedures. Repeat clinical laboratory tests a t local or central laboratory may be performed at the discretion of the Investigator, if necessary, to evaluate clinical laboratory abnormalities, results of which are to be included in the electronic data capture system or eCRF. MedPace central laboratory will provide

the reference ranges for all clinical laboratory parameters where applicable. Study site will provide the clinical laboratory parameters for any local laboratory used.

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 abnormal 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 criteria for determining whether an abnormal test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, or other therapy, and/or
- Test result is considered an AE by the Investigator or Sponsor

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.

8.5 Pregnancy and Contraception

In enrolled female subjects who are of child-bearing potential (pre-menopausal), use of 2 effective birth control methods is required for 3 months after signing of the informed consent form. For definition of women of childbearing potential and of fertile men please refer to Appendix 2.

Generally accepted forms of effective contraception for women include implants, injectables, combined oral contraceptives, intrauterine devices (IUDs), sexual abstinence, combined oral contraceptives with inhibition of ovulation or a partner who has been surgically sterile (e.g. by vasectomy) for at least 6 months.

Acceptable methods of contraception for a male include surgical sterility (e.g. by vasectomy) for at least 6 months, sexual abstinence, or condoms plus spermicide.

If the subject or partner of a subject participating in the study becomes pregnant during the study or within 35±3 days of last dose or discontinuing study medication, the Investigator should report the pregnancy to the Sponsor, or its representative, **within 24 hours of being notified**. The Exposure In-Utero form must be completed by the site.

The subject or partner should be followed by the Investigator for 30 days post expected date of delivery. A separate informed consent form may be obtained which will outline the follow-up. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or

congenital anomaly), the Investigator should follow the procedures for reporting an SAE. Otherwise, a follow up Exposure In-Utero form should be completed. See Appendix 2.

8.6 Overdose or Misuse

No treatment is required for overdose of PB2452, as the specificity of PB2452 for ticagrelor renders off-target effects extremely unlikely. Treat hypersensitivity reactions immediately with appropriate emergency medical care (e.g., oxygen, diphenhydramine, corticosteroids, volume expansion, and airway management). If a hypersensitivity reaction occurs during the infusion of PB2452, immediately terminate the infusion and administer appropriate treatment.

9 ANALYSIS

This is a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy of PB2452 in reversing the anti-platelet effects of ticagrelor and to evaluate the safety and tolerability of PB2452 in subjects aged 50 to 80 years old. The detailed strategy for the statistical analysis will be documented in a Statistical Analysis Plan (SAP) before any blinding of the treatment code.

9.1 Primary Hypothesis

Compared to placebo, PB2452 administered intravenously provides rapid and sustained reversal of the antiplatelet effects of ticagrelor.

The reversal will be assessed by the primary study endpoint of minimum % inhibition of PRU assessed by VerifyNow™ PRUTest™ (VerifyNow™, 2016)within 4 hours after the initiation of study drug. Percent inhibition of PRU is calculated as 100 * [(PRU_{bsl} – PRU_{trt})/PRU_{bsl}] where 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.

9.2 Population

9.2.1 Sample Size Rationale

Primary efficacy endpoint will be analyzed by comparing the minimum % inhibition of PRU assessed by VerifyNow™ PRUTest™ (VerifyNow™, 2016)within 4 hours after the initiation of study drug between the PB2452 group vs placebo group. A sample size (N) of approximately 200 subjects with 3:1 allocation ratio (active:placebo) will provide > 99% power to detect a 15% difference in % inhibition of PRU between PB2452 and placebo group using a two-sided test with type I error of 0.05 (20% standard deviation (SD) is assumed which is obtained from previous studies). The sample size of 200 (150 active vs 50 placebo) will provide substantial safety information on PB2452 in older and elderly volunteer subjects.

Compared to placebo intravenous PB2452 results in reversal of the antiplatelet effects of ticagrelor. The reversal will be assessed by the primary study endpoint of minimum % inhibition of PRU assessed by VerifyNow™ PRUTest™ (VerifyNow™, 2016) within 4 hours after the initiation of study drug. Percent inhibition of PRU is calculated as 100 * [(PRU_{bsl} – PRU_{trt})/PRU_{bsl}] where 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.

9.2.2 Analysis Subsets

The results from this study will be presented using the following populations: For purposes of analysis, the following populations are defined:

Population	Description
All Subjects	All subjects who sign the ICF
Modified Intention-to- Treat Population	Modified Intention-to-Treat (mITT) population includes all subjects randomly assigned to study treatment, who take any amount of study drug (PB2452 or placebo). Subjects will be

Population	Description
	analyzed according to the treatment they are randomized to.
Safety Population	The safety population includes all subjects who have received any amount of study drug. The safety population will be analyzed for all safety assessments. Subjects in the Safety population will be analyzed as treated.
Per Protocol Population	The Per Protocol (PP) population includes subjects in the safety population who do not have major protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock and unmasking. The PP population will be analyzed using observed data only for efficacy variables. Subjects in the PP population will be analyzed as treated.
Pharmacokinetic Population	The PK population includes all subjects with a measurable PK sample of the study drug. The PK population will be used to summarize all PB2452 blood concentrations. Subjects in the PK population will be analyzed as treated.

