STATISTICAL ANALYSIS PLAN

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SPONSOR:	PhaseBio Pharmaceuticals Inc. 1 Great Valley parkway, Suite 30, Malvern, PA, USA 19355
STUDY TITLE:	A Phase 2B, randomized, double-blind, multicenter, placebo-controlled study to evaluate the efficacy of PB2452 in reversing the antiplatelet effects of ticagrelor in subjects aged 50 to 80 years old
PHASE OF STUDY:	Phase 2
PROTOCOL NUMBER:	PB2452-PT-CL-0003
PROTOCOL VERSION/DATE:	Protocol Amendment 1 version 1 dated 29Oct2020

APPROVALS

Name and Title	Signature	Date
John Lee, MD, PhD. Chief Medical Officer Phase Bio Pharmaceuticals Inc		Oct 28, 2021
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1. ABBREVIATIONS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
ADA	Anti-drug Antibody
APRUmax	Maximal actual PRU
APRUmax4h	Maximal actual PRU within 4 h
ASA	Aspirin
AUC	Area under the concentration-time curve
BID	Twice daily
BMI	Body mass index
CL	Clearance
C_{max}	Maximum observed concentration
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DC	Discharged
ECG	Electrocardiogram
EOS	End of study
FUP	Follow up
HR	Heart rate
ISR	Infusion Site Reaction
LTA	Light Transmittance Aggregometry
MedDRA	Medical Dictionary for Regulatory Activities
PD	Pharmacodynamics
PK	Pharmacokinetic
PRI	Platelet reactivity index
PRU	$P2Y_{12}$ reaction units
PRUmax	Maximal percent of baseline PRU
QD	Once daily

RR	Respiratory rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
TAM	Ticagrelor active metabolite AR-C124910XX
SoA	Schedule of Assessments
SOP	Standard operating procedure
$t_{1/2}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
t_{max}	Time to maximum concentration
TPRUmax	Time to maximal actual PRU
TPRU180	Time to 180 or higher actual PRU
TPRU200	Time to 200 or higher actual PRU
TPRU220	Time to 220 or higher actual PRU
TPRU60%	Time to 60% of baseline PRU
TPRU80%	Time to 80% of baseline PRU
TPRU100%	Time to 100% of baseline PRU
WHO-DD	World Health Organization Drug Dictionary
VASP	Vasodilator-stimulated phosphoprotein
Vd	Volume of distribution

2. INTRODUCTION

The purpose of this plan is to prospectively outline in detail the data derivations, statistical methods and presentations of data so that valid conclusions can be reached to address the study objectives outlined in the PB2452-PT-CL-0003 protocol, dated 12 August 2019.

This Statistical Analysis Plan (SAP) will be signed before database lock and data analyses. The planned analyses identified in this SAP may be included in regulatory submissions and/or future manuscripts. Exploratory analyses, not identified in this SAP, may be performed to support the clinical development program. Any data analyses performed after signing of this SP and database lock will be considered post-hoc analyses, except if required by a regulatory agency. Any post-hoc or unplanned analyses that are performed but not identified in this SAP will be clearly identified in the clinical study report (CSR).

2.1. Responsibilities

Inference Inc. will perform the statistical analyses for all clinical data collected. Inference Inc. is responsible for production and quality control of all datasets, tables, figures and listings.

2.2. Timing of Analyses

Only one final analysis will take place after the database has been locked, following completion of recruitment and planned assessments for all subjects.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

Primary Objectives:

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

Secondary Objectives:

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

3.2. Endpoints

Hypothesis

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

Primary Endpoint

- The primary efficacy endpoint is the minimum % inhibition of PRU assessed by VerifyNow within 4 hours after the initiation of study drug. Percent inhibition of PRU is calculated as $100 * [(PRU_{bsl} – PRU_{trt})/PRU_{bsl}]$ where PRU_{bsl} refers to the PRU value measured before treatment with ticagrelor and PRU_{trt} refers to the PRU value measured posttreatment with the study drug.

Secondary Endpoints

- Safety, tolerability and immunogenicity will be assessed by monitoring and recording of adverse events (AEs), including infusion site and systemic infusion reactions, clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, oral body temperature,

respiratory rate, and heart rate), 12 lead electrocardiogram (ECG) results, physical examination findings, and immunogenicity.

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

  The following PK parameters for PB2452 will be assessed. Other PK parameters may be assessed depending on the availability of data.

