16.1.9 Documentation of Statistical Methods

This section contains the following document:

Statistical analysis plan version 2.0 dated 12 October 2018

PhaseBio Pharmaceuticals, Inc

PB2452-PT-CL-0001

A Phase 1, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of MEDI2452 (PB2452) With and Without Ticagrelor Pretreatment in Healthy Volunteers

12OCT2018

Statistical Analysis Plan

Final Version 2.0

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List of Abbreviations

ADA	anti-drug antibody
Ae	total amount of drug excreted in urine
AE	adverse event
AUC	area under curve
BID	twice daily
BLQ	below the limit of quantification
BMI	body mass index
CI	confidence interval
CL	total body clearance
CLr	renal clearance
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Event
CV	coefficient of variation
eCRF	electronic case report form
DLT	dose limiting toxicity
ECG	electrocardiogram
EOS	end of study
FA	final-extent of platelet aggregation
IV	intravenous
LTA	light transmittance aggregometry
MA	maximal-extent of platelet aggregation
NAb	neutralizing antibody
PD	pharmacodynamics
PK	pharmacokinetics

PRU	$P2Y_{12}$ reaction units
PT	preferred term
QTcB	Bazett's-corrected QT interval
QTcF	Fridericia-corrected QT interval
Rsq	regression coefficient (R squared)
SAE	serious adverse event
SAS	statistical analysis software
SD	standard deviation
SOC	system organ class
SRC	safety review committee
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{max}	time to reach the maximum plasma concentration
VASP	Vasodilator-stimulated phosphoprotein
V_d	volume of distribution
λz	terminal phase rate constant

1. Introduction

MEDI2452 (PB2452) is a specific and selective neutralizing antibody fragment that binds ticagrelor and AR-C124910XX, the major active circulating ticagrelor metabolite, with high affinity. MEDI2452 (PB2452) is intended to reverse the antiplatelet effects of ticagrelor in patients who experience major bleeding or who require urgent surgery or intervention, serious but rare conditions that represent an unmet medical need.

This is the first-in-human study with MEDI2452 (PB2452) and is designed to provide initial safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) data regarding MEDI2452 (PB2452) for future clinical studies.

This statistical analysis plan (SAP) reflects the protocol amendment 5 dated 03 August, 2018.

2. Objectives

2.1. Primary

The primary objectives of this study are:

- To evaluate the safety and tolerability of single ascending intravenous (IV) doses of MEDI2452 (PB2452) with or without ticagrelor
- To evaluate the effectiveness of single ascending doses of MEDI2452 (PB2452) dose on ticagrelor antiplatelet activity using light transmittance aggregometry (LTA)

2.2. Secondary

The secondary objectives of the study are:

- To determine the PK of ascending doses of IV MEDI2452 (PB2452) in the presence and absence of ticagrelor
- To determine the PK of ticagrelor and its active metabolite AR-C124910XX in the presence and absence of MEDI2452 (PB2452)

- To assess the effectiveness of a single IV MEDI2452 (PB2452) dose in reversing ticagrelor antiplatelet activity by measuring $P2Y_{12}$ reaction units (PRU) with VerifyNow™ $P2Y_{12}$ assay and platelet reactivity index (PRI) with vasodilator stimulated phosphoprotein (VASP) phosphorylation assay by enzyme-linked immunosorbent assay (ELISA)
- To evaluate the PK and PD of restarting a single dose of oral ticagrelor 24 hours after MEDI2452 (PB2452) administration if a sixth dose of ticagrelor is given
- To evaluate the immunogenicity potential of MEDI2452 (PB2452)

2.3. Exploratory

The exploratory objective is to evaluate the effect of MEDI2452 (PB2452) on the PK profile of unbound ticagrelor and unbound AR-C124910XX plasma concentrations.

3. Investigational Plan

This is a Phase 1, first-in-human, randomized, double-blind, placebo-controlled, single ascending dose, sequential group study to evaluate the safety, tolerability, PK, and PD of MEDI2452 (PB2452) with and without ticagrelor pretreatment when administered to healthy male and female subjects. All references to study drug within this statistical analysis plan (SAP) apply to MEDI2452 (PB2452) or matching placebo.

This study will have up to 10 cohorts and up to a total of 68 subjects with either 4 or 8 subjects in each cohort. The starting dose of MEDI2452 (PB2452) will be 100 mg and the planned doses for subsequent cohorts are 300, 1000, 3000, 9000, and 18000 mg. Other intermediate doses may also be tested but will not exceed 1800 mg.

The study will consist of a screening period (Days –45 to –4), check-in/pretreatment (Day -3 to Day -1), an in-house treatment period (Days 1 through 3 [Cohorts 1 through 8] or 4 [Cohorts 9 and 10]), and follow-up visits (Days 4, 7, and 28 [+2 days]). Subjects will receive an IV dose of study drug on Day 1.

On Day 1, subjects who meet all the inclusion criteria and none of the exclusion criteria will be randomly assigned to receive MEDI2452 (PB2452) or placebo in a ratio of 3:1 in all treatment cohorts as described below and as summarized in Table 3-1.

Table 3-1 Summary of Treatment per Cohort

Cohort	Pre-MEDI2452 (PB2452) ticagrelor dosing to steady state (180 mg + 90 mg bid for 5 doses total)	MEDI2452 (PB2452) Dose (mg)	Number of subjects MEDI2452 (PB2452):placebo
1		100	3:1
2		300	3:1
3		1000	3:1
4	180 mg + 90 mg bid	1000	6:2
5	180 mg + 90 mg bid	3000	6:2
6	180 mg + 90 mg bid	9000	6:2
7	180 mg + 90 mg bid	18000	6:2
8	180 mg + 90 mg bid	18000	6:2
9	180 mg + 90 mg bid	18000	3:1 or 6:2*
10	180 mg + 90 mg bid	18000	3:1 or 6:2*

Abbreviations: bid, twice daily.
*Initially the cohort size will be 4 subjects (3:1); if needed for confirmation of PK/PD an additional 4 subjects (3:1) will be randomized in that same cohort.