The statistical analysis of safety data will be performed for the Safety population. The analysis of efficacy data will primarily be performed for the mITT population. The efficacy analysis based on the PP population will serve as sensitivity analyses.

9.3 Testing Procedures

9.3.1 Analysis of the Primary Efficacy Endpoint

All efficacy analyses will primarily be based on the mITT population.

The primary efficacy analysis compares the primary endpoint between PB2452 and placebo. The primary endpoint is defined as the minimum % inhibition of PRU assessed by VerifyNow™ PRUTest™ (VerifyNow™, 2016)within 4 hours (inclusive) after the initiation of study drug. Percent inhibition of PRU is calculated as 100 * [(PRU_{bsl} – PRU_{trt})/PRU_{bsl}],where 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.

Results by treatment groups will be summarized at baseline, at the timepoint where minimum is achieved, and percentage inhibition from baseline using descriptive statistics: N, mean, SD, median, minimum, and maximum. To complete the clinical picture, the % inhibition of PRU from baseline will be summarized at all time points using descriptive statistics.

Hypothesis testing will also be conducted as a 2-sided test with a significance level of 0.05 to compare the efficacy of PB2452 and placebo. Assuming that the population median minimum % inhibition of PRU are expressed as μ_{PB2452} and $\mu_{Placebo}$ for the PB2452 and placebo groups, respectively, the treatment comparison to be tested is $\Delta = \mu_{PB2452} - \mu_{placebo}$. The null ($H_0$) and alternative ($H_1$) hypotheses for each comparison are:

$H_0: \Delta = 0$ vs. $H_1: \Delta \neq 0$

This test will be conducted using an exact Wilcoxon rank-sum test. The hypothesis test for the primary endpoint will be performed at 2-sided $\alpha = 0.05$. The Hodges-Lehman estimate of location shift and a 95% Hodges-Lehman confidence interval will be constructed on the difference in between PB2452 and placebo.

9.3.2 Analysis of Secondary Efficacy Endpoint(s)

The secondary efficacy analysis compares the secondary endpoints between the two treatment groups. The dichotomous secondary endpoints will be compared between the treatment groups using Fisher's Exact test. The continuous secondary endpoints will be compared between the two treatment groups using an exact Wilcoxon rank-sum test and Hodges-Lehman confidence interval, as used for the primary endpoint.

9.3.3 Population Analysis

9.3.3.1 Disposition

Subject disposition will be presented for all screened subjects, including number of screen- failed subjects and number of subjects randomized (all subjects).

Number and percentage of subjects in the following categories will be summarized as appropriate:

- Screen failed
- Enrolled
- Enrolled, but not randomized
- Randomized
- mITT population
- Safety population
- Per-Protocol population
- PK population

Additionally, a summary on study completion status and treatment completion will be presented along with reasons for discontinuation if any.

9.3.3.2 Demographics

The demographic and baseline characteristics will be summarized with respect to sex, age (years), height (cm), weight (kg), BMI (kg/m^2), race, and ethnicity by treatment group. These summaries will be calculated for both mITT and Safety populations.

9.3.3.3 Baseline Characteristics

The counts and percentage of subjects who had been on aspirin before or who initiated aspirin on Day -7 will be presented by treatment. Also, the platelet count at baseline will be summarized by treatment.

9.3.4 Safety Analysis

Safety will be assessed by examination of adverse events, physical examination findings, vital signs, clinical laboratory measurements, antibodies to study drug and 12 lead ECGs based on the Safety population.

9.3.4.1 Demographics

Demographics are described in Section 9.3.3.2.

9.3.4.2 Baseline Characteristics

Baseline characteristics are described in Section 9.3.3.3.

9.3.4.3 Disposition

Disposition is described in Section 9.3.3.1.

9.3.4.4 Adverse Events

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. TEAEs are defined as any AE not present before exposure to study drug or any AE already present that worsens in severity after exposure to study drug. All treatment-emergent SAEs, AESIs and TEAEs leading to discontinuation of study drug will be presented in the data listings.

9.3.4.5 Clinical Laboratory Results

Actual values and changes from baseline in clinical laboratory test results will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, standard deviation, median, minimum, and maximum). Clinical laboratory test results will be presented in data listings as well.

9.3.5 Other Prespecified Endpoint Analysis

Platelet-function biomarker data will be summarized for each time point as applicable using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum).

