STATISTICAL ANALYSIS PLAN

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STUDY TITLE:	A Phase 2A, Randomized, Double-blind, Placebo-controlled, Single Dose, Sequential Group Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of PB2452 with Ticagrelor Pretreatment in Older (age 50 to 64 years) and elderly (age 65 to 80 years) subjects (Part A), and a High Dose Ticagrelor Pretreatment in Healthy Subjects aged 15-50 (Part B)
PHASE OF STUDY:	Phase 2A
PROTOCOL NUMBER:	PB2452-PT-CL-0002: Part A and Part B
PROTOCOL VERSION/DATE:	Protocol version 2.0 / 25 July 2019 (Part A) Protocol version 1.0 / 25 July 2019 (Part B)

APPROVALS

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List of Abbreviations

AA	arachidonic acid
ACS	acute coronary syndrome
ADA	anti-drug antibodies
ADP	adenosine diphosphate
AE	adverse event
ASA	acetylsalicylic acid, aspirin
AUC	area under the plasma concentration versus time curve
BLQ	below the limit of quantification
BMI	body mass index
CLr	renal clearance
C_{max}	observed maximum plasma concentration
CrCl	creatinine clearance
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DAPT	dual antiplatelet therapy
DBP	diastolic blood pressure
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
FA	final-extent aggregation
HR	heart rate
IV	intravenous
LTA	light transmittance aggregometry
MA	maximal-extent aggregation
MedDRA	Medical Dictionary FOR Regulatory Activities
MI	myocardial infarction
NCS	not clinically significant
PD	pharmacodynamic
PK	pharmacokinetic
PRI	platelet reactivity index
PRU	$P2Y_{12}$ reaction units
PT	prothrombin time
QD	once daily
QTcB	Bazett's-corrected QT interval
QTcF	Fridericia-corrected QT interval
RBC	red blood cell(erythrocyte)
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SRC	Safety Review Committee
$t_{1/2}$	terminal elimination half-life

TAM	ticagrelor active metabolite AR-C124910XX
TEAE	treatment-emergent adverse event
T_{max}	time to reach the observed maximum (peak) concentration
TRAP	thrombin receptor activating peptide
VASP	vasodilator-stimulated phosphoprotein
WBC	white blood cell

1. Introduction

PB2452 is a specific and selective recombinant human neutralizing antibody IgG1λ monoclonal fragment antigen-binding antibody that binds with high affinity to ticagrelor and to AR-C124910XX (TAM), the major active circulating ticagrelor metabolite. PB2452 is intended to reverse the antiplatelet effects of ticagrelor in patients who experience major bleeding or who require urgent surgery or intervention. Platelet transfusion has appeared to be inferior to standard care for those taking antiplatelet therapy.(Baharoglu, 2016)

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

This statistical analysis plan (SAP) is written according to protocol PB2452-PT-CL-0002, version Final 2.0 (Part A) and Final 1.0 (Part B), both dated 29 July, 2019. This SAP will cover the final analysis for both parts, Part A and B, of the study.

2. Objectives

2.1 Primary Objectives:

- To evaluate the safety and tolerability of intravenous (IV) doses of PB2452 vs matching placebo with oral ticagrelor plus ASA pretreatment in older (age 50 to 64 years) and elderly (age 65 to 80 years) male and female subjects in Part A, and, to evaluate the safety and tolerability of intravenous (IV) doses of PB2452 vs matching placebo with a High Dose of oral ticagrelor plus ASA pretreatment in healthy patients (age 15 to 50) in Part B
- To assess the efficacy/PD of IV doses of PB2452 vs matching placebo in reversing ticagrelor antiplatelet activity by measuring $P2Y_{12}$ reaction units (PRU) with VerifyNow® $P2Y_{12}$ assay in older (age 50 to 64 years) and elderly (age 65 to 80 years) subjects, and in healthy patients (age 15 to 50) with a High Dose of oral ticagrelor plus ASA pretreatment in Part B

2.2 Secondary Objectives:

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

2.3 Exploratory Objectives:

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

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 2A, randomized, double-blind, placebo-controlled, single dose, sequential group study. Part A evaluates the safety, tolerability, PK and PD of PB2452 vs matching placebo with ticagrelor + ASA pretreatment when various dose levels and administration regimens are administered to 1) healthy older (age 50 to 64 years) and elderly (age 65 to 80 years) male and female subjects in Part A. Part B investigates various dose levels and regimens of PB2452 administered to healthy male and female subjects (ages 18-50) pretreated with a high dose of ticagrelor alone (180 mg) twice daily (BID).. All references to study drug within this SAP apply to PB2452 or matching placebo. Part B evaluates the safety, tolerability, PK and PD of PB2452 vs matching placebo with High Dose of ticagrelor + ASA pretreatment to healthy male and female subjects. All references to study drug within this SAP apply to PB2452 or matching placebo.

Each cohort was planned to include approximately 8 to 12 subjects randomized in a 3:1 ratio, PB2452:placebo.

PART A:

The initial cohort (Cohort 1) included approximately 8 subjects ages 50 to 80 years pretreated with ASA + ticagrelor randomized to 18 grams (g) of PB2452 or matching placebo administered as an initial 6 g bolus infused over 10 minutes, followed by 12 g infused over the next 15 hours and 50 minutes to complete a 16 hour administration regimen.

Following completion of Cohort 1, a subsequent cohort was tested, also at an 18 g dose level of PB2452 or matching placebo in the same population as in Cohort 1. A written Dosing Memo was provided by the Sponsor to the clinical site describing details of the dosing regimen, cohort population, cohort size, sampling schedules, and other cohort-specific study activities prior to initiation of each cohort. The maximum total dose of PB2452 administered to any subject as not to exceed 30g. Duration of study drug infusions was not to exceed 48 hours. The maximum administration rate of PB2452 was not to exceed 18g over 30 minutes.

