CLINICAL STUDY PROTOCOL

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

PROTOCOL NO. PB2452-PT-CL-0001

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Version of Protocol: Final 1.0

Date of Protocol: 01 Feb 2018

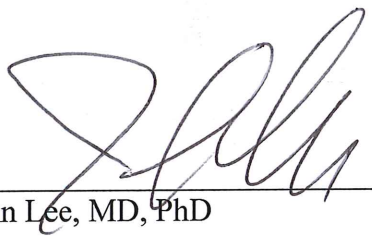
CONFIDENTIAL

The study will be conducted according to the International Council for Harmonisation (ICH) harmonised tripartite guideline E6(R2): Good Clinical Practice.

SIGNATURE PAGE

PROTOCOL TITLE: 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

PROTOCOL NUMBER: PB2452-PT-CL-0001



02-12-2018

John Lee, MD, PhD
CMO
PhaseBio Pharmaceuticals, Inc

Date

INVESTIGATOR PROTOCOL AGREEMENT PAGE

I agree to conduct the study as outlined in the protocol entitled "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" in accordance with the guidelines and all applicable government regulations including US Title 21 of the Code of Federal Regulations Part 54. I have read and understand all sections of the protocol.

LuAnn Bundrant, MD
Principal Investigator
PPD

10 Feb 2018
Date

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PROTOCOL SYNOPSIS

PROTOCOL NO.: PB2452-PT-CL-0001

TITLE: 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

STUDY PHASE: 1

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

OBJECTIVES:

Primary:

- To evaluate the safety and tolerability of single ascending intravenous (IV) doses of MEDI2452 (PB2452) with or without oral ticagrelor
- To evaluate the effectiveness of single ascending doses of MEDI2452 (PB2452) on ticagrelor antiplatelet activity by measuring inhibition of platelet activity (IPA) relative to predose ticagrelor using light transmittance aggregometry (LTA)

Secondary:

- To determine the pharmacokinetics of ascending doses of IV MEDI2452 (PB2452) in the presence and absence of ticagrelor
- To determine the pharmacokinetics 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 pharmacokinetics and pharmacodynamics of restarting a single dose of oral ticagrelor 24 hours after IV MEDI2452 (PB2452) administration
- To evaluate the immunogenicity potential of MEDI2452 (PB2452)

Exploratory:

- To evaluate the effect of MEDI2452 (PB2452) on the pharmacokinetic (PK) profile of unbound ticagrelor and unbound AR-C124910XX plasma concentrations

STUDY DESIGN AND METHODOLOGY:

This is a Phase 1, first-in-human, randomized, double-blind, placebo-controlled, single ascending dose, sequential group study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of MEDI2452 (PB2452) with and without ticagrelor pretreatment when administered to healthy male and female subjects.

Up to 6 dose levels will be evaluated. This study will have up to 9 cohorts and up to a total of approximately 60 subjects with either 4 or 8 subjects in each cohort depending on the dose.

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.

The study will consist of a screening period (Days –28 to –4), check-in/pretreatment (Day -3 to Day -1), an in-house treatment period (Days 1 through 3), and follow-up visits (Days 4, 7, and 28 [+2 days]). Subjects will receive an IV dose of MEDI2452 (PB2452) or placebo on Day 1.

On Day 1, subjects who meet all of 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 or 6:2 in the following treatment cohorts:

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 MEDI2452 (PB2452) or placebo 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 MEDI2452 (PB2452) or placebo 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 MEDI2452 (PB2452) or placebo over 30 minutes.

Cohorts 4 to 7:

Provided no safety concerns arise in Cohorts 1 through 3, 8 subjects in each of Cohorts 4 through 7 will be randomly assigned in a 6:2 ratio (6A:2P) to receive a single IV dose of MEDI2452 (PB2452) or placebo 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 MEDI2452 (PB2452) or placebo simultaneous with the 5th ticagrelor dose (Day 1). Subjects in each of Cohorts 4 through 7 will receive ticagrelor pretreatment, as described above, and a single IV dose of 1000, 3000, 9000, or 18000 mg of MEDI2452 (PB2452), respectively, or placebo over 30 minutes. Cohorts 4 through 7 will be dosed sequentially following the safety and dose-escalation assessment of each preceding dose cohort.