9.3.6 Pharmacokinetics Analysis

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 both on the linear and semi-log scale.

Plasma PK parameters of PB2452, ticagrelor, and TAM will be determined with noncompartmental methods and summarized by time point using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum). Geometric means will be reported for AUCs and C_{max}. Actual sampling times, rather than scheduled sampling times, will be used in all calculations of PK parameters.

The urine concentrations will be listed and summarized descriptively.

9.3.7 Pharmacodynamics Analysis

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.

9.3.8 Immunogenicity Analysis

The PB2454 antibodies will be summarized by visit and treatment. A listing of subjects will also be provided.

If positive ADA is observed, results may be reported by ADA status for AEs, efficacy and pharmacokinetics.

9.4 Planned Interim Analysis

No interim analysis is planned for this study.

9.4.1 Temporary Halting or Early Termination Criteria

There is no plan to halt this study before completion.

9.4.2 Specified Analyses for Independent Data Monitoring Committee Review

For this study, there will be no Independent Data Monitoring Committee (DMC).

9.5 Procedures for Reporting Changes to the Planned Analysis

The SAP will detail the strategy for statistical analyses for this study. Any change in the plan described in this protocol will be highlighted in the SAP.

10 ETHICAL CONSIDERATIONS

PhaseBio Pharmaceuticals, Inc and designées will carry 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) and ICH E6 (R2) as 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 Food and Drug Administration (FDA) Amendments Act of 2007 (FDAAA), EudraCT (European Union Drug Regulating Authorities Clinical Trials) Database and in other national or international registries as appropriate.

All Investigators are required to review and sign a Food and Drug Administration (FDA) Form 1572 or equivalent and financial disclosure form and agree to follow the study according to the general principles of ICH and GCP guidance documents.

10.1 Good Clinical Practice

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.

10.2 Ethics Review

The study protocol and amendments, ICFs, advertisements, the Investigator's Brochure (IB) and information given to study subjects will be reviewed and approved by the Institutional Review Board (IRB)/ Institutional Ethics Committee (IEC) of each study center prior to use. Each Investigator will be responsible for informing the IRB/IEC of the progress of the study and submitting annual reports. This study will be conducted in the US, and other countries at the discretion of the Sponsor.

The study will be conducted according to general principles of the Declaration of Helsinki, Protection of Human Subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312 Subpart D), Council forInternational Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, and applicable ICH Good Clinical Practice (GCP) Guidelines, per local laws and regulations.

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded identifier only. All study records will be kept in a secure location where only study staff have access. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, General Data Protection Regulation (EU) 2016/679) as applicable.

10.3 Informed Consent Form

Informed consent form (ICF) will be obtained in accordance with the principles of Declaration of Helsinki, ICH GCP, US CFR for Protection of Human Subjects, and with local regulations and data protection law (e.g. Health Insurance Portability and Accountability Act (HIPAA), etc.).

A valid, executed informed consent form will be obtained from every subject as per local regulations, and prior to entering the subject into the trial and conducting any screening, study procedures and activities. The Investigators must ensure that each subject is fully informed about the nature and objectives of the study, study procedures, and possible risks associated with participation; given ample opportunity to inquire about details of the study and freely consents to participation in the study. A copy of the signed and dated informed consent form or documented verbal consent will be given to the subject and the original will be maintained with the subject's records.

The Investigator will prepare the ICF, as per local privacy requirements and provide the document(s) to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent form will embody the elements of informed consent as described in the ICH and will also comply with applicable local regulations and sponsor requirements. The Investigator will send in a copy of the final IRB/IEC-approved ICF, along with all related correspondence to the Sponsor (or designee) for the study file.

Subjects who are rescreened are required to sign a new ICF.

The ICF will contain a section that addresses the use of remaining samples for exploratory research and genetic testing. Subjects will be told that they may withdraw their consent at any time and for any reason during the storage period. The subjects must be informed that if they revoke their consent all collected information and samples will be removed to the extent possible and if not already used, shared, transferred. Laboratory data may be pooled, and identification and removal of an individual subject's results may not be possible.

The subject must be informed that his/her personal study-related data willbe used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined either in-person or remotely by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.4 Data Privacy

In order to maintain subject confidentiality, only a site number, and subject number and subject age (or date of birth as per local regulations) will identify all study subjects on eCRFs and other documentation submitted to the Sponsor.

- Subjects will be assigned a unique identifier by the Sponsor. Anysubject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred
- The subject must be informed that his/her personal study-related data willbe used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the

Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities

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.

10.5 Financial Considerations

Investigators and Sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Neither the Sponsor nor the Investigator site 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 the Investigator site is financially responsible for further treatment of the disease under study.