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

  PK parameters for ticagrelor/TAM to be assessed are:

  - C_{max}
  - $AUC_{0\text{-}last}$
  - T_{max}
  - $AUC_{0\text{-}24}$
  - $AUC_{0\text{-}48}$
  - Area under the plasma concentration versus time curve from time zero to the end of the dosing interval ($AUC_{0\text{-}tau}$)
  - $t_{½}$; if data permit

- Pooled urine samples to assess urine PB2452, ticagrelor, and TAM concentrations will be collected according to predefined intervals. PK parameters for PB2452, ticagrelor, and TAM concentrations in urine for all subjects in the PK population to be calculated include:
  - Total amount of drug excreted in urine at 24 hours (Ae_{24}) and at 48 hours (Ae_{48})
  - AE from time t1 to t2 hours including 0 to 6, 6 to 12, 12 to 24 and 24 to 48 hours ($Ae_{t1\text{-}t2}$)
  - Fraction excreted in urine from 1 to 24 hours (Fe_{24}) and from 1 to 48 hours (Fe_{48})
  - Renal clearance (CLr) for 24 hours.

Additional Reversal Endpoints

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

4. STUDY DESIGN

This is a Phase 2B, randomized, double blind, multi centered, placebo-controlled study to evaluate the efficacy of PB2452 in reversing the antiplatelet effects of ticagrelor in subjects aged 50 to 80 years old. Subjects who provide informed consent and meet all study eligibility criteria will be enrolled in the study.

4.1. Study Treatments and Dose Administration

This Phase 2B study is a randomized, double-blind, multicenter, placebo-controlled study conducted across United States. The study is designed to evaluate the efficacy of PB2452 in reversing the anti-platelet effects of ticagrelor and to evaluate the safety and tolerability of PB2452 in subjects aged 50-80 years old.

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

All subjects will be administered aspirin 81 mg daily for at least 7 days prior to initiation of ticagrelor pretreatment with a 180 mg oral loading dose of ticagrelor, followed by 90 mg bid for a total of 5 doses of ticagrelor. Two hours following the last dose of ticagrelor, subjects will be randomized to either PB2452 (investigational / study drug) or a matching placebo administered intravenously (IV) to assess reversal at peak ticagrelor plasma concentrations.

The infusion regimen is as follows:

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

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

Table 1 Schedule of Events

	Out patient		Out patient			Treatment (in house)			Out patient	Out patient
Procedure	**Screening[a]**		**Check-in/ Pretreatment**			**Rand**		**Subject DC**	**FUP**	**FUP EOS**
Study Day(s)	**–45 to –4**	**-7**	**–3**	**-2**	**–1**	**1**	**2**	**3**	**7**	**35±3**
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 for occult blood	X									
Admission to study 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
Clinical laboratory testing	X		X		X		X		X	X
Randomization						X				
Drug administration										
ASA 81 mg QD[g]	X	X	X	X	X	X				
Ticagrelor administration[h]				X	X	X				
Administration PB2452 or placebo[i]						X				
PK sampling[j]: Plasma PB2452 Plasma Ticagrelor/TAM Unbound Plasma ticagrelor/TAM				X		X	X	X	X	X
PK urine sampling				X		X	X	X		
PD sampling (PRU/VASP)[k]				X		X	X	X		
Biomarkers					X		X		X	X
Serum immunogenicity			X			X			X	X[l]
Infusions site assessment[m]						X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant Medications[n]	X	X	X	X	X	X	X	X	X	X
Discharge from clinic[o]								X		