Cohorts 1 to 3:

For the initial cohort (Cohort 1), 4 healthy subjects will be randomly assigned in a 3:1 ratio of active treatment to placebo (3A:1P) to receive a single 100-mg IV dose of study drug over 30 minutes. For the second cohort (Cohort 2), 4 healthy subjects will be randomly assigned (3A:1P) to receive a single 300-mg IV dose of study drug over 30 minutes. For the third cohort (Cohort 3), 4 healthy subjects will be randomly assigned (3A:1P) to receive a 1000-mg IV dose of study drug over 30 minutes.

Cohorts 4 to 6:

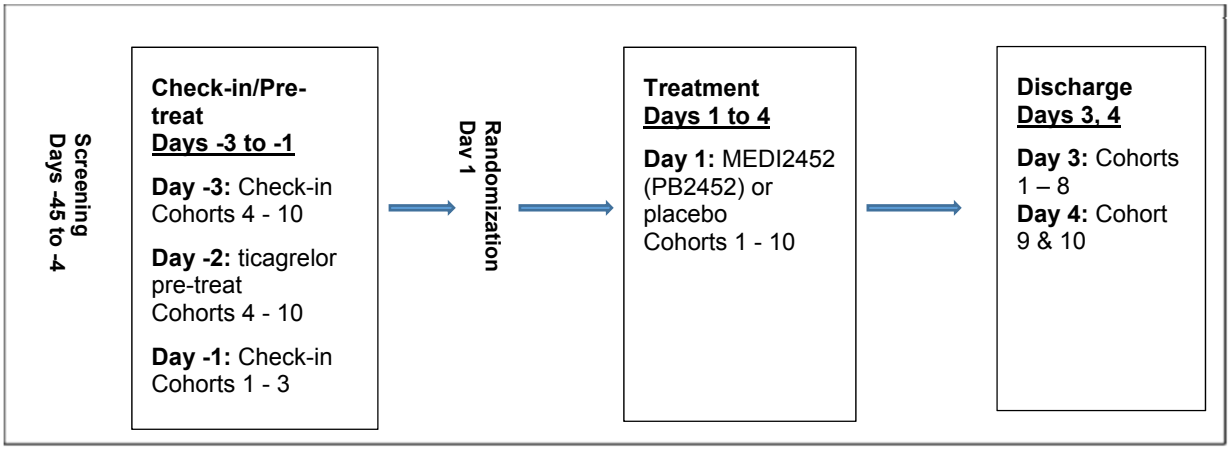
Provided no safety concerns arise in Cohorts 1 through 3, 8 subjects in each of Cohorts 4 through 6 will be randomly assigned in a 3:1 ratio (6A:2P) to receive a single IV dose of study drug simultaneous with the 5th dose of ticagrelor pretreatment. For ticagrelor pretreatment, subjects will receive an oral loading dose of 180-mg ticagrelor in the morning (Day -2), followed by 90-mg ticagrelor orally every 12 hours for 4 additional doses, prior to administration of a single IV dose of study drug simultaneous with the 5th ticagrelor dose (Day 1). Subjects in each of Cohorts 4 through 6 will receive ticagrelor pretreatment, as described above, and a single IV dose of 1000, 3000, or 9000 mg of study drug, respectively, over 30 minutes. Cohorts 4 through 6 will be dosed sequentially following the safety and dose-escalation assessment of each preceding dose cohort.

Cohorts 7 to 10:

For Cohorts 7 to 10, following ticagrelor pretreatment, subjects will be randomly assigned in a 3:1 ratio (3A:1P or 6A:2P) to receive a single IV dose of study drug. The IV infusion of study drug will be initiated 2 hours after the 5th ticagrelor dose. The duration of the infusion will be determined upon analysis of data from prior cohorts, and will range between 30 minutes and 24 hours. Total doses to be administered in these cohorts will be determined based upon analysis of data from prior cohorts, and will be within the range of 9000-18000 mg.

The overall Study design is presented in Figure 3-1.

Figure 3-1 Study Flow Diagram



Schedule of Events is presented in Table 3-2.

Table 3-2 Schedule of Events

Procedure	Screening	Check-in/ Pretreatment			Treatment				Follow-up[a]	EOS[a]
Study Day(s)	**–45 to –4**	**–3**	**-2**	**–1**	**1**	**2**	**3**	**4/FU**	**7**	**28 (+2 days)**
Informed consent	X									
Inclusion/exclusion criteria	X	X[c]		X[d]						
Demographics	X									
Medical history	X									
Urine drug screen (includes cotinine)	X	X[c]		X[d]						
Urine alcohol	X	X[c]		X[d]						
Serum pregnancy test	X	X[c]		X[d]						X
Serology testing	X									
Admission to clinic		X[c]		X[d]						
Physical examination[e]	X	X[c]		X[d]			X		X	X
Vital sign measurements[f]	X	X[c]		X[d]	X	X	X	X	X	X
12-lead electrocardiogram[g]	X				X	X	X		X	X
Cardiac telemetry monitoring[h]		X		X	X	X	X			
Clinical laboratory testing	X	X[c]		X[d]			X		X	X
Randomization					X					
Drug administration										
Ticagrelor			X[i]	X[i]	X[i]					
MEDI2452 (PB2452)/Placebo[k]					X					
PK blood sampling[l]										
Plasma MEDI2452 (PB2452)[l]					X	X	X	X[aa]	X	X
Plasma ticagrelor/AR-C124910XX[l]					X	X	X[x]	X		
Free plasma ticagrelor/AR-C124910XX[l]					X	X	X[x]	X		
PK urine sampling[q]			X		X	X	X			
PD sampling (LTA/PRU/VASP)[r]			X		X	X	X			
Infusion site assessment[t]					X	X	X	X	X	
Serum immunogenicity		X[c]		X[d]					X	X[w]
Adverse events		X[c]	X[c]	X	X	X	X	X	X	X
Discharge from clinic							X[u]	X		

Abbreviations: BID, twice daily; EOS, end-of-study; FU, follow-up; LTA, light transmittance aggregometry; PD, pharmacodynamic; PK, pharmacokinetic; PRU, $P2Y_{12}$ reaction units; VASP, vasodilator stimulated phosphoprotein.