Brief overview of the trial will be published upon clinical study report completion as per requirements on www.clinicaltrials.gov and the European Union 536/2014 regulations for the public or other local sites as applicable.

10.6 Biological Specimens and Data

Blood samples collected during the study for pharmacokinetic or immunogenicity analysis may be retained for future testing as necessary for at least 2 years post approval of the investigational product in any ICH country. If the Sponsor chooses to conduct further testing additional consent will not be obtained. The subject confidentiality will be maintained and only the site and subject number will identify the sample. No other linked or identifying information is maintained by the Sponsor.

11 OVERSIGHT

11.1 Independent Monitoring

11.1.1 Data and Safety Monitoring Committee

There is no Data Monitoring Committee (DMC) for this study.

11.2 Quality Control and Assurance

- All subject activities and data relating to the study will be recorded on electronic case report form (eCRF) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF
- The Investigator must permit study-related monitoring on-site (in-person) or remote monitoring using electronic or paper records, quality assurance audits (in-person or remotely), IRB/IEC review, and regulatory agency inspection(s) and provide direct access to source data documents
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements
- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site
- Data reported or entered on the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. All medical records must be available during the monitoring visits(s)

11.2.1 Monitoring

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 in-person or remotely 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 using paper or electronic records as applicable in compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and standard operating procedures (SOPs).

The sponsor or delegate will monitor the study either in-person or remotely to verify that, amongst other items, the:

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol, any other study agreements, GCP and all applicable regulatory requirements

The Investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents. The Investigator must ensure provision of reasonable time, space and qualified personnel for monitoring visits. The Investigator and institution involved in the study will permit study-related audits, IRB/IEC 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 on-site and in-person or remotely. The Investigator should promptly notify the Sponsor of any audits scheduled by any regulatory authorities and promptly forward to the Sponsor copies of any audit reports received.

Access to all study and site related materials and source data either in-person or remotely is mandatory for the purpose of monitoring review. The Sponsor (or delegate) will perform a review of the e-CRFs and source documents as required. Upon completion or premature discontinuation of the study, the Sponsor (or delegate) will conduct site closure activities with the Investigator or site staff, as per local and Federal requirements, GCP, and PhaseBio (or delegate) procedures.

11.2.2 Audits

Quality assurance audits will be performed in-person or remotely in compliance with the study defined audit plan. Sites may be audited (on-site and in-person) or remotely to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and applicable regulatory requirements at the discretion of the Sponsor (delegate).

11.2.3 Protocol Deviations

A protocol deviation occurs when the subject, Investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol deviations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication
- Dosing error (a subject is not given the correct dose of study drug or placebo)
- Unblinding
- Failure to adhere to procedures or timing of sample collection
- Failure to comply with Good Clinical Practice (GCP) guidelines
- Nonadherence to FDA regulations or ICH E6(R2) guidelines
- Nonadherence to timing of study procedures

The Sponsor will determine if a protocol deviation will result in withdrawal of a subject or if data analysis will be censored. The Sponsor does not permit protocol waivers (i.e., prospective protocol deviations).

When a protocol deviation occurs, it is entered directly on the eCRF or documented by either the clinical monitor or project manager in accordance with the Sponsor (or delegate) SOPs and procedures. As applicable, an impact assessment of the deviation, determination of the need for any subsequent root cause analysis and corrective actions to prevent future deviations will be assessed and documented. The protocol deviation page on the eCRF or a separate form will be reviewed and signed by a Sponsor representative and the Investigator. A copy of completed forms will be filed in the site's regulatory binder and in the Sponsor's files.

Any change, divergence, or departure from the study design or procedures defined in the protocol will be documented by the clinical monitor throughout the course of monitoring visits. The Investigator will be notified by the monitor of such situations in writing. The IRB/IEC should be notified of protocol deviations where appropriate, and as per IRB/IEC requirements in a timely manner.

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/IEC 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/IEC for review and approval, to the Sponsor for agreement, and to the regulatory authorities, if required.

11.2.4 Records

11.2.4.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number and subject number.

If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. Copies of final completed eCRFs will be provided electronically for archiving at the study site following database lock and at or prior to study closure.

11.2.4.2 Data Capture and Management

Data must be recorded on the eCRF as the study is in progress. All site personnel must log into the system using their secure username and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR

Part 11), applicable ICH guidelines and local regulations. All passwords will be strictly confidential. 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.

The data will be entered into a validated database. The data management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA, ICH and applicable guidelines for the handling and analysis of data for clinical trials.

11.2.4.3 Data Validation

Validation checks programmed within the electronic data capture (EDC) system and the eCRF, as well as supplemental validation performed via review of the uploaded data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the investigative site for resolution through data queries.

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.

The eCRFs must be reviewed and electronically signed by the principal Investigator.