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

a Screening Period = Days -45 to -4 (including Day -7, when ASA is started).
b Serum pregnancy test for women of childbearing potential only.
c A full physical examination is conducted at Screening, Day -3 and Day 35±3).
Height and BMI calculation are completed at Screening and Day 35±3 only.
Weight is collected at Screening, Day -3 and Day 35±3.
d Brief physical examination and 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 15, 30, 45, 60 min, 24 and 48 hours following initiation of study drug. Vital Signs are also collected on Day 7 and 35±3. Vital signs at 15, 30, 45, and 60 minutes following infusion require only SBP and DBP, and HR.
f 12-lead ECGs will be obtained at Screening before initiation of PB2452/placebo, pre-treatment Day -1, and on treatment Days 1, 2, 7 and 35±3. The specific time points for 12-lead ECG on Day 1 and 2 will be pre-dose, after bolus, end of infusion, and after 24 hours from initiation of infusion. ECGs will be collected anytime on Day 3, 7, and 35±3.
g ASA 81 mg 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.
h 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).
i PB2452/placebo will be administered at Hour 0 of Day 1.
j Blood samples for determination of plasma PB2452, plasma ticagrelor/TAM and unbound plasma ticagrelor/TAM will be collected within 10 minutes prior to the initiation of PB2452/placebo infusion (Hour 0) and at 5, 10, 30 minutes and 1, 2, 4, 8, 12, 20, 24, 36, and 48 hours after initiation of study drug infusion. And on days -2, 1, 2, 3, 7, and 35±3 after initiation of study drug infusion.
k Blood samples for PD analysis (PRU/VASP testing) will be collected at the following timepoints: Day -2 (up to 60 minutes prior to first ticagrelor dose) and Hour 0 (up to 10 minutes prior to PB2452/placebo infusion), 5, 10, 30 minutes, 1, 2, 4, 8, 12, 20, 24, 36 and 48 hours after initiation of PB2452/placebo infusion.

If there is sufficient material leftover from PK and/or PD blood samples, additional platelet function-related biomarkers, such as P-selectin, will be tested to support hypothesis generation for future studies.
l Subjects may be required to return to the site for collection of additional follow-up samples, if the sample collected at Day 35±3 tests positive for treatment-emergent ADAs. These visits may occur approximately 3 months after the final study visit and approximately every 6 months thereafter or until antibody levels return to baseline level.
m Infusion site assessments will be performed for all subjects within 15 minutes before initiation of PB2452/placebo infusion at Hour 0, 1, 3, 24, and 48 hours after initiation of PB2452/placebo infusion, and on Day 7.
n All concomitant medications (prescription, over the counter and supplements) to be collected -45 days from the date informed consent is signed. New and changes to medications are captured at every visit until Day 35±3.
o Subjects are discharged from the clinic on Day 3. Subjects are permitted, if necessary/convenient to the subject to remain housed at the clinic following discharge through Day 7. In such events, adverse events and changes to concomitant medications are to be collected on days 4, 5, and 6.

4.2. Sample Size Justification

Approximately 200 subjects 50-80 years old inclusive will be enrolled across US or, if needed, other countries at 5-15 sites. The subjects will be randomized in a 3:1 ratio receiving either the

PB2452 investigational study drug or placebo. Hence, a total of approximately 150 subjects will be receiving PB2452 and approximately 50 subjects will be receiving placebo.

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

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

4.3. Randomization, Stratification, and Blinding

As described above, subjects will be randomized in a 3:1 (PB2452:placebo) ratio. The randomization will be employed via Medidata's RTSM, a central Interactive Web Response system (IWRS). No stratification will be utilized.

This is a double-blind study. Neither the subjects nor the investigator will be aware of the treatment assignment. Blinding will be maintained throughout the study by use of active and placebo dose forms prepared to be similar in appearance. To maintain the blind, only designated pharmacy staff at the study site will have access to the randomization code.

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

4.4. Primary Statistical Hypothesis

The primary objective of the study is to assess the estimand defined as the comparative treatment effect in reversal of the antiplatelet effects of ticagrelor in all subjects randomly assigned to study treatment, who take any amount of study drug and have at least one measurable post dose PRU value (i.e. the modified ITT (mITT) population as further detailed in Section 5).

The reversal will be assessed by the primary study endpoint of minimum % inhibition of PRU assessed by VerifyNow within 4 hours after the initiation of study drug. Percent inhibition of PRU is calculated as $100 * [(PRU_{bsl} - PRU_{trt})/PRU_{bsl}]$ where PRU_{bsl} refers to the PRU value measured before treatment with ticagrelor and PRU_{trt} refers to the PRU value measured posttreatment with the study drug.

The analysis will test whether PB2452 is superior to Placebo according to the following Null (H_0) and Alternative (H_1) statistical hypotheses:

$$H_0: \Delta = 0 \quad \text{vs.} \quad H_1: \Delta \neq 0$$

where $\Delta = \mu_{PB2452} - \mu_{placebo}$ with

μ_{PB2452} = population mean minimum %inhibition of PRU in the PB2452 arm, and

$\mu_{placebo}$ = population mean minimum %inhibition of PRU in the placebo arm

4.5. Estimated Duration of Subject Participation and Follow-up

The study will consist of a Screening period (Days –45 to –4), a Check-in day (Day –3), a pre-treatment period (Day -2 and -1), an on-site Randomization/Treatment day (Day 1), a 2-day on-site Follow-up period (Days 1 through 3), a Day 7 Follow-up visit, and a final Follow-up visit (Day 35+3 days). The estimated duration of the study for each subject, excluding screening, is approximately 35+3 days.