[a] Follow-up visits will be conducted as outpatient.

[c] Cohorts 4 through 10 only.

[d] Cohorts 1 through 3 only.

[e] Full physical examination (including height, weight, and body mass index calculation) will be performed at screening and Day 28 only. Brief physical examinations will be performed at all other time points.

[f] Vital sign measurements (systolic and diastolic blood pressures, oral body temperature, respiratory rate, and heart rate) will be collected at screening, check-in, before dosing (30 minutes prior to the initiation of the study drug infusion) and at 0.5, 0.75, 1, 2, 4, 8, and 24 hours after the initiation of the study drug infusion, and at 30, 36, 42, and 48 hours after the initiation of the study drug infusion and on Days 4, 7, and 28. Starting with the 1 hour after initiation of the study drug timepoint for the collection of vitals a ±5 minute window will be permitted. During the initial 30 minutes of study drug infusion, systolic and diastolic blood pressures and heart rate will be collected every 5 minutes.

[g] Electrocardiograms will be obtained in triplicate for all subjects at screening, before dosing (within 1 hour prior to the initiation of the study drug infusion) and at 1 (±10 minutes), 4 (±10 minutes), 5 (±10 minutes), 24 (±30 minutes), and 48 hours (±30 minutes) after the initiation of the study drug infusion and on Days 7 and 28.

[h] Cardiac telemetry monitoring will begin on Day -1 approximately 12 hours prior to the initiation of the study drug infusion (Hour 0) and will continue until the subject is discharged from the clinical site for Cohorts 1-10. For Cohorts 4-10, cardiac telemetry monitoring will begin on Day-3 (check in) approximately 12 hours prior to the first dose of Ticagrelor and will be removed once dosed with the initial dose of Ticagrelor.

[i] For Cohorts 4 through 6 only: Beginning in the morning on Day –2, ticagrelor will be administered as a single oral dose of 180 mg, followed by 90 mg every 12 hours for 4 additional doses through Hour 0 (i.e., 5 total doses of ticagrelor). For Cohorts 7 through 10 only: Beginning in the morning on Day –2, ticagrelor will be administered as a single oral dose of 180 mg, followed by 90 mg every 12 hours for 4 additional doses through to Hour -2 (two hours prior to dosing at Hour 0) (i.e., 5 total doses of ticagrelor).

[k] For all cohorts: MEDI2452 (PB2452) or placebo will be administered at Hour 0 of Day 1.

[l] For timing of pharmacokinetic plasma samples for each cohort, refer to section 3.5.1 of the protocol.

[q] For Cohorts 4 through 10 only: Urine samples for PK analysis of ticagrelor and AR-C124910XX concentrations will be collected before dosing (within 60 minutes prior to the first ticagrelor dose on Day -2), and 0 to 6, 6 to 12, 12 to 24 and 24 to 48 hours after the initiation of the study drug infusion.

[r] For timing of pharmacodynamic samples for each cohort, refer to section 3.5.2 of the protocol.

[t] Infusion site assessments will be performed for all subjects within 15 minutes prior to the initiation of the study drug infusion (Hour 0), and at 1, 3, 24, 48, and 72 hours after initiation of the study drug infusion and on Day 7.

[u] For Cohorts 1 through 8 only.

[w] Subject may be required to return to collect additional follow-up samples should the sample collected at day 28 test positive for anti-drug antibody development. These visits may be done approximately 3 months after their final visit and approximately every 6 months thereafter or until their levels return to baseline.

[x] For Cohorts 4-10: Blood samples for determination of plasma ticagrelor and AR-C124910XX AND unbound plasma ticagrelor and AR-C124910XX will be collected 48 hours after the initiation of the study drug infusion.

[aa] Omitted for Cohorts 7-10.

Note: Footnotes b, j, m, n, o, p, s, v, y, z are intentionally omitted.

4. General Statistical Considerations

All statistical analyses will be conducted using statistical analysis system SAS® software (SAS Institute, Cary, NC USA) Version 9.3 or higher (version to be delineated in the clinical study report [CSR]). All tables and data listings will appear in landscape format employing Courier New 9-point font.

4.1. General Data Presentation Rules

All data will be provided in individual by-subject listings.

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

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

Unless otherwise noted, the following treatment groups will be used in summaries:

- 100 mg PB2452 (C1)
- 300 mg PB2452 (C2)
- 1000 mg PB2452 (C3)
- Placebo C1-C3
- 1000 mg PB2452 (C4)
- 3000 mg PB2452 (C5)
- 9000 mg PB2452 (C6)
- Placebo C4-C6
- 18000 mg PB2452 (C7)
- 18000 mg PB2452 (C8)
- 18000 mg PB2452 (C9)

- 18000 mg PB2452 (C10)
- Placebo C7-C10
- All Placebo (for safety summaries only)
- All PB2452 (for safety summaries only)
- All subjects

where ‘C’ means ‘Cohort’.

Demographic data, baseline characteristics, adverse events (AEs), laboratory tests, vital signs, 12-lead electrocardiogram (ECG) measurements, and subject disposition will be summarized descriptively.