Cohorts 8 and 9:

For the final 2 dose cohorts (Cohorts 8 and 9), following ticagrelor pretreatment, subjects will be randomly assigned (6A:2P) to receive a single IV dose of 9000 or 18000 mg of MEDI2452 (PB2452), respectively, or placebo, and will also receive an additional single oral dose of 180-mg ticagrelor 24 hours after the initiation of the MEDI2452 (PB2452) or placebo infusion. Cohort 8 may be initiated following the safety and dose escalation assessment of Cohort 6 (9000-mg MEDI2452 [PB2452]), and Cohort 9 may be initiated following the safety and dose escalation assessment of Cohort 7 (18000-mg MEDI2452 [PB2452]).

Cohort	Pre-MEDI2452 (PB2452) Ticagrelor dosing to steady state (180 mg + 90 mg bid for 5 doses total)	MEDI2452 (PB2452) Dose (mg)	Post-MEDI2452 (PB2452) Ticagrelor (180 mg) 24 hours following MEDI2452 (PB2452) or placebo	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	9000	180 mg	6:2
9	180 mg + 90 mg bid	18000	180 mg	6:2

Abbreviations: bid, twice daily

Subjects in Cohorts 1 through 3 will check in to the clinical site on Day -1. On Day 1, subjects will receive a single IV dose of MEDI2452 (PB2452) or placebo in the morning. Subjects will undergo end-of-study (EOS) procedures and will be discharged from the clinical site on Day 3. Subjects will return for follow-up visits on Days 4, 7, and 28 (+2 days).

Subjects in Cohorts 4 through 9 will check in to the clinical site on Day -3. In the morning on Day -2, subjects will begin pretreatment with ticagrelor. On Day 1, simultaneous with the 5th ticagrelor dose, subjects will receive a single IV dose of MEDI2452 (PB2452) or placebo in the morning. Subjects in Cohorts 4 through 7 will undergo EOS procedures and will be discharged from the clinical site on Day 3 and will return for follow-up visits on Days 4, 7, and 28 (+2 days). On Day 2, subjects in Cohorts 8 and 9 will receive an additional dose of ticagrelor in the morning 24 hours after the initiation of the MEDI2452 (PB2452) infusion and 5th ticagrelor dose. Subjects in Cohorts 8 and 9 will undergo EOS procedures and will be discharged from the clinical site on Day 4 and return for follow-up visits on Days 7 and 28 (+ 2 days).

Plasma samples for PK and pharmacodynamic (PD) analysis of MEDI2452 (PB2452), ticagrelor, and its active metabolite, AR-C124910XX, and urine samples for the PK analysis of ticagrelor and AR-C124910XX will be collected at specified intervals up to 28 days after dosing. Pharmacokinetic and PD samples will be obtained at identical time points; Hour 0 will be the initiation of the MEDI2452 (PB2452) infusion (Cohorts 1 through 3) and the simultaneous administration of the MEDI2452 (PB2452) infusion and the 5th ticagrelor dose (Cohorts 4 through 9).

Safety and tolerability will be carefully monitored throughout the study. Immunogenicity will be determined in all subjects at baseline and for up to 28 days following administration of MEDI2452 (PB2452).

The estimated duration of the study for each subject, excluding screening, is approximately 30 days.

Sentinel Dosing

Dosing for Cohort 1 (first exposure of MEDI2452 [PB2452] in humans) will proceed with two sentinel subjects initially randomly assigned to receive a single IV dose of MEDI2452 (PB2452) or placebo. Blinded safety data from the sentinel subjects up to 24-hours following the MEDI2452 (PB2452) or placebo dose will be reviewed by the investigator before the remaining 2 subjects in Cohort 1 are dosed. The remaining subjects will be dosed at least 24 hours after the sentinel subjects. Additionally, dosing for Cohort 4 (first exposure of the combination of MEDI2452 [PB2452] with ticagrelor in humans) will proceed with 2 sentinel subjects pre-treated with ticagrelor prior to receiving a single IV dose of MEDI2452 (PB2452) or placebo randomized in a 1:1 ratio of active to placebo. Blinded safety data from the sentinel subjects up to 24 hours following the ticagrelor and MEDI2452 (PB2452) or placebo dose will be reviewed by the investigator before the remaining 6 subjects in Cohort 4 are dosed. The remaining subjects will be dosed at least 24 hours after the sentinel subjects.