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

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

Safety and tolerability were carefully monitored throughout the study. Immunogenicity samples were collected from all subjects at Day -3, Day 1, Day 7, and Day 28 (±2 days).

PART B:

In Part B one dose level (36 g) and administration regimens of PB2452 was evaluated in one cohort. Each cohort will include up to 12 subjects randomized in a 3:1 ratio (PB2452:placebo).

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

Following completion of Cohort 3, subsequent cohort(s) may have been enrolled to test the same, higher or lower dose levels, and/or different infusion regimens of PB2452 or matching placebo in the same population as in Cohort 3, or in different populations such as elderly subjects (65 to 80 years old), as determined by the Sponsor after examination of available PD and safety data from the prior cohort(s) and described in a subsequent Dosing Memo. Duration of study drug infusions will not exceed 48 hours. No cohort was enrolled following Cohort 3.

A Safety Review Committee (SRC) reviewed all available safety data from ongoing or completed cohorts and documented their review and assessment in written SRC minutes prior to initiation of a subsequent cohort. Dose escalation would occur only if the SRC affirms the dose

and regimen from the previously completed cohorts were safe and well tolerated and no dose-limiting toxicities (DLTs) were observed.

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

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

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

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

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

The overall schedule of required evaluations is provided in Appendix 15.1.

3.2. Study Endpoints

3.2.1. Safety Endpoints

Safety and tolerability will be assessed by monitoring and recording of adverse events (AEs), clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), vital sign measurements (systolic blood pressure [SBP] and diastolic blood pressure [DBP], oral body

temperature, respiratory rate, and resting heart rate [HR]), 12-lead electrocardiogram (ECG), continuous 12-lead ECG (Holter monitoring), immunogenicity, and physical examination findings.

3.2.2. Pharmacokinetic Endpoints

Plasma PK concentration for PB2452 at each sampling timepoint as specified on the Dosing Memo will be assessed. The following PK parameters will be calculated:

- Area under the curve (AUC) from time zero to the time of the last quantifiable concentration ($AUC_{0-\tau}$)
- Observed maximum plasma concentration (C_{max})
- 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})
- AUC from time zero extrapolated to infinity ($AUC_{0-\infty}$); if data permit
- Terminal elimination half-life ($t_{1/2}$; if data permit)
- Clearance (CL; if data permit)
- Volume of distribution (Vd)

Plasma PK concentration for ticagrelor and the metabolite TAM at each sampling timepoint as specified on the Dosing Memo will be assessed. The following PK parameters will be calculated:

- C_{max}
- T_{max}
- AUC_{0-t}
- $AUC_{0-\tau}$
- AUC_{0-24}
- AUC_{0-48}
- $AUC_{0-\infty}$; if data permit
- $t_{1/2}$; if data permit

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

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

3.2.3. Pharmacodynamic Endpoints

Pharmacodynamic data and parameters will be generated from PRU, LTA and PRI assays:

VerifyNow®P2Y12:

- PRU at each assessment point
- Percent of reversal (%baseline) in ticagrelor antiplatelet activity by PRU at each assessment point
- Maximum PRU
- Maximal percent of baseline PRU
- Time to maximum PRU
- Maximum PRU within 4 hours
- Time to ≥180 PRU
- Time to ≥200 PRU
- Time to ≥220 PRU
- Time to 60%, 80%, and 90% of reversal in PRU

LTA:

- The maximum and final extent of aggregation for up to 4 platelet agonists (20μM adenosine diphosphate [ADP], 5μM ADP, 1.6 mM arachidonic acid [AA], and 15μM thrombin receptor activating peptide [TRAP]), will be recorded at each assessment point.
- Percent of reversal (%baseline) in ticagrelor antiplatelet aggregation
- Maximum platelet aggregation
- Maximum percent of baseline platelet aggregation
- Time to maximum platelet aggregation
- Maximum platelet aggregation within 4 hours
- Time to 60%, 80%, and 90% of reversal in platelet aggregation

VASP by ELISA:

- PRI at each assessment point
- Percent of reversal (%baseline) in PRI at each assessment point
- Maximum PRI
- Maximum percent of baseline PRI
- Time to maximum PRI
- Maximum PRI within 4 hours
- Time to 60%, 80%, and 90% of reversal in PRI
- Time to minimum PRI

3.3. Treatments

Study Drug will refer to PB2452 or matching placebo.

PART A:

PB2452: PB2452 IV infusion, prepared according to the Pharmacy Manual, was administered on Day 1 for up to 48 hours. The total dose for each subject was 18g. The infusion rate was not to

exceed 18g over 30 minutes and the concentration was not to exceed 24g in 250mL. Subjects were not to receive more than 250 mL of study drug infusion within any 1-hour period. Two cohorts were enrolled in Part A, both at a total dose of 18g.

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

Matching Placebo: 0.9% sodium chloride single IV infusion, administered on Day 1, was delivered at a rate and volume matching the active infusion.

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

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

PART B:

PB2452: PB2452 IV infusion, prepared according to the Pharmacy Manual, was administered on Day 1 for up to 48 hours. For each cohort, the dose, infusion rate, and duration was communicated from the Sponsor to the study site, PPD, in a Dosing Memo issued prior to initiation of each treatment cohort. One cohort in Part B was enrolled, at a total dose of 36 g.

Matching Placebo: 0.9% sodium chloride single IV infusion, was delivered at a rate and volume matching the active infusion.

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

4. General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS® Version 9.4 or higher (SAS Institute, Cary, NC). For tables and data listings with no data, titles and footnotes will be presented, and “No data to display” will be presented.

Descriptive statistics for continuous variables will include number of subjects, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise noted. Minimum and maximum will be presented to the same number of decimal places as the raw data, mean and median will be presented to one more decimal place than the raw data, and SD will be presented to two more decimal places than the raw data, unless otherwise specified.