Unless otherwise noted, the summary of the continuous variables will include the number of subjects with non-missing data (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized descriptively by their counts and associated percentages. Percentages will be calculated using the number of subjects within a summary group as the denominator.

Minimum and maximum values will be presented as the same precision as the original value. Means and medians will be presented as 1 decimal place greater than the precision of the original value. Standard deviations will be presented as 2 decimal places greater than the precision of the original value. Percentages for summarizing categorical data will be presented with 1 decimal place. If the percentage value is less than 0.1, then "<0.1" will be displayed.

Unless specified otherwise, baseline for safety analyses is defined as the last non-missing measurement (including repeated and unscheduled measurements) prior to the first study drug administration; baseline for PD analyses is defined as the last non-missing measurement (including repeated and unscheduled measurements) prior to the first ticagrelor administration.

Listings will be sorted by treatment group and subject identifier.

4.2. Sample Size

The sample size (N) of up to 68 for this study is based on clinical and practical considerations and not on a formal statistical power calculation. The sample size is considered sufficient to adequately assess the safety, PK, and PD profiles of MEDI2452 (PB2452) and the PK and PD profiles of ticagrelor.

4.3. Randomization, Stratification, and Blinding

Randomization to MEDI2452 (PB2452) or placebo within each one of the ten cohorts will be based on a randomization schedule prepared by PPD before the start of the study using SAS® software. The randomization scheme within each cohort is specified in Table 3-1. There will be no stratification factors in the randomization.

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 dosage forms of similar appearance once prepared. To maintain the blind, only designated pharmacy staff at the clinical site will have access to the randomization code and will prepare each dose for each subject. The PK and PD samples will be shipped to the designated laboratories who are only responsible for analyzing the PK and PD samples and will not be involved in any other study activities. In order to prepare preliminary summaries of safety, PK, and/or PD data as needed to make timely decisions regarding adjustment of study procedures, dosing regimens, or potentially early termination of the study, certain designated staff at PhaseBio and PPD who are not involved in the study design or conduct may be unblinded during the conduct of the study (study director, a single biostatistician, bioanalytical scientist, and programming team) before data is more generally unblinded. These summaries will not reveal individual subjects' treatment assignments. All other members of PhaseBio research and development and members from PPD will remain blinded. Access to the randomization code will be strictly controlled according to PPD and PhaseBio standard operating procedures.

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

4.4. Breaking the Blind

A subject may be unblinded in the event of a dose limiting toxicity (DLT), serious AE (SAE), or other event, or if there is a medical emergency where the identity of the drug must be known to properly treat a subject. A cohort may be unblinded to determine if dose escalation to the next dose level will terminate. If a subject becomes seriously ill during the study, the blind will be broken only if knowledge of the administered study drug will affect that subject's treatment options. In the event of a medical emergency requiring identification of the study drug administered to an individual subject, the investigator will make every attempt to contact the medical monitor to explain the need for opening the code within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

4.5. 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 DLT may be replaced. Any replacement subject will be assigned to receive the same treatment as the subject he or she is replacing.

4.6. Repeated/Unscheduled Measurements

For safety summary tables summarized by time point, excluding baseline, if there are repeated measurements for a subject at a scheduled time point, the original scheduled measurement at that time point will be used in the summary tables.

Unscheduled results, i.e. results that are not from a scheduled event or repeated measurements for a scheduled event, will not be included in the summary tables except for determining baseline, but will be presented in data listings.

4.7. Handling of Missing Data

Subjects with missing data for some summary statistic will not be included in the calculation of that statistic but are eligible for inclusion in any other summary statistic for which they provide data. For the purpose of determining inclusion of AEs in 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.

4.8. Analysis Populations

The Randomized population includes all subjects who are randomized.

The Safety population includes all subjects who receive any amount of study drug.

The PK population includes subjects who receive at least 1 dose of study drug and have at least 1 measurable PK concentration.

The PD population includes subjects who receive at least 1 dose of ticagrelor and have at least 1 measurable post dose LTA value.

5. Subject Disposition

Screen failures will be listed together with screening date and reason for failure.

Subject disposition data including screening date, randomization information, reasons for subjects excluded from the analysis populations, and study completion will be presented in data listings. The frequency and percentage of subjects who completed and discontinued from the study together with reason for premature withdrawal, and subjects who completed and discontinued the study drug together with reason for not completing the study drug will be summarized for the randomized subjects by treatment group and overall. Subjects included in each analysis population will be summarized for each treatment group and overall.

5.1. Protocol Deviations and Eligibility Criteria Deviations

Protocol deviations will be listed. Eligibility with regards to inclusion and exclusion criteria will be listed.

6. Demographics and Baseline Characteristics

6.1. Demographics

Demographic information will be presented in a listing and summarized in a table. Descriptive statistics will be calculated for age (years, calculated as the integer part of [date of informed consent - date of birth]/365.25), screening weight, height, and body mass index (BMI). Frequency counts and percentages will be tabulated for sex, race, and ethnicity. The summaries will be presented by treatment groups (as defined in Section 4.1) and overall for the Safety population.

6.2. Medical History

The medical history findings will be presented in a listing.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

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

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.

Prior and concomitant medications will be coded using the latest version of the World Health Organization Drug Dictionary (version March 2018 or later) and presented in a listing.

7.2. Medical and Surgical Procedures

Medical and surgical procedures will be presented in a listing.