Dose Escalation

A safety review committee (SRC) will be formed for blinded reviews of safety (eg, clinical laboratory results, adverse events [AEs], 12-lead electrocardiograms [ECGs], vital signs) and available PK data through Day 4 for each dose cohort. The SRC will be minimally composed of the on-site investigator, PPD medical monitor, and clinical pharmacologist, and the PhaseBio study director and clinical operations lead. Dose escalation to successive cohorts will be based upon safety of the preceding cohort. The investigator will make a recommendation on whether to proceed to the next predefined dose level, pause dosing for review of additional safety and/or PK data, or to adjust the dose of the next dose cohort. The decision to adjust or pause the dose or proceed to the next cohort will be made by the SRC. The safety data will be reviewed in a blinded manner and must be deemed acceptable to the SRC prior to dosing of the next higher dose group.

Based on the review of safety and PK data, if available, the SRC may choose to repeat a dose level, administer a dose less than the previous dose, or escalate to a dose lower than the next planned dose.

Stopping Criteria

After completion of Day 4 for each dose cohort, the SRC will review and assess all available safety (eg, clinical laboratory results, AEs, ECGs, vital signs), tolerability, and available PK data to make a decision on the dose for next dose cohort. Dose escalation may be suspended if any of the following scenarios occur with a reasonable possibility of causal relationship with MEDI2452 (PB2452):

- Events that, in the opinion of the medical monitor and SRC, contraindicate further dosing of additional subjects
- Any serious adverse event with a suspected relationship to MEDI2452 (PB2452) in a dose cohort
- Data from a previous dose cohort indicating safety concerns for the next cohort to be dosed at a higher level, such as unanticipated responses (eg, clinically significant changes in clinical laboratory data, ECGs, cardiac telemetry, vital signs, or physical examinations)
- More than 50% of the subjects in a given dose cohort are withdrawn due to poor tolerability of MEDI2452 (PB2452)

- Two or more subjects experiencing severe AEs assessed at least possibly related to MEDI2452 (PB2452), or 1 or more subjects experiencing severe AEs at least possibly related to MEDI2452 (PB2452) at the discretion of the investigator
- Two or more subjects have > 3 × upper limit of normal (ULN) of either alanine aminotransferase or aspartate aminotransferase, or > 2 × ULN for bilirubin or alkaline phosphatase where no other reason can be found to explain the combination of increases
- Two or more subjects experiencing a severe infusion reaction

Dose escalation may also be suspended if, in the opinion of the investigator or sponsor, any other significant safety or tolerability issues are identified in the comprehensive review of available data that warrant further evaluation before additional subjects are dosed. This may include emerging nonclinical data, clinically relevant AEs, or relevant data from other sources indicating safety concerns even if the event(s) per se does not meet the protocol-specified definition of a dose-limiting toxicity.

INCLUSION CRITERIA:

1. The subject is male or female between 18 and 50 years of age, inclusive.
2. The subject has a body mass index between 18 and 35 kg/m^2 and a weight of ≥50 kg but ≤120 kg, inclusive, at screening.
3. The subject is considered by the investigator to be in good general health as determined by medical history, clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings at screening.
4. Female subjects of childbearing potential must not be pregnant, lactating, or planning to become pregnant before 3 months after the last dose of study drug, and have a negative serum pregnancy test at screening and check-in. Female subjects of childbearing potential must use 2 effective methods of birth control (ie, oral, implantable, patch, or injectable contraceptives in combination with a condom, hormone-containing intrauterine device that has been in place for at least 2 months prior to screening in combination with a condom, double-barrier method [ie, condoms, sponge, diaphragm, or cervical cap with spermicidal gels or cream], or vasectomy for male subjects or male partners of female subjects) from 30 days before study drug administration through the end of the study. Women are considered not to be of childbearing potential if they have fulfilled one of the following criteria: documentation of irreversible surgical sterilization (ie, hysterectomy, or bilateral oophorectomy [not tubal ligation]), or postmenopausal (defined as amenorrhea for 12 consecutive months following cessation of all exogenous hormonal treatments, and documented plasma follicle-stimulating hormone level >40 IU/mL). Male subjects with partners of childbearing potential must agree to use appropriate and effective measures of contraception (eg, condom plus diaphragm with spermicide; condom plus spermicide) during the study and for 30 days after the last dose of study drug, and to refrain from donating sperm for at least 7 days prior to the first dose of study drug and until at least 90 days following the last dose of study drug.
5. The subject agrees to comply with all protocol requirements.
6. The subject is able to provide written informed consent.