After data have been entered a system of computerized data validation checks will be applied to the database on a regular basis. Queries are entered, tracked, and resolved through the EDC system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

11.2.4.4 Source Documentation

Site personnel will maintain source documentation to support subject data that is entered into the eCRF and participation in the study.

Both paper and electronic medical records may be used for collection of source data. If the Investigator study site uses an electronic medical record system, the Investigator is required to ensure the system is validated and compliant with US Title 21 CFR Part 11 and applicable local regulatory requirements. 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 medical 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.

Source documentation includes but is not limited to the following types of information: current and past medical records generated at the Investigator site and collected from primary care or/or other subject providers, ICFs, records of assessments performed as part of study participation, lab requisition forms and results, imaging results, medication administration records etc. Please

note any changes to site-specific processes due to COVID-19 pandemic must be fully documented and identified within source documents and eCRF.

11.2.4.5 Study Files

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent Form or documented verbal consent, HIPAA Authorization or country-specific and local regulatory requirements as applicable and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the eCRF was derived.

11.2.4.6 Records Retention

Study-related records and documents should be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or for at least 2 years have elapsed since the formal discontinuation of clinical development of PB2452. These documents may be retained for a longer period 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.

11.2.4.7 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis will be either frozen or locked respectively, and cleaned per established procedures.

11.3 Sponsor Trial Discontinuation Criteria

Premature termination of this study or study site closure may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of PhaseBio Pharmaceuticals, Inc. In addition, PhaseBio Pharmaceuticals, Inc. retains the right to discontinue development of the referenced investigational drug at any time.

11.3.1 Study Termination

If the study is prematurely terminated or discontinued, PhaseBio Pharmaceuticals, Inc. will promptly notify the Investigator. After notification, the Investigator must contact all participating subjects within 5 business days. As directed by PhaseBio Pharmaceuticals, Inc. or delegate, all study materials must be collected and all eCRFs completed to the extent possible.

11.3.2 Study Site Closure

Study sites will be closed upon study completion or at the discretion of PhaseBio (delegate). A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study treatment development

12 PUBLICATION POLICY

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996 and the General Data Protection Regulation 2016/679.

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement
- Authorship will be determined by mutual agreement and in line with the International Committee of Medical Journal Editors authorship requirements

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.

13 DISEMINATION OF STUDY DATA

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report. The Investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a mutually agreeable location. Phase Bio will also provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study subjects, as appropriate. PhaseBio will provide the Investigator with the randomisation codes for their site only after completion of the full statistical analysis. The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with PhaseBio internal policies.

14 FINANCING AND INSURANCE

Financing and insurance information is addressed in the Clinical Trial Agreement between PhaseBio and the study site.

15 REFERENCES

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16 APPENDICES

The following appendices are included:

Appendix 1 - List of Abbreviations

Appendix 2 - Pregnancy Testing and Reporting Guidance and Contraception Methods

Appendix 3 – Schedule of Events (SOE)

Appendix 4 - Examples of Inhibitors of CYP3A

APPENDIX 1 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACS	acute coronary syndrome
ADA	anti-drug antibodies
ADME	absorption, distribution, metabolism, excretion
ADP	adenosine diphosphate
AE	adverse event
Ae_{t1-t2}	Ae from time t1 to t2 hours
Ae_{24}	total amount of drug excreted in urine at 24 hours after dosing
Ae_{48}	total amount of drug excreted in urine at 48 hours after dosing
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AR	adverse reaction
ASA	acetylsalicylic acid
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC_{0-24}	AUC from time zero to 24 hours after dosing
AUC_{0-30}	area under the plasma concentration versus time curve from time zero to thirty
AUC_{0-48}	area under the plasma concentration versus time curve from time zero to forty-eight
$AUC_{0-\infty}$	area under the plasma concentration versus time curve from time zero extrapolated to infinity

$AUC_{0\text{-last}}$	area under the plasma concentration versus time curve from time zero to the time of the last quantifiable concentration
$AUC_{0\text{-t}}$	area under the plasma concentration versus time curve from time zero to the specified time of the last quantifiable concentration
$AUC_{0\text{-tau}}$	area under the plasma concentration versus time curve from time zero to the time of the end of the dosing period
bid	twice daily
BL	baseline
BLQ	below the assay limit of quantification
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CL	clearance
CLr	renal clearance
C_{max}	observed maximum plasma concentration
COVID-19	Coronavirus disease 2019
CS	clinically significant
CSR	clinical study report
CTCAE	common terminology criteria for adverse events
CV	coefficient of variation
CYP3A	cytochrome P450 3A
DAPT	dual antiplatelet therapy
DBP	diastolic blood pressure
DLT	dose-limiting toxicity
DMC	data monitoring committee
ECG	electrocardiogram

eCRF	electronic case report form
EDC	electronic data capture
EEA	European economic area
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EOS	end of study
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
Fab	antibody fragment
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
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FUP	follow-up
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
Hgb	hemoglobin
HbA1c	glycosylated hemoglobin Hgb
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIPPA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
Hr	hour
HR	heart rate