7.3. Study Treatments

The dosing regimens of study drugs in each cohort are as follows:

- Cohort 1: single 30-minute IV infusion of 100 mg MEDI2452 (PB2452) or matching placebo in the morning on Day 1
- Cohort 2: single 30-minute IV infusion of 300 mg MEDI2452 (PB2452) or matching placebo in the morning on Day 1
- Cohort 3: single 30-minute IV infusion of 1000 mg MEDI2452 (PB2452) or matching placebo in the morning on Day 1
- Cohort 4: simultaneous with the 5th ticagrelor dose, a single 30-minute IV infusion of 1000 mg MEDI2452 (PB2452) or matching placebo on Day 1
- Cohort 5: simultaneous with the 5th ticagrelor dose, a single 30-minute IV infusion of 3000 mg MEDI2452 (PB2452) or matching placebo on Day 1
- Cohort 6: simultaneous with the 5th ticagrelor dose, a single 30-minute IV infusion of 9000 mg MEDI2452 (PB2452) or matching placebo on Day 1

- Cohort 7: 2 hours following the 5th ticagrelor dose, a single IV infusion of 18000 mg MEDI2452 (PB2452) or matching placebo on Day 1. The single IV infusion of 18000 mg MEDI2452 (PB2452) or matching placebo will be delivered as a 3000 mg loading dose (41.7 mL) in the first 5 minutes at a rate of 500 mL/hour, followed by a 15000 mg maintenance dose (208.3 mL) delivered over the remaining 7 hours and 55 minutes at a rate of 26.3 mL/hour. The final volume is 250 mL (Memo Re: PB2452-PT-CL-0001 Cohort 7 Dosing Regimen).
- Cohort 8: 2 hours following the 5th ticagrelor dose, a single IV infusion of 18000 mg MEDI2452 (PB2452) or matching placebo on Day 1. The single IV infusion of 18000 mg MEDI2452 (PB2452) or matching placebo will be delivered as a 6000 mg loading dose (83.3 mL) in the first 15 minutes at a rate of 333 mL/hour, followed by a 6000 mg dose (83.3 mL) over the next 3 hours at a rate of 27.7 mL/hour, and followed by a 6000 mg dose (83.4 mL) over the remaining 8 hours and 45 minutes at a rate of 9.53 mL/hour. The final volume is 250 mL (Memo Re: PB2452-PT-CL-0001 Cohort 8 Dosing Regimen).
- Cohorts 9 and 10: 2 hours following the 5th ticagrelor dose, a single IV infusion of 18000 mg MEDI2452 (PB2452) or matching placebo on Day 1. The single IV infusion of 18000 mg MEDI2452 (PB2452) or matching placebo will be delivered as a 6000 mg loading dose (83.3 mL) in the first 15 minutes at a rate of 333 mL/hour, followed by a 6000 mg dose (83.3 mL) over the next 4 hours at a rate of 20.8 mL/hour, and followed by a 6000 mg dose (83.4 mL) over the remaining 12 hours and 5 minutes at a rate of 6.9 mL/hour. The final volume is 250 mL (Memo Re: PB2452-PT-CL-0001 Cohorts 9 and 10 Dosing Regimens).

Study drug administration data will be presented in a listing.

8. Safety Analysis

Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), vital

sign measurements (systolic and diastolic blood pressures, oral body temperature, respiratory rate, and heart rate), ECG results, cardiac telemetry, and physical examination findings.

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 considered drug-related.

A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in intensity or frequency after the exposure. For analysis purposes, TEAEs are the events with onset on or after initiation of study drug.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDra), version 21.0 or higher, by system organ class (SOC) and preferred term (PT).

All summary tables except from the overall summary table will be based on TEAEs. 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 treatment groups as defined in Section 4.1. Percentages will be based upon the number of subjects in the safety population overall and within each treatment group.

8.1.1. Incidence of Adverse Events

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 presenting the number of events and percentage of subjects with:

- 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 death

The definition of DLT is defined in Section 8.1.6. For the purpose of above summary, a study-drug-related or ticagrelor-related AE is an AE with definite, probable, possible, or missing relationship to the study drug or ticagrelor respectively on eCRF.

8.1.2. 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 with at least 2 different non-missing severities will be counted only once using the most severe AE.

The Common Terminology Criteria for Adverse Event (CTCAE) v5 grading scale will be used by the SRC to assess all infusion-related reactions for the purposes of determining whether premedication to mitigate future potential infusion-related reactions is required for subsequent study subjects. Details of infusion-related reactions are provided in Section 8.1.5 Additionally, CTCAE v5 will be used by the SRC to assess all AEs and laboratory

abnormalities for the purposes of determining whether a DLT and/or stopping criteria have been reached. Details of the definition of DLT are provided in Section 8.1.6.

8.1.3. Relationship of Adverse Events to Study Drug

The relationship of AE to study drug and ticagrelor (if applicable) will be classified by the Investigator as unrelated, possible, probable, and definite. TEAEs will be summarized by SOC, PT, relationship to PB2452 and ticagrelor (if applicable), including category 'Missing', and treatment group. 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.

8.1.4. Adverse Events Leading to Early Discontinuation

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

8.1.5. Infusion Site Assessments

The infusion site will be examined by the investigator or designee for pain, tenderness, erythema/redness, and induration/swelling at Day 1 (within 15 minutes prior to the initiation of the MEDI2452 [PB2452] infusion [Hour 0], and at 1, 3 hours after initiation of the MEDI2452 [PB2452] infusion), at Day 2, Day 3, Day 4 and Day 7.

The infusion site assessments will not be recorded in the database and will only be kept in the source documents. Any infusion-related reaction will be documented as an AE for each individual symptom. The individual symptom will be noted in the AE comments data field. Assessment of severity of the infusion-related reactions be classified as mild, moderate, or severe, and will also be assessed according to CTCAE v5 grading scale and should be followed until resolution.

8.1.6. Dose Limiting Toxicities

The SRC will review all AEs and all laboratory and ECG abnormalities according to CTCAE v5 to determine whether a DLT has been identified in a subject who is confirmed to have received MEDI2452 (PB2452). If the SRC determines that an AE is related to

administration of ticagrelor (Cohorts 4-10), or another confirmed cause, the AE will not be considered a DLT.