EXCLUSION CRITERIA:

1. History of any clinically significant disease or disorder which, in the opinion of the investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.
2. History or presence of gastrointestinal, hepatic, or renal disease (with the exception of Gilbert's syndrome) or renal insufficiency (ie, estimated glomerular filtration rate <60 ml/min/1.73m^2), or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.
3. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of study drug.
4. Any clinically relevant abnormal findings in physical examination, vital signs, hematology and coagulation parameters, clinical chemistry, or urinalysis results during screening or check-in, which in the opinion of the investigator or medical monitor may compromise the safety of the subject in the study or interfere with the evaluation of the study drug or reduce the subjects' ability to participate in the study. Specific exclusionary values at screening or check-in blood tests are any of the following:
    - Aspartate transaminase level >1.5 × ULN
    - Alanine transaminase level >1.5 × ULN
    - Hemoglobin level below the lower limit of normal (hemoglobin levels within 0.5 g/L of the lower cut off point may be acceptable based on the judgment of the investigator and medical monitor)
    - Thyroid stimulating hormone level above the ULN at screening
    - Prothrombin time or partial thromboplastin time level outside the normal range
5. The subject has an increased risk of bleeding, including the following:
    - Recent history (within 30 days preceding the first dose of study drug) of gastrointestinal bleeding
    - Any history of intracranial, intraocular, retroperitoneal, or spinal bleeding
    - Any recent (within 30 days preceding the first dose of study drug) major trauma
    - History of hemorrhagic disorders that may increase the risk of bleeding (eg, hemophilia, von Willebrand's disease)
    - Inability to discontinue therapy with nonsteroidal anti-inflammatory drugs at screening (must discontinue medication within at least 7 days or 5 half-lives, whichever is longer, prior to first dose of study drug)
    - Subjects who have taken, within 30 days of screening, any oral or parenteral anticoagulant, including low molecular-weight heparin
    - Platelet count <100,000 mm^3
6. Any clinically important abnormalities in rhythm, conduction, or morphology of the resting 12-lead ECG or any abnormalities that may interfere with the interpretation of

serial ECG changes, including corrected QT interval (QTc) interval changes at screening, as judged by the investigator, and also including:

- Prolonged Fridericia-corrected QT interval (QTcF) >450 milliseconds (msec), shortened QTcF <340 msec, or pause >3 seconds at screening, or family history of long QT syndrome
- Prolonged PR (PQ) interval >240 msec, intermittent second- or third-degree atrioventricular (AV) block or AV dissociation, or shortened PR interval <120 msec at screening
- Incomplete, full, or intermittent bundle branch block (QRS <110 msec with normal QRS and T wave morphology is acceptable if there is no evidence of left ventricular hypertrophy)

7. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus types 1 or 2 antibodies at screening.
8. Abnormal vital signs after 10 minutes supine rest, defined as any of the following:
    - Systolic blood pressure >140 mm Hg
    - Diastolic blood pressure >90 mmHg
    - Heart rate <50 or >100 beats per minute

    Note: Abnormal results may be repeated once for confirmation, at the discretion of the investigator.
9. The subject should not participate in the study if they have any ongoing or recent (ie, during the screening period) minor medical complaints that may interfere with the interpretation of the study data or are considered unlikely to comply with study procedures, restrictions, and requirements as judged by the investigator.
10. History of transient ischemic attack or cardiovascular accident (ischemic or hemorrhagic), severe head trauma, intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, aneurysm, or proliferative retinopathy.
11. The subject is receiving chronic treatment with nonsteroidal anti-inflammatory drugs (including aspirin [greater than 100 mg daily]), anticoagulants, or other antiplatelet agents that cannot be discontinued (including clopidogrel, prasugrel, ticlopidine, dipyridamole, or cilostazol).
12. The subject is considered to be at risk of bradycardic events (eg, known sick sinus syndrome, atrial fibrillation, or second- or third-degree AV block) unless already treated with a pacemaker.
13. Concomitant oral or IV therapy with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers, which cannot be stopped within at least 5 half-lives, but not shorter than 10 days, before randomization (a list of examples can be found in Section 6.2).