Frequency and percentage will be calculated for categorical variables. Percentages will be presented with 1 decimal place, and if the value is less than 0.1, then "<0.1" will be displayed.

All data will be provided in by-subject listings.

For summary of safety assessments, if there are repeated measurements at a time point, the original measurement at that time point will be used in the summary tables. If the original measurement is missing, the next available measurement at that time point will be used in the summary tables.

Baseline will be defined as the last nonmissing assessment before study drug (PB2452 or matching placebo) administration.

Unscheduled results will not be included in the summary tables except for determining Baseline but will be presented in data listings.

Unless otherwise stated, the following treatment groups will be used in the summaries, there C denotes Cohort:

- 18 g PB2452 (C1)
- 18 g PB2452 (C2)
- 36 mg PB2452 (C3)
- Placebo
- All PB2452 (for safety analyses only)
- All Subjects (for safety analyses only)

Outputs will be provided for Part A and Part B, separately.

4.1. Sample Size

The sample size (N) of up to 5 cohorts (Part A) up to 3 cohorts (Part B) of up to 12 subjects per cohort for this study is based on clinical and practical considerations rather than on formal statistical power calculation. The sample size is considered sufficient to adequately assess the safety, PK, and PD profiles of PB2452 and the PK and PD profiles of ticagrelor and its active metabolite TAM.

4.2. Randomization, Stratification, and Blinding

This is a double-blind study. Neither the subjects nor the investigator will be aware of the treatment assignment. Blinding will be maintained throughout the study by use of active and placebo dose forms prepared to be similar in appearance. Subjects will be randomized in a 3:1 (PB2452:placebo) ratio. No stratification will be utilized.

In order to prepare preliminary summaries of safety, PK, and/or PD data, as needed, to make timely decisions concerning adjustment of study procedures, dosing regimens, or potentially

early termination of the study, certain designated staff at PhaseBio (e.g., study director, a single biostatistician, and bioanalytical scientist[s], study drug accountability monitor) will receive unblinded data after each cohort completes Day 3 assessments.

The scheduled unblinding event to all study members will occur after the database is locked (hard-locked).

4.3. Replacements

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

4.4. Handling of Missing data

For the purpose of determining inclusion of AEs in the treatment-emergent AE (TEAE) summary tables, incomplete or missing AE onset and end dates will be imputed as follows:

Incomplete or missing onset dates (where UK and UNK indicate unknown or missing day and month, respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the dose of study drug month and year, and the end date (after any imputation) is on or after the dose of study drug, then assume the date of the dose of study drug. If the month and year are the same as the dose of study drug month and year and the end date (after any imputation) is prior to the dose of study drug, then assume the end date for the onset date.
- DD-UNK-YYYY or UK-UNK-YYYY: If the year is different from the year of dose of study drug, assume DD-JAN-YYYY or 01-JAN-YYYY of the onset year, respectively. If the year is the same as the dose of study drug year, and the end date (after any imputation) is on or after the dose of study drug, then assume the date of the dose of study drug. If the year is the same as the dose of study drug, and the end date (after any imputation) is prior to the dose of study drug, then assume the end date for the onset date.
- Missing onset date: If the onset date is completely missing and the end date (after any imputation) is on or after the dose of study drug, then assume the date of the first dose of study drug. If the end date (after any imputation) is prior to the dose of study drug, then assume the end date for the onset date.

Incomplete or missing end dates (where UK and UNK indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UNK-YYYY or UK-UNK-YYYY: Assume DD-DEC-YYYY or 31-DEC-YYYY, respectively;

- Missing end date: Assume 31-DEC-YYYY, where YYYY is the year of the dose of study drug.

An AE with missing onset time but with an onset date the same as the dosing date of study drug will be classified as treatment-emergent, unless the AE was reported pre-dose with the same or worse intensity or frequency.

Medications with missing start time but with a start date the same as the dosing date of study drug will be considered as being taken on or after the initiation of study drug, unless the electronic case report form (eCRF) question "Was the medication/therapy taken prior to the study" is answered as "Yes" which is considered as being taken prior to the initiation of study drug.

Handling of missing PK data is specified in Section 10 and handling of PD data is specified in Section 11.

4.5. Analysis Populations

4.5.1. Safety Population

The Safety Population includes all subjects who receive any amount of study drug (PB2452 or matching placebo). The Safety Population will be analyzed for all safety assessments. Subjects in the Safety Population will be analyzed as treated.

4.5.2. Pharmacokinetic (PK) Population

The PK population includes subjects in the safety population who have ≥1 measurable PK concentration. The PK population will be used to summarize all PB2452 blood concentrations. Subjects in the PK population will be analyzed as treated.

4.5.3. Modified Intention-to-Treat (mITT) 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 analyzed according to the treatment they are randomized to.

5. Subject Disposition

5.1. Disposition

Subject disposition will be presented by Part for all screened subjects, including number of screen-failed subjects, number of subjects enrolled (i.e. receiving ticagrelor) and number of subjects randomized.

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 of study completion and treatment completion status will be presented along with reasons for discontinuation if any.

All tables and listings will be done for both Part A and Part B of the study, separately.

5.2. Protocol Deviations and Eligibility Criteria Deviations

Protocol deviations will be presented by Part in a data listing. Eligibility with regards to inclusion and exclusion criteria will be listed in a separate listing.

6. Demographics and Baseline Characteristics

6.1. Demographics

Demographic information collected at screening will be presented by Part in a data listing for both Part A and Part B. Descriptive statistics will be calculated for the following continuous demographic characteristics: age (years, calculated as the integer part of [date of informed consent - date of birth]/365.25), weight (kg), height (cm), and body mass index (BMI, kg/m^2). Frequency counts will be tabulated for the categorical variables of sex, race, ethnicity and renal function (Normal [GFR ≥90], Mild [GFR 60-89], Moderate [GFR 30-59], Severe [GFR ≤29]). The summaries will be presented by treatment groups and overall for the safety population.