5. ANALYSIS POPULATIONS

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

Population	Description
All Subjects	All subjects who sign the Informed Consent Form (ICF).
Intention-to-Treat Population	All randomized subjects.
Modified Intention-to-Treat Population	Modified Intention-to-Treat (mITT) population includes all subjects randomly assigned to study treatment, who take any amount of study drug (PB2452 or placebo). Subjects will be analyzed as treated.
Safety Population	The Safety Population includes all subjects who have received any amount of study drug (PB2452 or placebo). The Safety Population will be analyzed for all safety assessments. Subjects in the Safety population will be analyzed as treated.
Per Protocol Population	The Per Protocol (PP) population includes subjects in the mITT Population who do not have major protocol deviations and who complete the study. Protocol deviations will be assessed prior to database lock and unmasking. The PP population will be analyzed using observed data only for efficacy variables. Subjects in the PP population will be analyzed as treated.
PK Population	The PK population includes all subjects with a measurable PK sample of the study drug. The PK population will be used to summarize all PB2452 blood concentrations. Subjects in the PK population will be analyzed as treated.

6. GENERAL ASPECTS OF THE STATISTICAL ANALYSIS

6.1. Key Definitions

The Study Day is the day relative to the date of treatment (Day 1). In other words,

Study Day = Date – Date of treatment + 1,

if Date is on or after Date of treatment; or

Study Day = Date – Date of treatment,

if Date is before Date of dosing.

For efficacy endpoints, baseline values will be defined as the last value before ticagrelor is administered, which is expected to be on Day -2. The pre-treatment value is defined as the last value before study drug is administered, which is expected to be on Day 1 (up to 10 minutes prior to PB2452/placebo infusion). If Day 1 value is missing, the value prior to that will be used as pre-treatment.

For all other endpoints, unless otherwise specified, baseline is the last non-missing observation before exposure to study treatment PB2452 or placebo, which is expected to be the pre-study drug measurement on Day 1, or Screening if the Day 1 data are not available.

6.2. Subgroup Analyses

The primary efficacy endpoint and some of the safety, PK and immunogenicity endpoints may be analyzed for the older (50-64 years old) and elderly (65-80 years old) separately in an exploratory fashion. Also, these endpoints may be listed and summarized for specific subjects of interest (e.g. renally impaired group).

6.3. Missing Data

For subjects with missing data on efficacy endpoints, no imputation will be used. For binary endpoints, the missing data will be excluded from the calculation of proportions.

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 first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first 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 for the onset date. 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 start of administration of study drug, then assume the onset date to be the start of administration of study drug. If the end date (after any imputation) is prior to the start of administration of study drug, then assume the end date to be 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 start of administration of study drug.

An AE with missing onset time but with an onset date the same as the start of administration 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 start of administration of study drug date 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 9.5 and handling of PD data is specified in Section 9.6.

7. SUBJECT DISPOSITION

7.1. Disposition

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

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

- Screen failed
- Randomized (ITT Population)
- 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.

7.2. Protocol Deviations, Inclusion, and Exclusion Criteria

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

8. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

8.1. Demographic and Baseline Characteristics

The demographic and baseline characteristics will be summarized with respect to sex, age (years), height (cm), weight (kg), BMI (kg/m^2), race, and ethnicity by treatment group. These summaries will be calculated for mITT, ITT and Safety Populations. Summary statistics include number of subjects with non-missing data, mean, standard deviation, median, minimum, and maximum for continuous variables, and number and percentage of patients in each category for categorical variables.

The counts and percentage of subjects who had been on aspirin before Day -7 or who initiated aspirin on Day -7 will be presented by treatment.

8.2. Medical History

Medical and surgical history and concomitant diseases will be coded according to the latest version of MedDRA and presented in listings.

8.3. Prior and Concomitant Medication

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.

Medications taken prior to ticagrelor, concomitant with ticagrelor and concomitant with the study treatments PB2452 and placebo will be presented separately.