14. The subject has used any prescription (excluding hormonal birth control) or over-the-counter medications (except paracetamol [up to 2 g per day]), including herbal or nutritional supplements, within 14 days before the first dose of study drug.
15. The subject has consumed grapefruit or grapefruit juice, Seville orange or Seville orange-containing products (eg, marmalade), or alcohol-, or xanthine-containing products within 48 hours before dosing with study drug.
16. The subject is participating in any other study or is taking part in a non-medication study which, in the opinion of the investigator, would interfere with the outcome of the study.
17. The subject has received another new chemical entity (defined as a compound which has not been approved for marketing) or any marketed or investigational biologic agent within 30 days of the first administration of study drug in this study. The period of exclusion begins 30 days after the final dose or 5 half-lives of the experimental medication has elapsed, whichever is longer.
18. The subject has involvement with any PhaseBio or study site employee or their close relatives (eg, spouse, parents, siblings, or children whether biological or legally adopted).
19. The subject has previously received MEDI2452 (PB2452).
20. The subject is a smoker or has used nicotine or nicotine-containing products (eg, snuff, nicotine patch, nicotine chewing gum, mock cigarettes, or inhalers) within 3 months before the first dose of study drug.
21. The subject has a known or suspected history of drug abuse (including alcohol) as judged by the investigator.
22. The subject has a positive test result for drugs of abuse, alcohol, or cotinine (nicotine level above 300 ng/mL) at screening or check-in.
23. The subject has a planned surgical procedure that will occur during the study (from screening through EOS).
24. The subject is involved in strenuous activity or contact sports within 24 hours before the first dose of study drug and while confined in the clinical site.
25. The subject has donated blood or plasma within 1 month of screening or any blood donation/loss more than 500 mL during the 3 months prior to the first dose of study drug.
26. The subject has a history of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the investigator or history of hypersensitivity to drugs with a similar chemical structure or class to ticagrelor, any biologic therapeutic agent, or any significant food allergy that could preclude a standard diet in the clinical site.
27. Concern for the inability of the subject to comply with study procedures and/or follow-up, or, in the opinion of the investigator, the subject is not suitable for entry into the study.

EVALUATION CRITERIA:

Safety Assessments:

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), 12-lead ECG results, cardiac telemetry monitoring, immunogenicity, and physical examination findings.

Pharmacokinetic Assessments:

Plasma Collection:

Blood samples for PK analysis of MEDI2452 (PB2452) in serum will be collected from all subjects at the following time points: before dosing (Hour 0) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours, and at 7 and 28 days after initiation of the MEDI2452 (PB2452) infusion.

Plasma samples for determining total concentrations of ticagrelor and its active metabolite, AR-C124910XX, will be collected from subjects in Cohorts 4 through 9 at the following timepoints: before dosing (within 10 minutes prior to the initiation of MEDI2452 [PB2452] infusion and 5th ticagrelor dose [Hour 0]), and at 0.5, 1, 2, 3, 6, 12, and 24 hours after the initiation of the MEDI2452 (PB2452) infusion and 5th ticagrelor dose. Additional samples will be collected from subjects in Cohorts 8 and 9 at 0.5, 1, 2, 3, 6, 12, 24, and 48 hours after the Day 2 post-MEDI2452 (PB2452) 6th ticagrelor dose.

Plasma samples for determining unbound ticagrelor and AR-C124910XX concentrations will be collected from subjects in Cohorts 4 through 9 at the following timepoints: before dosing (within 10 minutes prior to the initiation of MEDI2452 [PB2452] infusion and 5th ticagrelor dose [Hour 0]), and at 0.5, 1, 2, 3, 6, 12, and 24 hours after the initiation of the MEDI2452 (PB2452) infusion and 5th ticagrelor dose. Additional samples will be collected from subjects in Cohorts 8 and 9 at 0.5, 1, 2, 3, 6, 12, and 24 hours after the Day 2 post-MEDI2452 (PB2452) 6th ticagrelor dose.