IB	Investigator's brochure
IC	informed consent
ICF	informed consent form
ICH	International Council for Harmonization
IDMS-Traceable MDRD	Isotope-dilution mass spectrometry-traceable modification of diet in renal disease
IEC	independent ethics committee
INR	international normalized ratio
IP	investigational product
IPA	inhibition of platelet aggregation
IRB	institutional review board
IRR	infusion-related reaction
IUD	intrauterine device
IV	intravenous- (ly)
IWRS	interactive web response system
kDa	kilo dalton
LDH	lactate dehydrogenase
LDL	Low-density lipoprotein
LLN	lower limit of normal
max	maximum
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDMA	methylenedioxymethamphetamine
medDRA	medical dictionary for regulatory activities
MI	myocardial infarction
mITT	modified intent to treat
msec	millisecond
N	sample size

NCS	not clinically significant
NOAEL	no adverse effect level
NSAID	non-steroidal anti-inflammatory drugs
OTC	over the counter
PD	pharmacodynamic
PEF	peak expiratory flow
PI	Principal Investigator
PK	pharmacokinetic
PO	by mouth
pp	per protocol
PRI	platelet reactivity index
PRU	$P2Y_{12}$ reaction units
PT	prothrombin time
PT/INR	prothrombin time/international normalized ratio
PTT	partial thromboplastin time
QD	once daily
$QT_{interval}$	time from the start of the Q wave to the end of the T wave
QTcB	Bazett-corrected QT interval
QTcF	Fridericia-corrected QT interval
RBC	red blood cells
RR	respiration rate
SAE	serious adverse event
SAP	statistical analysis plan
SAR	suspected adverse reaction
SBP	systolic blood pressure
SD	standard deviation
SDV	source document verification
SOC	system-organ-class

SOE	schedule of events
SOP	standard operating procedure
SpGr	specific gravity
SRC	safety review committee
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TAM	ticagrelor active metabolite AR-C124910XX
TEAE	treatment-emergent adverse event
TG	triglycerides
T_{max}	time to reach the observed maximum (peak) concentration
TSH	thyroid stimulating hormone
ULN	upper limit of normal
US/USA	United States of America
VASP	vasodilator-stimulated phosphoprotein
Vd	volume of distribution
w/v	weight over volume
WBC	white blood cell
WHO-DD	World Health Organization drug dictionary
WOCBP	women of child-bearing potential

APPENDIX 2 PREGNANCY TESTING, REPORTING GUIDANCE AND CONTRACEPTION METHODS

PREGNANCY TESTING

- Urine pregnancy testing must be performed using the test kit provided by the central laboratory in accordance with instructions provided in its package insert
- Serum pregnancy testing will be performed and assayed in the local and central laboratory as per schedule of events (Appendix 3)

COLLECTION OF PREGNANCY INFORMATION

Female subjects who become pregnant within 35±3 days post last dose of study drug

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study and will complete the Exposure In-Utero form and submit to the Sponsor within 24 hours of learning of a subject's pregnancy
- Subject will be followed to determine the outcome of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE
- A spontaneous abortion is always considered to be an SAE and will be reported as such
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor. While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting
- Any female subject who becomes pregnant while participating will discontinue treatment (as applicable)
- Generally, follow-up will be approximately 30 days following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure

Male subjects with partners who become pregnant

- Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while participating in this study and report it to PhaseBio within 24 hours of learning of the partner's pregnancy
- Partner may also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to PhaseBio
- Generally, follow-up will be 30 days following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure

CONTRACEPTION METHODS AND DEFINITIONS

Definition of Women of Childbearing Potential and of Fertile Men

A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Female subjects who have bene sterilized are not deemed to be of childbearing potential and do not need to maintain 2 methods of contraception.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy (CTFG, 2014)

Recommended Methods of Contraception

For women

- Implants, injectables, combined oral contraceptives, intrauterine devices (IUDs), sexual abstinence, combined oral contraceptives with inhibition of ovulation or a partner who has been surgically sterile (e.g. by vasectomy) for at least 6 months

For men

- Surgical sterility (e.g. by vasectomy) for at least 6 months, sexual abstinence, or condoms plus spermicide.