Ticagrelor and aspirin, which will be received by all study subjects, are considered pre-treatments and will be excluded from the prior medication list.

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

9. EFFICACY

9.1. Analysis of Primary Efficacy Endpoint

All efficacy analyses will primarily be based on the mITT Population. Supportive analyses will be performed based on the ITT and Per-Protocol Population.

The primary endpoint is defined as the minimum % inhibition of PRU assessed by VerifyNow within 4 hours (inclusive) after the initiation of study drug. Percent inhibition of PRU is calculated as 100 * [(PRU_{bsl} – PRU_{trt})/PRU_{bsl}], where PRU_{bsl} refers to the PRU value measured before treatment with ticagrelor and PRU_{trt} refers to the PRU value measured posttreatment with the study drug.

Results by treatment groups will be summarized at baseline, at the timepoint where minimum is achieved (nadir), and percent inhibition from baseline using descriptive statistics: number of subjects with non-missing data, mean, standard deviation, median, minimum, and maximum. To complete the clinical picture, the % inhibition of PRU from baseline will be summarized at all time points using descriptive statistics.

Hypothesis testing will also be conducted using a 2-sided two-sample t-test test with a significance level of 0.05 to compare the efficacy of PB2452 and placebo. The corresponding 95% confidence interval will be provided for the mean difference between PB2452 and placebo.

In order to compare the response to the Phase 3 patient study which does not include a pre-ticagrelor baseline, percent inhibition of PRU will also be calculated as 100 * [(180 – PRU_{trt})/180], where $PPPPPP_{tttttt}$ refers to the PRU value measured at a given visit following start of study drug infusion. A PRU value of 180 is considered the lower limit of normal (LLN) platelet function, as described in the VerifyNow® $P2Y_{12}$ PRUTest® manufacturer's user guidance. This alternative calculation will be used to analyze the primary endpoint in an exploratory manner using the methods described above.

9.2. Analysis of Secondary Efficacy Endpoints

The secondary efficacy analysis compares a number of secondary endpoints between the two treatment groups. The secondary endpoints below will be formally evaluated if the primary efficacy hypothesis was supported. A hierarchical approach will be used to control for multiplicity. The secondary endpoints will be tested in the order presented below. There are three types of endpoints:

Continuous endpoints:

- Minimum %inhibition of PRI assessed by VASP within 4 hours after the initiation of study drug. %inhibition of PRI is calculated as 100 * [(PRI_{bsl} – PRI_{trt})/PRI_{bsl}]. PRI_{bsl} refers to the PRI value measured before treatment with ticagrelor and PRI_{trt} refers to the PRI value measured posttreatment with the study drug.
- Percent reversal of PRU within 4 hours after the initiation of study drug. Percent reversal is calculated as 100 * [(PRU_{trt} – $PRU_{pre\text{-}trt}$)/(PRU_{bsl} – $PRU_{pre\text{-}trt}$)]. $PRU_{pre\text{-}trt}$ is the PRU value prior to administration of study drug.

- Percent reversal of PRI within 4 hours after the initiation of study drug. Percent reversal is calculated as 100 * [(PRI_{trt} – $PRI_{pre\text{-}trt}$)/(PRI_{bsl} – $PRI_{pre\text{-}trt}$)]. $PRI_{pre\text{-}trt}$ is the PRI value prior to administration of study drug.
- PRU AUC for the first 4 hours.
- PRI AUC for the first 4 hours.

The continuous endpoints will be compared between the two treatment groups using a two-sample t-test, as used for the primary endpoint.

Binary endpoints:

- Proportion of patients with normalized platelet reactivity units within 4 hours after the initiation of study drug. Normalized platelet reactivity is defined as PRU ≥ 180.
- Proportion of patients with ≥60%, ≥80%, and 100% of PRU response rate within 4 hours after the initiation of study drug. A PRU response is defined as the 100 * (PRU_{trt}/PRU_{bsl}).
- Proportion of patients with ≥60%, ≥80%, and 100% of PRI response rate within 4 hours after the initiation of study drug. A PRI response is defined as the 100 * (PRI_{trt}/PRI_{bsl}).

Number and percent of patients achieving normalized PRU, or 60%, 80%, 90% and 100% of baseline platelet aggregation, and with normalized platelet activity will be summarized by timepoint and treatment. A similar analysis will be done for proportion of patients with ≥60%, ≥80%, 90% and 100% of PRI response rate.