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

Definitions for DLT are described below:

1. A DLT is defined as any AE that is assessed as grade 2 or higher based on the CTCAE v5 grading scale and has occurred in a subject confirmed to have received MEDI2452 (PB2452).
2. A DLT is defined as any grade 2 or higher laboratory abnormality (outside the clinical laboratory normal reference range) that occurs in a subject confirmed to have received MEDI2452 (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].
3. A DLT is defined as any TEAE that leads to study withdrawal of a subject confirmed to have received MEDI2452 (PB2452).

8.1.7. Serious Adverse Events

An AE or suspected adverse reaction is considered a 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 and suspected unexpected serious adverse reactions including deaths will be presented in a data listing.

8.2. Clinical Laboratory Evaluations

Blood samples for laboratory safety tests (hematology, coagulation and serum chemistry) and urine samples for urinalysis will be collected at Screening, Day -3 (Cohorts 4 through 10 only), Day -1 (Cohorts 1 through 3 only), Day 3 (Cohorts 1 through 8 and 10 only), Day 4 (Cohort 9 only if a 6^{th} dose of ticagrelor was given on Day 2), Day 7, and Day 28/EOS.

Serology testing will be performed at Screening.

Urine drug, alcohol screen, and Hemoglobin A1C for diabetic patients, will be performed at Screening, Day -3 (Cohorts 4 through 10 only), and Day -1 (Cohorts 1 through 3 only).

Serum pregnancy test for female subjects will be performed at Screening, Day -3 (Cohorts 4 through 10 only), Day -1 (Cohorts 1 through 3 only), and Day 28/EOS.

Stool occult blood test will be performed at Screening for Cohort 10 only.

The following clinical laboratory assessments will be performed:

Hematology: Hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, red blood cell count, and total and differential leukocyte count

Coagulation: Activated partial thromboplastin time, international normalized ratio, partial thromboplastin time, and prothrombin time

Serum Chemistry: Alanine aminotransferase, albumin, alkaline phosphatase, aspartate aminotransferase, bicarbonate, bilirubin (total and direct), blood urea nitrogen, calcium, chloride, cholesterol (total, high-density lipoprotein, and calculated low-density lipoprotein), creatine phosphokinase, creatinine, gamma-glutamyltransferase, globulin, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, thyroid stimulating hormone (Screening only), total protein, triglycerides, and uric acid

Urinalysis: Appearance, bilirubin, color, glucose, ketones, leukocyte esterase, reflex microscopy (performed if dipstick is positive for protein or blood value of 1+ or greater; and includes bacteria, casts, crystals, epithelial cells, red blood cells, and white blood cells), nitrites, occult blood, pH, protein, specific gravity, turbidity, and urobilinogen

Serology: Hepatitis B surface antigen, hepatitis C virus antibody, and human immunodeficiency virus types 1 and 2 antibodies

Other analyses: Urine drug screen (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine, methylenedioxymethamphetamine, opiates, phencyclidine, propoxyphene, and tetrahydrocannabinol), urine alcohol. Follicle-stimulating hormone and serum pregnancy test (human chorionic gonadotropin) will be collected for female subjects.

The investigator will determine whether any of the abnormally high or low results are clinically significant or not clinically significant.

The hematology and coagulation, 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. Refer to Section 4.1 for the definition of baseline for this summary. 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.

8.3. Vital Signs

Vital signs will be measured at Screening, Day -3 (Cohorts 4 through 10 only), Day -1 (Cohorts 1 through 3 only), Day 1 (30 minutes prior to the initiation of the study drug infusion, and at 0.5, 0.75, 1, 2, 4, 8 hours after initiation of the study drug infusion), Day 2 (at 24, 30, and 36 hours after initiation of the study drug infusion), Day 3 (at 42 and 48 hours after the initiation of the study drug infusion), Day 4, Day 7, Day 28/EOS. Vital sign

measurements will include systolic and diastolic blood pressures, oral body temperature, respiratory rate, and heart rate.

During the initial 30 minutes of study drug infusion, systolic and diastolic blood pressures and heart rate will be collected every 5 minutes.

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.

8.4. Twelve-Lead Electrocardiogram and Telemetry Monitoring

Triplicate 12-lead ECGs will be obtained after the subject has been in the supine position for at least 10 minutes at Screening, within 1 hour prior to the initiation of the study drug infusion, and at 1 hour, 4 hours, 5 hours, 24 hours, and 48 hours after the initiation of the study drug infusion, and on Day 7 and Day 28/EOS and as indicated by AEs or telemetry findings. Electrocardiogram assessments will include comments on whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST-segment, T-Wave, and U-Wave abnormalities. In addition, measurements of the following intervals will be measured and reported: RR interval, PR interval, QRS width, and Fridericia-corrected QT interval (QTcF). The investigator will determine whether any of the 12-lead ECG results are clinically significant or not.

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 based on the International Council for Harmonisation (ICH) harmonized tripartite guideline E14. 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 using the average values of the triplicate ECG assessments at each timepoint. Baseline is defined as the last non-missing average value prior to the first study drug administration.

Cardiac telemetry will be collected starting on Day -1 approximately 12 hours prior to the initiation of the study drug infusion (Hour 0) and will continue until subject is discharged from the clinical site for Cohorts 1-9. Cohort 10 subjects will discontinue cardiac telemetry monitoring on Day 3. For Cohorts 4-10, cardiac telemetry monitoring will begin on Day -3 (check in) approximately 12 hours prior to the first dose of Ticagrelor and will be removed once dosed with Ticagrelor. Telemetry assessment results will be listed.