Exceptions

- Female subjects who have been sterilized are not deemed to be of childbearing potential and do not need to maintain 2 methods of contraception
- Female subjects with a male partner may each use one of the contraception methods as defined within Appendix 2 and Section 8.5
- Confirmed abstinence does not require a second form of contraception
- Follicle stimulating hormone (FSH) level may be performed at Screening using local or central laboratory, for confirmation of postmenopausal status as directed by the Investigator

APPENDIX 3 SCHEDULE OF EVENTS (SOE)

	Outpatient		Outpatient/In-Clinic			Treatment (In-Clinic)			Outpatient[s]	
Procedure	**Screening[a]**		**Check-in/ Pretreatment**			**Rand**		**Subject DC**	**FUP**	**FUP EOS**
Study Day(s)	**–45 to –4**	**-7**	**–3**	**-2**	**–1**	**1**	**2**	**3**	**7**	**35±3**
Informed consent[b]	X									
Inclusion/exclusion criteria	X		X		X	X				
Demographics	X									
Medical history	X									
Urine drug screen	X		X							
Urine alcohol screen	X		X							
Serum pregnancy test[c]	X		X							X
Serology testing	X									
Stool for occult blood[d]	X							X[d]		
Admission to study clinic			X	X	X	X	X	X		
Physical examination[e,f]	X[e]		X[e]					X[f]	X[f]	X[e]
Vital signs[g]	X		X			X	X	X	X	X
12-lead ECG[h]	X				X	X	X		X	X
Clinical laboratory testing[i]	X		X		X[i]		X		X	X
Randomization[j]						**X**				
Drug administration										
ASA 81 mg QD[k]	X	X	X	X	X	X				
Ticagrelor administration[l]				X	X	X				
Administration PB2452 or placebo[m]						X				
PK sampling[n]: - Plasma PB2452 - Plasma ticagrelor/TAM - Unbound plasma ticagrelor/TAM				X[n]		X	X	X	X	X
PK urine sampling[o,p]				X[p]		X	X	X		
PD sampling (PRU/VASP)[q]				X		X	X	X		
Platelet function biomarkers[r]					X		X		X	X

	Outpatient		Outpatient/In-Clinic			Treatment (In-Clinic)			Outpatient[s]	
Procedure	**Screening[a]**		**Check-in/ Pretreatment**			**Rand**		**Subject DC**	**FUP**	**FUP EOS**
Study Day(s)	**–45 to –4**	**-7**	**–3**	**-2**	**–1**	**1**	**2**	**3**	**7**	**35±3**
Serum immunogenicity (ADA testing)[s]			X			X[s]			X	X[s]
Infusions site assessment[t]						X	X	X	X	X
AEs/SAEs[u]	X	X	X	X	X	X	X	X	X	X
Concomitant medications[v,w]	X[v]	X[v]	X[v]	X[v]	X[v]	X[w]	X[w]	X[w]	X[w]	X[w]
Discharge from clinic[x]								X	X[x]	X[x]

Abbreviations: AE=adverse event; ADA=anti-drug antibody; ASA= aspirin; BMI=body mass index; DBP=diastolic blood pressure; DC = discharged; ECG=electrocardiogram; EDC=electronic data capture; EOS=end of study; FUP=follow-up; HR=heart rate; PD=pharmacodynamics; PK=pharmacokinetics; PRU=$P2Y_{12}$ reaction units; QD=once daily; Rand=Randomization; RR=respiratory rate; SAE=serious adverse event; SBP=systolic blood pressure; TAM=ticagrelor active metabolite AR-C124910XX; VASP=vasodilator-stimulated phosphoprotein

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

b If verbal consent is obtained, it must be witnessed by an impartial witness. The details and full process to be fully documented in source documents

Note: Any changes to site-specific processes due to COVID-19 pandemic must be fully documented and identified within source documents and eCRF

c Serum pregnancy test for women of childbearing potential only. May utilize central or local laboratory as needed

d Stool for occult blood test may be conducted at either the central or local laboratory as needed. The Day 3 stool occult sample may be collected on Day 2 if needed

e A full physical examination is conducted at Screening, Day -3 and Day 35±3

Height and weight collected at Screening and Day 35±3 only

BMI is calculated within the electronic data capture system

f Brief physical examination and querying the subject concerning any changes from baseline. A brief physical examination will include assessment of heart, skin, lungs, cardiovascular system, and abdomen, and extremities

g Vital sign measurements (SBP and DBP, body temp, RR, and HR) will be collected at screening, check-in (Day -3), before dosing (30 to 60 minutes prior to the initiation of the study drug infusion) and at 15±5, 30±10, 45±10, 60±15 min, 24 hours±15 min and 48 hours±15 min following initiation of study drug

Vital Signs are also collected on Day 7 and 35±3. Vital signs at 15, 30, 45, and 60 minutes following infusion require only SBP and DBP, and HR

h 12-lead ECGs will be obtained at Screening before initiation of PB2452/placebo, pre-treatment Day -1, and on treatment Days 1, 2, 7 and 35±3. The specific time points for 12-lead ECG on Day 1 and 2 will be pre-dose, 10 minutes after bolus, end of infusion, and after 24 hours (± 30 minutes) from initiation of infusion. ECGs will be collected anytime on Days 7 and 35±3

i All scheduled clinical laboratory tests will be performed centrally with the exception of Day -1 clinical laboratory testing which should be performed locally to provide results prior to randomization