All tables and listings for Demographics and Baseline Characteristics will be done for both Part A and Part B of the study, separately.

6.2. Medical History

All tables and listings for Medical History will be done by Part for both Part A and Part B of the study.

The medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA; version 21.0 or higher) and presented in a data listing.

7. Treatments and Medications

All tables and listings for Treatments and Medications will be done for both Part A and Part B of the study.

7.1. Prior and Concomitant Medications

Prior medications are defined as medications taken prior to the initiation of study drug. Concomitant medications are defined as medications that were taken on or after the initiation of study drug. A medication can be considered as both prior and concomitant if the medication is taken prior to the initiation of study drug and continued into the treatment period. Ticagrelor and aspirin, which will be received by all study subjects, are considered pre-treatments. Medications taken prior to ticagrelor, concomitant with ticagrelor and concomitant with the study treatments PB2452 and placebo will be presented separately.

Prior and concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary (version March 2019 or later) and presented in a listing.

All tables and listings for prior and concomitant medications will be done for both Part A and Part B of the study.

7.2. Medical and Surgical Procedures

Medical and surgical procedures will be presented in a listing, by Part.

7.3. Study Treatments

Study drug (PB2452 or matching placebo), aspirin, and ticagrelor administration will be presented in data listings, by Part.

8. Safety Analysis

All tables and listings for Safety Analysis will be done for both Part A and Part B of the study, separately.

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. These results will be presented for the Safety Population by Part.

8.1. Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered drug-related.

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

All AEs will be coded using MedDRA (version 21.0 or higher) by system organ class (SOC) and preferred term (PT).

All summary tables, except from the overall summary table and summary by relationship to ticagrelor, will be based on TEAEs. Frequency and percentage at subject level as well as number of events will be presented in the summaries. The SOCs will be displayed in descending order of overall frequency and then alphabetically. The PTs will be displayed in descending order of overall frequency and then alphabetically within SOC. A subject with 2 or more AEs within the same level of summarization will be counted only once in that level using the most severe (for the severity table) or most related (for the relationship to study drug table) incident.

Summary tables will be presented by Part and by treatment group. Percentages will be based upon the number of subjects in the safety population overall (for the corresponding Part) and within each treatment group.

8.1.1. Incidence of Adverse Events

All AE tables and listings will be provided by Study Part.

All AEs will be presented in a data listing, and all TEAEs will be presented in a summary table by SOC, PT, treatment group and overall. Additional table of TEAEs will be presented in a summary by PT only.

An overall summary table, will be created with following categories:

- Any TEAE
- Any study-drug-related TEAE
- Any severe TEAE
- Any severe study-drug-related TEAE
- Any serious adverse event (SAE)
- Any treatment-emergent, study-drug-related SAE
- Any AE leading to early study discontinuation
- Any DLT
- Any Infusion Site Reactions (ISR)
- Any death

The definition of DLT is defined in Section 8.1.4. For the purpose of above summary, a study-drug-related AE is an AE with definite, probable, possible, or missing relationship to the study drug on eCRF. Study drug refers to PB2452 or matching placebo.

8.1.2. Relationship of Adverse Events

The relationship of AE to study drug and ticagrelor will be classified by the Investigator as unrelated, possible, probable, and definite. Treatment-emergent AEs will be summarized by SOC, PT, and relationship to study drug; AEs will be summarized by SOC, PT, and relationship to ticagrelor. A subject with 2 or more TEAEs within the same level of summarization will be counted only once in that level using the most related incident.

8.1.3. Severity of Adverse Event

The severity (or intensity) of an AE refers to the extent to which it affects the subject's daily activities and will be classified as mild, moderate, or severe. The TEAEs will be summarized by SOC, PT, severity (including category 'Missing' for events with missing severity assessment on eCRF) and treatment group. A subject with 2 or more TEAEs within the same level of summarization will be counted only once using the most severe event.

8.1.4. Dose Limiting Toxicities

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

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

The SRC will provide an external spreadsheet which contains all DLT events and this external spreadsheet will be used in the summaries and listings.

8.1.5. Infusion Site Assessments

The infusion site will be examined by the investigator or designée concerning pain, tenderness, erythema/redness, and induration/swelling within 15 minutes before the initiation of the study drug infusion at Hour 0, and at 1, 3, 24, and 48 hours after initiation of the study drug infusion and on Day 7. Infusion site reactions will be assessed according to the CTCAE v5 grading scale and will be recorded as AEs and included in the AE listings.

8.1.6. Serious Adverse Events

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

- Death
- Life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization

- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Congenital anomaly or birth defect

All SAEs including deaths will be presented in a data listing, by Part.

8.1.7. Adverse Events Leading to Early Discontinuation

All AEs that lead to early discontinuation will be presented in a listing, by Part.

8.2. Clinical Laboratory Evaluations

Clinical laboratory tests will be performed by PPD Central Laboratory. Repeat clinical laboratory tests may be performed at the discretion of the investigator, if necessary, to evaluate inclusion and exclusion criteria or clinical laboratory abnormalities. The clinical laboratory performing the tests will provide the reference ranges for all clinical laboratory parameters.