The dichotomous secondary endpoints will be compared between the treatment groups using Fisher's Exact test at two-sided 5% significance level.

9.3. Other Efficacy Endpoints:

The following PD parameters may be calculated and summarized using %baseline/actual PRU data from the VerifyNow assay. The maximal endpoints will be presented as other continuous endpoints using summary statistics. The median time-to-event endpoints will be summarized using the Kaplan Meier method. Time will be censored if the event is not attained before the study end.

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
TPRU100%	Time to 100% of baseline PRU, calculated as the first observed time point (no extrapolation) when %baseline PRU reaches 100%

Similar parameters may also be reported for PRI.

10. SAFETY

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 treatment group and overall.

10.1. Adverse Events

Adverse events will be coded by preferred term (PT) and system-organ-class (SOC) using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). All AE data will be presented in data listings.

Treatment Emergent Adverse Events.

Treatment-emergent AEs (TEAEs) will be summarized by treatment and overall, as well as by severity and relationship to study drug. TEAEs are defined as any AE that is not present before exposure to study drug or any AE already present that worsens in severity after exposure to study drug.

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 for subject counts 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. Percentages will be based upon the number of subjects in the Safety Population overall and within each treatment group.

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 with following categories:

- Any AE
- Any ticagrelor-related AE
- Any TEAE
- Any study-drug-related TEAEAny 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 Infusion Site Reactions (ISR)

- Any death

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.

Relationship to Adverse Event

The relationship of AE to study drug or 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.

Severity

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.

Infusion Site TEAEs

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

Serious Adverse Events

An AE or suspected adverse reaction is considered a SAE 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.

Adverse Events Leading to Early Discontinuation

All SAEs and TEAEs leading to discontinuation of study drug will be presented in the data listings.

10.2. Clinical Laboratory Assessments

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

10.3. Vital Signs

Actual values and changes from baseline in clinical laboratory test results will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, standard deviation [SD], median, minimum, and maximum). Vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP], oral body temperature, respiratory rate, and heart rate [HR]) 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.

10.4. Electrocardiogram (ECG)

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.

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, but QTcB interval is missing in the database the Bazett's-corrected QT interval (QTcB) measured in msec will be calculated using the formula below, where RR interval is measured in msec:

- $QQQQQQQ = \frac{QQQQ}{\sqrt{RRRR/1000}}$

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 the formula below, where RR interval is measured in msec:

- $QQQQQQQ = \frac{QQQQ}{\sqrt{RRRR/1000}}$

Electrocardiogram results will be presented in data listing sorted by treatment group, subject, and date/time of assessment. Actual results and change from baseline will be summarized for the safety

population at each timepoint using descriptive statistics. All ECG results will be presented in a data listing.

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) meeting the outlying criteria using count and percentage.

10.5. Physical Exams

Physical exam results are collected at the screening visit only. These will be presented in a listing.

11. PHARMACOKINETIC ANALYSIS

The ticagrelor and TAM pharmacokinetic results will be analyzed for all randomized subjects, and the PB2452 results will be analyzed for the PK Population.

Plasma Concentrations

Plasma concentrations will be listed by nominal timepoints and subject, and summarized descriptively (number of subjects, mean, SD, coefficient of variation [CV], geometric mean, geometric CV, median, minimum, and maximum). Plasma concentration versus time profiles for each subject will be presented graphically. The mean plasma concentration versus time profiles will be presented graphically both on the linear and semi-log scale. All concentration plots will be presented using nominal times from the time of PB2452 dosing.

Plasma concentration values below the limit of quantification (BLQ) will be set to zero for calculation of all summary statistics except for geometric mean and geometric CV. In case any value is BLQ, the geometric mean and geometric CV will be presented as NA. For the semi-log plots if the mean value is zero (i.e., if all values are BLQ at a timepoint) then it will be set to LLOQ/2 in the plot.

Scatter plots of pharmacokinetic data versus total and unbound PB2452 plasma concentrations may be prepared for including both treatment groups with placebo group concentration set to zero.

Plasma Pharmacokinetic Parameters

Plasma pharmacokinetic parameters of PB2452, ticagrelor, and TAM will be determined using noncompartmental models using Phoenix WinNonlin Version 8.1 or higher and summarized by time point using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum). In addition, geometric means and geometric CVs will be reported for AUCs and Cmax. Actual sampling times, rather than scheduled sampling times, will be used in all calculations of PK parameters.