Note: There is no scheduled clinical laboratory test o Day 3. However, if required the clinical laboratory tests (hematology, chemistry, coagulation, and urinalysis) may be repeated if considered clinically significant by the Investigator based on Day 2 lab results

j Local/central laboratory results must be confirmed to ensure continued eligibility prior to randomization

k ASA 81 mg will be taken on Days -7, -6, -5, -4, -3, -2, -1, and on Day 1 no less than 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. Subjects will receive daily ASA 81 mg between Day -3 (or Day -2 if the subject 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 theclinical facility on Day 3

l 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 (or BID) for 4 additional doses through to Day 1. The final dose of ticagrelor should occur 2 hours±15 min before study drug is initiated)

m PB2452/placebo will be administered at Hour 0 of Day 1

Infusion of PB2452/placebo is initiated on Hour 0 of Day 1 and will continue for approximately 16 hours for a total of 18 g (180 mL), as described in the protocol and pharmacy manual.

In subjects with known or reported concomitant use of moderate or strong CYP3A inhibitors (Appendix 4), an alternative 36 g (360 mL) regimen of PB2452 infused for approximately 24 hours will be administered as directed by the pharmacy manual

n A pre-ticagrelor blood sample will be collected on Day -2, within 60 mins prior to the dose of ticagrelor. Blood samples for determination of plasma PB2452, plasma ticagrelor/TAM and unbound plasma ticagrelor/TAM will be collected on Days 1 to 3 within 10 minutes prior to the initiation of PB2452/placebo infusion (Hour 0) and at 5, 10, 30 minutes and 1, 2, 4, 8, 12, 20, 24, 36, and 48 hours after initiation of study drug infusion

Plasma PK samples will also be collected on Day 7, and Day 35±3 after initiation of study drug infusion

o Urine samples for PK ticagrelor/AR-C124910XX to be collected at i) 0 to 6 hours; ii) 6 to 12 hours and iii) 12 to 24 hours and iv) 24 to 48 hours after the initiation of the study drug infusion

p Collection of Day -2 urine PK sample is a single sample collected within 60 minutes prior tothe first ticagrelor dose

q Blood samples for PD analysis (PRU/VASP testing) will be collected at the following timepoints: Day -2 and Day 1 (within 60 minutes prior to first ticagrelor dose) and Hour 0 (up to 10 minutes prior to PB2452/placebo infusion), 5, 10, 30 minutes, 1, 2, 4, 8, 12, 20, 24, 36 and 48 hours after initiation of PB2452/placebo infusion

If there is sufficient material leftover from PK and/or PD blood samples, additional platelet function-related biomarker testing, such as P-selectin, may be performed

r One sample for platelet biomarker testing will be collected into a plasma tube (3.2% Na Citrate) at the indicated timepoints. A single Qiagen PAXgene DNA tube per subject is collected at any convenient sampling timepoint throughout the study. Detailed instructions are provided in the laboratory manual

s Subjects may be required to return to the site for collection of additional follow-up samples, if the sample collected at Day 35±3 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

Note: serum immunogenicity sample on Day 1 must be collected prior to initiation of study drug infusion

t Infusion site assessments will be performed for all subjects within 15 minutes before initiation of PB2452/placebo infusion at Hour 0, 1, 3, 24, and 48 hours after initiation of PB2452/placebo infusion, and on Days 7 and 35±3

u All AEs/SAEs from the time of consent to Day 35±3 are to be reported, regardless of subject being within or outside the facility/study site

v All concomitant medications (prescription, over the counter and supplements) to be collected -45 days from the date informed consent is signed until Day 35±3. Subjects must be on a stable dose (meaning no changes in dose) of their medications for at least 30 days prior to initiation of study drug (time of randomization)

w New medications and changes to dosing of existing medications can occur post Day 1 (randomization) and are to be captured at schedule visit up to Day 35±3

x Subjects are discharged from the clinic on Day 3. However, if needed and at the discretion of the Investigator, a subject may remain in the study facility beyond the scheduled Day 3 discharge to accommodate Day 7 and Day 35±3 follow-up visits. All applicable study-related assessments for Day 7 and Day 35±3 will occur as outlined in the protocol

APPENDIX 4 EXAMPLES OF INHIBITORS OF CYP3A

CYP3A	Strong Inhibitors	Moderate Inhibitors
	boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavi, grapefruit juice, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole	aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil

Note: Investigators are advised to note the list in Appendix 4 may not be 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 (#table3-1) (Website, n.d.) periodically and as needed.