The following clinical laboratory assessments will be performed:

Hematology	Complete blood count with differential hematocrit hemoglobin mean corpuscular hemoglobin mean corpuscular hemoglobin concentration mean corpuscular volume mean platelet volume platelet count erythrocyte (red blood cell [RBC]) count total and differential leukocyte (white blood cell [WBC]) count

Serum Chemistry	alanine aminotransferase albumin alkaline phosphatase aspartate aminotransferase bicarbonate bilirubin (total and direct) blood urea nitrogen calcium chloride cholesterol total high-density lipoprotein calculated low-density lipoprotein creatine phosphokinase creatinine gamma-glutamyl transferase glucose Hgb A1C lactate dehydrogenase magnesium phosphorus potassium sodium thyroid stimulating hormone (Screening only) total protein triglycerides (repeat fasting triglyceride if TG >500) uric acid
Coagulation	activated partial thromboplastin time international normalized ratio partial thromboplastin time prothrombin time
Urinalysis (should be aligned to PPD urinalysis)	appearance bilirubin color glucose ketones leukocyte esterase reflex microscopy (at Screening and Check-in only, if dipstick is positive for protein or blood value ≥1+); includes bacteria — casts crystals — epithelial cells RBCs — WBCs nitrites — occult blood pH — protein specific gravity — turbidity urobilinogen
Serology	hepatitis B surface antigen hepatitis C virus antibody human immunodeficiency virus types 1 and 2 antibodies (Screening only)

Other analyses	urine drug screen (Screening and Check-in only): amphetamines barbiturates benzodiazepines cannabinoids cocaine cotinine methylenedioxymethamphetamine opiates phencyclidine propoxyphene tetrahydrocannabinol urine alcohol (Screening and Check-in only) female subjects: follicle-stimulating hormone (Screening only) serum pregnancy test (human chorionic gonadotropin [Screening, Check-in, and Day 28 (±2 days) only])

Hematology, clinical chemistry, coagulation, and urinalysis laboratory tests will be performed on Screening, at Check-in Days -3, on Days -1, 2, 7, and 28 (±2).

Urine drug screen and urine alcohol screen tests will be performed on screening and at Check-in Day -3.

Serum pregnancy test will be performed on Screening, at Check-in Day -3, and on Day 28 (±2).

Serology tests and stool occult blood will be only performed on Screening.

Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter. The investigator will determine whether any of the abnormally high or low results are clinically significant (CS) or not CS (NCS).

The hematology and coagulation, clinical chemistry, and urinalysis test results will be presented in the data listings sorted by treatment group, subject, laboratory test, and sample collection date/time. Values that are outside of the normal range as well as the clinically significance information will be flagged in the listings. Actual results and change from baseline will be summarized for the safety population. Shift tables will be generated for the safety population.

All other laboratory tests will be presented in a data listing sorted treatment group, subject, laboratory test category, laboratory test, and sample collection date/time.

All laboratory tables and listings will be provided by Part.

8.3. Vital Sign Measurements

Vital signs (SBP and DBP, oral body temperature, respiratory rate, 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 10, 20, 30, 45, 60 minutes, 24 and 48 hours following initiation of the study drug, and on Days 7 and 28 (±2).

Vital signs results will be presented in a data listing sorted by treatment group, subject, and collection date/time. Actual results and change from baseline will be summarized for the safety population.

All vital sign tables and listings will be provided by Part.

8.4. Twelve-Lead Electrocardiogram

Twelve-lead ECGs will be obtained after the subject has rested in the supine position for ≥10 minutes or as clinically indicated based on reported AEs or laboratory findings, as necessary. Scheduled visit and timepoints for 12-lead ECG will be specified on the Dosing Memo.

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: HR, PR interval, QRS duration, QT interval, Fridericia-corrected QT interval (QTcF), and RR interval. The investigator will determine whether any of the 12-lead ECG results are CS or NCS.

If both QT and RR intervals are not missing, the Bazett's-corrected QT interval (QTcB) measured in msec will be calculated using below formula, where RR interval is measured in msec:

- $QTCB = \frac{QT}{\sqrt{RR/1000}}$

If both QT and RR intervals are not missing but QTcF interval is missing in the database, QTcF measured in msec will be calculated using below formula, where RR interval is measured in msec:

- $QTCF = \frac{QT}{\sqrt[3]{RR/1000}}$

Electrocardiogram results will be presented in data listing sorted by treatment group, subject, and date/time of assessment. In addition, subjects with outlying QTcF, and QTcB intervals (absolute value > 500 msec, absolute value > 480 msec, absolute value > 450 msec, or increase from baseline value >30 or >60 msec) will be listed in a separate data listing. A summary table will be presented for maximum QTcF and QTcB intervals (including scheduled and unscheduled assessments) meet the outlying criteria using count and percentage.

Actual results and change from baseline will be summarized for the safety population at each timepoint.

All ECG results will be presented in a data listing.

All ECG tables and listings will be provided by Part.

8.5. Holter Monitoring (Continuous Twelve-lead Electrocardiogram)

Continuous 12-lead Holter monitor will be placed 2 hours before administration of study drug and will remain in place for 24 hours after the initiation of study drug. The continuous ECG waveform data recorded by the Holter device will be stored for optional exposure-response QTc analysis.

The eCRF collected interpretation from the Holter device will be presented in a data listing, by Part.

8.6. Physical Examination and Physical Measurement

A full physical examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities, and will be performed on Screening, at Check-in Day -3, and at Day 28 (±2).

A brief physical examination will include assessment of skin (including any signs of cutaneous erythema), lungs, cardiovascular system, and abdomen (liver, spleen) and will be performed at Day 3 and Day 7.

Interim physical examinations will be performed at the discretion of the investigator, if necessary, to evaluate AEs or clinical laboratory abnormalities.

Physical exam results will be presenting in a data listing, by Part. Physical measurements will be presented in a separate listing, by Part.

9. Immunogenicity Assessments

Immunogenicity (antibody) samples will be screened for the presence of binding anti-drug antibodies (ADA) at Check-in Day -3, on Days 1, 7, and 28 (±2). A subject who tests positive for ADAs at the final scheduled visit (Day 28 ±2 days) will be asked to return for follow-up sampling approximately 3 months after the final visit and approximately every 6 months thereafter until ADAs no longer test positive or until levels return to a predose state.