8.5. Physical Examination and Physical Measurements

Full physical examination (including height, weight, and BMI calculation, assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities) will be performed at screening and Day 28 only. Brief physical examinations will include assessment of skin (including any signs for cutaneous erythema), lungs, cardiovascular system, and abdomen (liver, spleen) and will be performed at Day -3 (Cohorts 4 through 10 only), Day -1 (Cohorts 1 through 3 only), 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 examination data will be listed. Screening height, weight and BMI will be summarized together with demographics variables.

9. Immunogenicity Analysis

Immunogenicity (antibody) samples will be screened for the presence of binding anti-drug antibody (ADA) on Day -3 (Cohorts 4 through 10 only), Day -1 (Cohorts 1 through 3 only), Day 7, and Day 28/EOS. A subject testing positive for ADA at the final planned visit (Day 28) will be asked to return for follow-up sampling approximately 3 months after their final visit and approximately every 6 months thereafter until these no longer test positive or until levels return to a pre-dose 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 (NAb) results may be listed and summarized in the clinical study report if the assay is available.

10. Pharmacokinetic Analysis

The PK population will be used for all PK analysis tables and figures.

10.1. Plasma Pharmacokinetics

10.1.1. Plasma Pharmacokinetics Concentration

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. Since ticagrelor is not administered to cohort 1-3 subjects, only unbound PB2452 concentration data will be collected for cohort 1-3 subjects. Specific collection times for each cohort relative to the initiation of the study drug (PB2452 or placebo) infusion on Day 1 are listed in the table below:

Summary of Pharmacokinetic Assessments for PB2452	
Cohorts 1-6	-10 minutes, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours, and 7 and 28 days
Cohorts 7-8	-10 minutes 5 minutes and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 8.25, 8.5, 9, 10, 11, 12, 16, 20, 24, 32, and 48 hours, and 7 and 28 days
Cohorts 9-10	-10 minutes, 5 minutes, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, 16, 20, 24, 28, 32, 36, 48 hours, 7 and 28 days

Plasma samples for determining total and unbound concentrations of ticagrelor and its active metabolite AR-C124910XX, will be collected from subjects in Cohorts 4 through 10 at the following timepoints: before dosing (within 10 minutes prior to the initiation of the study drug infusion [Hour 0]), and up to 48 hours following the initiation of study drug infusion on Day 1. Of note, subjects in Cohorts 4-6 will be administered the 5th ticagrelor dose and study drug infusion simultaneously, whereas subjects in Cohorts 7-10 will be administered the 5th ticagrelor dose two hours before the study drug infusion initiation on Day 1.

Specific collection times for each cohort relative to the initiation of the study drug (PB2452 or placebo) infusion are listed in the table below:

Summary of Pharmacokinetic Assessments for Ticagrelor and Active Metabolite AR-C124910XX	
Cohorts 4-6	-10 minutes and 0.5, 1, 2, 3, 6, 12, 24 and 48 hours
Cohorts 7-8	-10 minutes, 5 minutes and 0.25, 0.5, 1, 2, 3, 6, 8, 10, 12, 14, 16, 20, 24, 32 and 48 hours
Cohorts 9-10	-10 minutes, 5 minutes, 0.25, 0.5, 1, 2, 3, 6, 8, 12, 14, 16, 20, 24, 28, 36 and 48 hours

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, 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 by dose will be presented graphically.

Scatter plots of total and unbound plasma ticagrelor and AR-C124910XX 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 AR-C124910XX will be determined using noncompartmental methods using Phoenix WinNonlin Version 6.4 or higher or SAS® Version 9.3 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 calculations.

The following PK parameters, if data permits, 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 Clast is the last quantifiable plasma drug concentration and λz is the terminal phase rate constant.
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 $t_{1/2}= \ln(2)/ \lambda z$.
CL	Total body clearance, calculated as $Dose/AUC_{0-inf}$
V_d	Volume of distribution, calculated as $CL/\lambda z$.

The following PK parameters, as appropriate and when data permit, will be calculated for ticagrelor and AR-C124910XX (total and unbound plasma) using actual sampling times:

Ticagrelor/ AR-C124910XX PK parameters:

Parameter	**Description**
C_{max}	Observed maximum plasma concentration
T_{max}	Time to reach the observed maximum plasma concentration
AUC_{0-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-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_{0-48}	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 $t_{1/2}= \ln(2)/ \lambda z$.

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}.

10.1.3. Plasma Pharmacokinetic Parameters Analysis

Dose proportionality will be tested using the power regression model for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} of total and unbound PB2452 in Cohorts 4, 5, and 6.

A power model will be fit to describe the relationship between Y (C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$) and X (dose) using the least-squares linear regression model [$\ln(Y) = \ln(\alpha) + \beta \ln(X)$, which is the logarithmic form of $Y = \alpha X^{\beta}$]. From each model, the intercept of regression line [$\ln(\alpha)$] and the slope of the regression line β will be presented along with the 90% confidence interval (CI) of the slope. This model will be fit for total and unbound PB2452 in Cohorts 4, 5, and 6. The dose proportionality will be declared when the 90% CI for β lies entirely within the critical region,

$$\left(1 + \frac{\ln(0.5)}{\ln(r)}, 1 + \frac{\ln(2.0)}{\ln(r)}\right)$$

where r is the ratio of the highest and the lowest dose included in the power model.

10.2. Urine Pharmacokinetics

10.2.1. Urine pharmacokinetic Concentrations

Pooled urine samples to assess urine ticagrelor and AR-C124910XX concentrations will be collected from subjects in Cohorts 4 through 10 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, 12 to 24, and 24 to 48 hours after the initiation of the study drug infusion.

Urine concentration data will be listed by collection interval for each subject.