For calculating the PK parameters, BLQ values will be treated as zero with the exception that a BLQ value between 2 quantifiable concentrations will be set as missing. If 2 or more 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 not be imputed for calculating the PK parameter.

The terminal elimination phase will be identified by regression analysis using logarithmically transformed plasma concentrations. An elimination phase will be considered invalid for the following situations:

- It has less than 3 data points;
- It has a positive slope (or correlation coefficient [r]>0);
- Adjusted $r^2 \leq 0.8$. (Adjusted $r^2 = 1-\{(1-r^2)\times(n-1)\}/(n-2)$, where n is the number of data points in the regression and r2 is the square of the correlation coefficient.).
- In cases where $Ct/\lambda z$ (i.e., the extrapolated portion of $AUC_{0-\infty})_{is} \geq 20\%$ of $AUC_{0-\infty}$, $AUC_{0-\infty}$ will be considered invalid.

Urine PK Concentration

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.

For PB2452 concentration, urine concentration will be summarized by the time-intervals mentioned above. For Ticagrelor and TAM concentrations, the summary will be presented by treatment.

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

Urine Parameters

The urine PK parameters Ae_{24}, Ae_{48}, and $Ae_{t1\text{-}t2}$ (for 0 to 6, 6 to 12, 12 to 24 and 24 to 48 hours), Fe_{48}, and CLr for PB2452, ticagrelor and TAM in urine will be listed by subject and summarized for using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum).

12. BIOMARKER AND IMMUNOGENICITY ANALYSIS

Biomarker data, e.g. P-selectin, will be summarized for each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). A listing will be presented by subject.

The PB2452 antibodies will be summarized by visit and treatment. A listing for subjects will also be provided by treatment and visit.

If positive ADA is observed, results may be reported by ADA status for AEs, efficacy and pharmacokinetics. 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. In all other cases, a subject is considered negative for ADA.

13. ANALYSIS CONVENTIONS

Post-text tables and listings will be prepared in accordance with the current ICH Guidelines. The information and explanatory notes to be provided in the "footer" or bottom of each table and listing will include the following information:

1. Date and time of output generation;
2. SAS® program name that generates the output;
3. Any other output specific details that require further elaboration.

In general, tables will be formatted with a column displaying findings for all subjects combined. Row entries in tables are made only if data exists for at least one subject (*i.e.*, a row with all zeros will not appear). The only exception to this rule applies to tables that list the termination status of subjects (*e.g.*, reasons for not completing the study). In this case, zeros will appear for study termination reasons that no subject satisfied. The summary tables clearly indicate the number of subjects to which the data apply and unknown or not performed are distinguished from missing data.

This section details general conventions to be used for the statistical analyses. The following conventions will be applied to all data presentations and analyses.

- All summary tables will include the analysis set sample size (i.e., number of subjects).

- Study Day 1 is defined as the first day the subject is exposed to the study drug. All *study days* are determined relative to the day of exposure to the study drug

- Baseline values will be defined as those values recorded closest to, but prior to, the first study treatment on Day 1 for all measurements except for PD/efficacy endpoints. For these endpoints baseline is the last value before ticagrelor is administered.

- Change from baseline will be calculated as follows:

  Change = Post-baseline value – baseline value.

- Subject data obtained during unscheduled visits/assessments will not be summarized but will be included in subject data listings only; except for the determination of minimum % inhibition of PRU or PRI within 4 hours post-baseline. Unscheduled visit values will not be used to impute missing scheduled visit values, except for baseline calculation.

- No visit windows will be used to select efficacy data for analysis. Data collected at the nominal visit will be used for analysis (note that Day 35 is defined as 35±3, but will be reported as Day 35/End-of-study for simplification).

- Date-time variables will be formatted as *yyyy-mm-dd*T*hh:mm* for presentation (i.e., in ISO8601 format).

- Date variables will be formatted as *yyyy-mm-dd* for presentation.

- SAS® Version 9.4[1] or higher will be the statistical software package used for all data analyses.

- The study visit and subject number will be included in all data listings. All listings will be sorted by subject number and visit date, as applicable.

14. REFERENCES

1. SAS Institute Inc., SAS® Version 9.4 software, Cary, NC.
2. United States, Department of Health and Human Services. (2017). Common terminology criteria for adverse events: (CTCAE).