The ADA result (positive or negative) will be summarized by treatment group and visit using counts and percentages. All ADA results with corresponding titer values will be presented in a data listing. The neutralizing antibody results may be listed and summarized in the clinical study report if the assay is available.

An ADA-positive subject is defined as a subject with at least one ADA-positive sample at any time during the treatment or follow-up observation period. In case of a positive pre-treatment sample, if the titer of at least one post-treatment ADA is elevated at least 2 folds of the titer in pre-treatment sample, this subject is also ADA positive otherwise ADA negative.

All immunogenicity tables and listings will be provided by Part.

10. Pharmacokinetics

All tables and listings for pharmacokinetics will be provided by Part.

10.1. Plasma Pharmacokinetics

The ticagrelor and TAM pharmacokinetic results will be analyzed for all randomized subjects, and the PB2452 results will be analyzed for the PK Population. All summary tables, graphs are listings will be provided by Part.

10.1.1. Plasma Pharmacokinetics Concentration

Throughout this document, the total MEDI2452 (PB2452) includes free MEDI2452 (PB2452), protein-bound MEDI2452 (PB2452), ticagrelor-complexed MEDI2452 (PB2452), and TAM-complexed MEDI2452 (PB2452). The unbound MEDI2452 (PB2452) includes free MEDI2452 (PB2452) and protein-bound MEDI2452 (PB2452). Similarly, total ticagrelor (or TAM) includes free ticagrelor (or TAM), protein bound ticagrelor (or TAM), and MEDI2452 (PB2452)-complexed ticagrelor (or TAM). The unbound ticagrelor (or TAM) includes free ticagrelor (or TAM).

Blood samples for PK analysis of total and unbound PB2452 concentration in plasma will be collected from all subjects at the following time points: before dosing (0 hour) and up to 28 days after initiation of the study drug (PB2452 or placebo) infusion. Collection time points for cohorts were be specified in a Dosing Memo from Sponsor prior to initiation of each cohort, and are provided below.

Collection times relative to the initiation of the study drug (PB2452 or placebo) infusion on Day 1 were: Hour 0 (up to 10 minutes prior to PB2452 infusion), 5 minutes, 0.25, 0.5, 1, 2, 4, 8, 12, 20, 24, 36, 48 hours, and 7 and 28 days post-dose.

Plasma samples for determining total and unbound concentrations of ticagrelor and its active metabolite TAM, will be collected at the following timepoints: before dosing (within 10 minutes prior to the initiation of the study drug infusion [Hour 0]), and up to 28 days following the initiation of PB2452 or placebo infusion on Day 1. Subjects will be administered the 5th ticagrelor dose two hours before the study drug infusion initiation on Day 1.

Specific collection times relative to the initiation of the study drug (PB2452 or placebo) infusion were: Hour 0 (up to 10 minutes prior to PB2452 infusion), 5 minutes, 0.25, 0.5, 1, 2, 4, 8, 12, 20, 24, 36, 48 hours, and 7 and 28 days post-dose.

Concentrations that are below the limit of quantification (BLQ) will be treated as zero for descriptive statistics. Mean BLQ concentrations will be presented as BLQ, and the SD and

coefficient of variation (CV) will be reported as not applicable. Missing concentrations will be excluded from the calculations.

For each analyte, plasma concentration data will be listed by subject and summarized by time point for each dose level using descriptive statistics (number of subjects, arithmetic mean, SD, CV, median, minimum, and maximum). Plasma concentration versus time profiles for each subject will be presented graphically. The mean plasma concentrations versus scheduled time profiles will be presented graphically by dose.

Scatter plots of total and unbound plasma ticagrelor and TAM versus total and unbound PB2452 plasma concentration will be prepared for all cohorts, as appropriate.

10.1.2. Plasma Pharmacokinetic Parameters

The PK parameters of PB2452, ticagrelor, and TAM will be determined using noncompartmental methods using Phoenix WinNonlin Version 8.0 or higher or SAS® Version 9.4 or higher. For PK analysis, BLQ values will be treated as zero with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing. If consecutive BLQ concentrations are followed by quantifiable concentrations in the terminal phase, those concentrations after BLQ concentrations will be treated as missing. Missing concentrations will be treated as missing from the PK parameter calculation

The following PK parameters, if data permit, will be calculated for total and unbound plasma PB2452 using actual sampling times.

PB2452 PK parameters:

Parameter	Description
C_{max}	Observed maximum plasma concentration
T_{max}	Time to reach the observed maximum plasma concentration
AUC_{0-t}	Area under the plasma concentration versus time curve (AUC) from time 0 to the time of last quantifiable concentration (C_{last}); calculated using the linear-up/ log-down trapezoidal rule
AUC_{0-inf}	AUC from time 0 extrapolated to infinity, calculated as $AUC_{0-t} + C_{last}/ \lambda z$, where C_{last} is the last quantifiable plasma drug concentration and λz is the terminal phase rate constant.
AUC_{0-24}	AUC from time 0 to 24 hours post-dose; calculated using the linear-up/log-down trapezoidal rule
AUC_{0-48}	AUC from time 0 to 48 hours post-dose; calculated using the linear-up/ log-down trapezoidal rule
%AUCextrap	Percentage of AUC_{0-inf} due to extrapolation from the time for the last quantifiable concentration to infinity, calculated as $(AUC_{0-inf} - AUC_{0-t})/AUC_{0-inf}*100$

λz	Terminal phase rate constant, determined by linear regression of the terminal points of the log-linear plasma concentration-time curve. The λz will not be estimated if the terminal phase of the log-concentration-time profile does not exhibit a linear decline phase, or if the regression coefficient (Rsq) is less than 0.8.
Rsq	Regression coefficient for calculation of λz
$t_{1/2}$	Terminal elimination half-life, calculated as $t_{1/2}$= ln(2)/ λz.
CL	Total body clearance, calculated as Dose/$AUC_{0\text{-}inf}$
Vd	Volume of distribution, calculated as CL/λz.