10.2.2. Urine Parameters

The following PK parameters for ticagrelor and AR-C124910XX concentrations in urine will be calculated whenever data permits:

Parameter	Description
Ae_{48}	Total amount of drug excreted in urine from time 0 to 48 hours
$Ae_{t1\text{-}t2}$	Ae from time t1 to t2 hours where the values of t1 to t2 are 0 to 6, 6 to 12, 12 to 24, and 24 to 48
Fe_{48}	Fraction excreted in urine from 0 to 48 hours after dosing
CLr_{48}	Renal clearance, calculated as $Ae_{48}/AUC_{0\text{-}48}$

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. Pharmacodynamic Analysis

The PD population will be used for all PD analysis tables and figures, except otherwise noted.

11.1. Pharmacodynamic Data

Blood samples for PD analysis will be collected from subjects in Cohorts 4 through 10 at the following time points: 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. Specific collection times are listed in the table below:

Summary of Pharmacodynamic Assessments	
Cohorts 4-6	Day -2 (60 minutes prior to 1st ticagrelor dose) and Day 1 (-10 minutes, 0.5, 1, 2, 3, 6, 12, 24 and 48 hours)
Cohorts 7-8	Day -2 (60 minutes prior to first 1st dose) and Day 1 (-10 minutes, 5 minutes and 0.25, 0.5, 1, 2, 3, 6, 8, 10, 12, 16, 20, 24 and 48 hours)
Cohort 9-10	Day -2 (60 minutes prior to first ticagrelor dose) and Day 1 (-10 minutes, 5 minutes, 0.25, 0.5, 1, 2, 3, 6, 8, 12, 16, 20, 24, 28, 36 and 48 hours)

Platelet aggregation will be assessed using the LTA, VerifyNow, and VASP assays. 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 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. 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. PD data will be listed by subject with ADA status and summarized for each treatment group for each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). A 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.

Mean PD data versus scheduled time profiles will be presented graphically.

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.

Correlation between LTA assay, VerifyNow assay and VASP assay will be investigated graphically. Scatter plots of individual subject MA versus PRU (5µM ADP and 20µM ADP), MA versus PRI (5µM ADP and 20µM ADP), and PRU versus PRI will be plotted, and the correlation coefficient *r* (Spearman's rank correlation coefficient) and *p*-value will be displayed.

11.2. Pharmacodynamic Parameters

Pharmacodynamic parameters will be calculated using actual timepoints using SAS® Version 9.3 or higher. Missing PD values will be treated as missing for PD parameter calculation.

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.

Parameters following study drug infusion:	
APA_{max}	Maximal actual platelet aggregation
PA_{max}	Maximal percent of baseline platelet aggregation
TPA_{max}	Time to maximal actual platelet aggregation
$TPA_{60\%}$	Time to 60% of baseline platelet aggregation, calculated as the first time point when %baseline platelet aggregation reaches 60% or above.
$TPA_{80\%}$	Time to 80% of baseline platelet aggregation, calculated as the first time point when %baseline platelet aggregation reaches 80% or above
$TPA_{90\%}$	Time to 90% of baseline platelet aggregation, calculated as the first time point when %baseline platelet aggregation reaches 90% or above

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

Parameters following study drug infusion:	
PRU_{max}	Maximal actual PRU
$TPRU_{max}$	Time to maximal actual PRU
$TPRU_{200}$	Time to 200 or higher PRU, calculated as the first time point when the actual PRU reaches 200 or above
$TPRU_{60\%}$	Time to 60% of baseline PRU, calculated as the first time point when %baseline PRU reaches 60% or above
$TPRU_{80\%}$	Time to 80% of baseline PRU, calculated as the first time point when %baseline PRU reaches 80% or above
$TPRU_{90\%}$	Time to 90% of baseline PRU, calculated as the first time point when %baseline PRU reaches 90% or above

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

Parameters following study drug infusion:	
$APRI_{max}$	Maximal actual PRI
PRI_{max}	Maximal percent of baseline PRI
$TPRI_{max}$	Time to maximal actual PRI
$TPRI_{60\%}$	Time to 60% of baseline PRI, calculated as the first time point when %baseline PRI reaches 60% or above
$TPRI_{80\%}$	Time to 80% of baseline PRI, calculated as the first time point when %baseline PRI reaches 80% or above
$TPRI_{90\%}$	Time to 90% of baseline PRI, calculated as the first time point 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).

12. Changes in the Planned Analysis

For ECG measurements, QTcB interval will be calculated and a summary table for QTcF and QTcB values outside of pre-defined criteria will be produced.

13. Interim Analysis

There's no planned formal interim analysis for this study. Blinded safety data review for each dose cohort will be performed before dosing in the next cohort is allowed (Section 3.4.2.1 of the protocol).

Interim noncompartmental analyses of PK data and/or PK/PD modeling will be performed as needed.

14. Reference

Memo Re: PB2452-PT-CL-0001 Cohort 7 Dosing Regimen. To: Lu Ann Bundrant, MD, Principal Investigator, PPD Early Development Services; Tiffany Reyes, Associate Director, Project Management, PPD Early Development. CC: Casey Davis, Project Manager, PPD Early Development. From: JoAnn Malatesta, Director, Clinical Operations. Date: July 3, 2018.

Memo Re: PB2452-PT-CL-0001 Cohort 8 Dosing Regimen. To: Lu Ann Bundrant, MD, Principal Investigator, PPD Early Development Services; Tiffany Reyes, Associate Director, Project Management, PPD Early Development. CC: Casey Davis, Project Manager, PPD Early Development. From: JoAnn Malatesta, Director, Clinical Operations. Date: July 25, 2018.

Memo Re: PB2452-PT-CL-0001 Cohort9 and 10 Dosing Regimens. To: Lu Ann Bundrant, MD, Principal Investigator, PPD Early Development Services; Tiffany Reyes, Associate Director, Project Management, PPD Early Development. CC: Casey Davis, Project Manager, PPD Early Development. From: Janet Rush, MD, Sponsor Medical Consultant. Date: August 8, 2018.

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