The following PK parameters, as appropriate and when data permit, will be calculated for total and unbound ticagrelor and TAM using actual sampling times:

Ticagrelor/ TAM PK parameters:

Parameter	**Description**
C_{max}	Observed maximum plasma concentration
T_{max}	Time to reach the observed maximum plasma concentration
$AUC_{0\text{-}t}$	AUC from time 0 to the time of last quantifiable concentration (C_{last}); calculated using the linear-up/log-down trapezoidal rule
$AUC_{0\text{-}inf}$	AUC from time 0 extrapolated to infinity, calculated as $AUC_{0\text{-}t}$ + C_{last}/ λz, where C_{last} is the last quantifiable plasma drug concentration and λz is the terminal phase rate constant.
$AUC_{0\text{-}24}$	AUC from time 0 to 24 hours post-dose; calculated using the linear-up/log-down trapezoidal rule
$AUC_{0\text{-}48}$	AUC from time 0 to 48 hours post-dose; calculated using the linear-up/ log-down trapezoidal rule
%AUCextrap	Percentage of $AUC_{0\text{-}inf}$ due to extrapolation from the time for the last quantifiable concentration to infinity, calculated as ($AUC_{0\text{-}inf}$ - $AUC_{0\text{-}t}$)/$AUC_{0\text{-}inf}$*100
λz	Terminal phase rate constant, determined by linear regression of the terminal points of the log-linear plasma concentration-time curve. The λz will not be estimated if the terminal phase of the log-concentration-time profile does not exhibit a linear decline phase, or if the regression coefficient (Rsq) is less than 0.8.
Rsq	Regression coefficient for calculation of λz
$t_{1/2}$	Terminal elimination half-life, calculated as $t_{1/2}$= ln(2)/ λz.

Additional PK parameters may be calculated, as necessary. Pharmacokinetic parameters will be listed by subject and summarized for each dose level using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum), with the exception of %AUCextrap, λz and Rsq, which will be listed only. Geometric means will be reported for AUCs and C_{max}.

10.2. Urine Pharmacokinetics

10.2.1. Urine pharmacokinetic Concentrations

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

For each analyte, urine concentration and volume data will be listed by collection interval for each subject.

10.2.2. Urine Parameters

The following PK parameters for PB2452, ticagrelor and TAM concentrations in urine will be calculated for Day 1 whenever data permit:

Parameter	Description
Ae_{24}	Total amount of drug excreted in urine from time 0 to 24 hours post-dose.
$Ae_{t1\text{-}t2}$	Ae from time t1 to t2 hours where the values of t1 to t2 are 0 to 6, 6 to 12, and 12 to 24 post-dose.
Fe_{24}	Fraction excreted in urine from 0 to 24 hours after dosing (ticagrelor only).
CLr_{24}	Renal clearance, calculated as $Ae_{24}/AUC_{0\text{-}24}$

Additional urine PK parameters may be calculated, as necessary. Urine parameters will be listed by subject and summarized for each dose level using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum).

11. Pharmacodynamics

The PD population will be used for all PD analysis tables and figures, except otherwise noted. All tables and listings for PD will be done for both Part A and Part B of the study, separately.

11.1. Pharmacodynamic Data

Blood samples for PD analysis will be collected from subjects at the following time points: Day -3, before dosing (within 60 minutes prior to 1st ticagrelor dose on Day -2) and again before dosing (within 10 minutes prior to the initiation of the study drug infusion [Hour 0]), and up to 48 hours after the initiation of study drug infusion. Collection time points for each cohort will be specified in a Dosing Memo from Sponsor to PPD prior to initiation of each cohort. The

sampling schedule for a given cohort may differ from that of other cohorts to accommodate various infusion durations that may be examined in the protocol in order to fully characterize the PK/PD profile.

Specific collection times were identical for all 3 cohorts: Day -3, Day -2 (up to 60 minutes prior to 1st ticagrelor dose) and Hour 0 (up to 10 minutes prior to PB2452 infusion), 5 minutes, 0.25, 0.5, 1, 2, 4, 8, 12, 20, 24, 36 and 48 hours after initiation of PB2452 or placebo infusion

Platelet aggregation will be assessed using the VerifyNow, LTA and VASP assays. The results for the VerifyNow assay will be expressed as PRU and %baseline PRU, which will be calculated from the platelet aggregation-time profile for each sampling time point. The results of platelet aggregation from the LTA assay using 5µM ADP and 20µM ADP will be expressed as maximal-extent aggregation (MA), %baseline MA, final-extent aggregation (FA) and %baseline FA, which will be calculated from the platelet aggregation-time profile for each sampling time point. The results of platelet aggregation from the LTA assay using agonists 1.6 mM AA and 15 uM TRAP will be included in SDTM PD dataset only and not included in tables, listings or figures. Similarly, PD results from the VASP assay will be expressed as PRI and %baseline PRI, which will be calculated from the platelet aggregation-time profile for each sampling time point.

Blood drawn for LTA PD assessments will be further processed for testing soluble and surface P-selectin/CD62p after completion of LTA, as per instructions. All LTA timepoints will have samples processed for testing however only the time points as defined below are planned for testing P-selectin. The remaining samples will be stored, as per their stability profiles, for future testing if needed to help elucidate the results. The sampling schedule for P-selectin for subsequent cohorts will be specified in a Dosing Memo provided by Sponsor to PPD prior to initiation of each cohort.

Specific P-selectin collection times were: Day -2 (up to 60 minutes prior to first ticagrelor dose), Hour 0 (up to 10 minutes prior to PB2452 infusion), 12 and 24 hours.

Pharmacodynamic data will be listed by subject and ADA status and summarized for each treatment group for each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Mean PD data versus scheduled time profiles will be presented graphically. Biomarker data (P-selectin) will be listed and summarized by each cohort for each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum).

Scatter plots of PD data versus total and unbound PB2452 plasma concentrations will be prepared for all cohorts, as appropriate. A box plot of PD data versus sampling time point will be prepared for each dose level.

Scatter plots of CrCl versus total and unbound ticagrelor and TAM plasma concentrations will be prepared for all cohorts, as appropriate.

Correlation between VerifyNow assay, LTA assay, and VASP assay will be investigated graphically. Scatter plots of individual subject PRU versus MA (5µM ADP and 20µM ADP),

PRU versus PRI, and MA (5µM ADP and 20µM ADP) versus PRI will be plotted, and the correlation coefficient *r* (Spearman's rank correlation coefficient) and p-value will be displayed.

11.2. 10.2 Pharmacodynamic Parameters

Pharmacodynamic parameters will be calculated using actual timepoints using SAS® Version 9.4 or higher. Missing PD values will be treated as missing for PD parameter calculation.

The following PD parameters will be calculated using %baseline/actual PRU data from the VerifyNow assay.

Day 1 parameters following 5th ticagrelor dose	
APRUmax	Maximal actual PRU
APRUmax4h	Maximal actual PRU within 4 h
PRUmax	Maximal percent of baseline PRU
TPRUmax	Time to maximal actual PRU
TPRU180	Time to 180 or higher actual PRU, calculated as the first observed time point (no extrapolation) when the actual PRU reaches 180 or above
TPRU200	Time to 200 or higher actual PRU, calculated as the first observed time point (no extrapolation) when the actual PRU reaches 200 or above
TPRU220	Time to 220 or higher actual PRU, calculated as the first observed time point (no extrapolation) when the actual PRU reaches 220 or above
TPRU60%	Time to 60% of baseline PRU, calculated as the first observed time point (no extrapolation) when %baseline PRU reaches 60% or above
TPRU80%	Time to 80% of baseline PRU, calculated as the first observed time point (no extrapolation) when %baseline PRU reaches 80% or above
TPRU90%	Time to 90% of baseline PRU, calculated as the first observed time point (no extrapolation) when %baseline PRU reaches 90% or above

The following PD parameters will be calculated using %baseline/actual MA and FA data, as appropriate, from the LTA assay for both the 5µM and 20µM ADP conditions.

Day 1 parameters following 5th ticagrelor dose	
APAmax	Maximal actual platelet aggregation
APAmax4h	Maximal actual platelet aggregation within 4 h
PAmax	Maximal percent of baseline platelet aggregation
TPAmax	Time to maximal actual platelet aggregation
TPA60%	Time to 60% of baseline platelet aggregation, calculated as the first observed time point (no extrapolation) when %baseline platelet aggregation reaches 60% or above
TPA80%	Time to 80% of baseline platelet aggregation, calculated as the first observed time point (no extrapolation) when %baseline platelet aggregation reaches 80% or above

TPA90%	Time to 90% of baseline platelet aggregation, calculated as the first observed time point (no extrapolation) when %baseline platelet aggregation reaches 90% or above

The following PD parameters will be calculated using %baseline/actual PRI data from the VASP assay.

Day 1 parameters following 5th ticagrelor dose	
APRImax	Maximal actual PRI
APRImax4h	Maximal actual PRU within 4 h
PRImax	Maximal percent of baseline PRI
TPRImax	Time to maximal actual PRI
TPRI60%	Time to 60% of baseline PRI, calculated as the first observed time point (no extrapolation) when %baseline PRI reaches 60% or above
TPRI80%	Time to 80% of baseline PRI, calculated as the first observed time point (no extrapolation) when %baseline PRI reaches 80% or above
TPRI90%	Time to 90% of baseline PRI, calculated as the first observed time point (no extrapolation) when %baseline PRI reaches 90% or above

Additional PD parameters may be calculated, as necessary. Pharmacodynamic parameters will be listed by subject and summarized for each cohort using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Number and percent of subjects achieving 60%, 80%, and 90% of reversal in PRU, LTA, and PRI within 30 minutes or 4 h will be summarized.

12. Interim Analysis

There is no interim analysis planned for this study.

13. Changes in the Planned Analysis

There is no change in the SAP compared to the protocol

14. References

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15. Appendices

15.1. Schedule of Study Procedures

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

Plasma ticagrelor/TAM						X	X	X	X	X
Free plasma ticagrelor/TAM						X	X	X	X	X
PK urine sampling***				X		X	X	X		
PD sampling (LTA/PRU/VASP)[k]			X	X		X	X	X		
Biomarkers**					X		X		X	X
Infusion site assessment[l]						X	X	X	X	
Serum immunogenicity			X			X[k]			X	X[m]
Adverse events			X	X	X	X	X	X	X	X
Discharge from clinical site								X[n]		

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

* In successive cohorts in Part A following Cohort 1, if indicated in a Dosing Memo from Sponsor to site, one or more cohorts may also receive a 6th dose of ticagrelor 90 mg, 24 hours after initiation of PB2452 (or placebo) infusion on Day 1. And in successive cohorts in Part B following Cohort 3, if indicated in a Dosing Memo from Sponsor to site, one or more cohorts may also receive a 6th dose of ticagrelor 90 mg, 24 hours after initiation of PB2452 (or placebo) infusion on Day 1.

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

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

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

b=Serum pregnancy test for women of childbearing potential

c=A full physical examination is conducted at Screening, Day -3, and Day 28. Height and BMI calculation are completed at Screening and Day 29 only. Weight is collected at Screening, Day -3, and Day 28.

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

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

f=12-lead ECGs collection time will be communicated in Dosing Memos.

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

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

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

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

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

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

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

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