The following plasma PK parameters for MEDI2452 (PB2452) will be calculated:

- Area under the plasma concentration versus time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUC_{0-t})
- Observed maximum plasma concentration (C_{max})
- Time to reach the observed maximum plasma concentration (T_{max})
- AUC from time 0 extrapolated to infinity (AUC_{0-inf}) (if data permit)
- Terminal elimination half-life (t½) (if data permit)
- Apparent clearance (CL) (if data permit)

The following plasma PK parameters for ticagrelor and AR-C124910XX will be calculated:

- C_{max}
- T_{max}
- AUC from time 0 to 12 hours after dosing (AUC_{0-12})
- AUC from time 0 to 24 hours after dosing (AUC_{0-24})

- $AUC_{0\text{-}inf}$ (if data permit)
- t½ (if data permit)

The following plasma PK parameters for the metabolite AR-C124910XX will be calculated:

- C_{max} ratio (metabolite:parent)
- $AUC_{0\text{-}24}$ ratio (metabolite:parent)

Urine Collection:
Pooled urine samples to assess urine ticagrelor and AR-C124910XX concentrations will be collected from subjects in Cohorts 4 through 9 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 after the initiation of the MEDI2452 (PB2452) infusion and 5th ticagrelor dose.

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

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

Additional PK parameters may be generated, if needed.

Pharmacodynamic Assessments:
Blood samples for PD analysis will be collected from subjects in Cohorts 4 through 9 at the following time points: before dosing (within 60 minutes prior to first ticagrelor dose on Day -2) and again before dosing (within 10 minutes prior to the initiation of the MEDI2452 [PB2452] infusion and 5th ticagrelor dose [Hour 0]), and at 0.5, 1, 2, 3, 6, 12, 24, and 48 hours after the initiation of the MEDI2452 (PB2452) infusion and 5th ticagrelor dose. Additional samples will be collected from subjects in Cohorts 8 and 9 at 1, 2, 6, and 12 hours after the Day 2 post-MEDI2452 (PB2452) 6th ticagrelor dose.

The following PD parameters will be calculated using the data generated by LTA, $P2Y_{12}$ reaction units (PRU), and platelet reactivity index (PRI) assays:

LTA:

- Inhibition of platelet aggregation (IPA) (max and final extent) induced by 20μM adenosine diphosphate (ADP) at each assessment point
- inhibition of maximal platelet aggregation (IPA_{max})
- time to IPA_{max} ($TIPA_{max}$)

VerifyNow™$P2Y_{12}$:

- PRU at each assessment point

VASP by ELISA:

- PRI at each assessment point

Additional PD parameters may be generated, if needed.

Immunogenicity:
Blood samples will be screened for the presence of binding anti-drug antibodies (ADA) at check-in and on Days 7 and 28.

STUDY DRUG, DOSAGE, AND ROUTE OF ADMINISTRATION:

MEDI2452 (PB2452):
All cohorts: MEDI2452 (PB2452) (concentration will vary between 0.4 mg/mL up to 72 mg/mL) single IV infusion, 250 mL to be delivered over 30 minutes in escalating doses of 100, 300, 1000, 3000, 9000, or 18000 mg

Matching Placebo:
All cohorts: 0.9% sodium chloride single IV infusion, 250 mL to be delivered over 30 minutes

Ticagrelor:
Cohorts 4 through 9: ticagrelor 90-mg oral tablet (immediate release); administered as 180 mg (2 × 90-mg tablet) loading dose plus 90 mg every 12 hours for 4 additional doses

Cohorts 8 and 9: ticagrelor 90-mg oral tablet (immediate release); one additional dose administered as 180 mg (2 × 90-mg tablet) 24 hours after the initiation of the MEDI2452 (PB2452) infusion

STATISTICAL METHODS:

Sample Size:
The sample size (N = 60) 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 effectively assess the safety, PK, and PD profiles of MEDI2452 (PB2452) and the PK and PD profiles of ticagrelor.

Analysis Populations:
- The Safety population will include all subjects who receive any amount of study drug.
- The PK population will include subjects who receive at least 1 dose of study drug and have at least 1 measurable PK concentration.
- The PD population will include subjects who receive at least 1 dose of ticagrelor and have at least 1 measurable post dose LTA value.

Safety Analyses:
Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities. All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized by treatment and overall, as well as by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will be presented in the data listings.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Clinical laboratory test results, vital sign measurements, 12-lead ECG results, immunogenicity results, and physical examination findings will be presented in data listings.

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

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

Dose proportionality will be tested using the power regression model for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} of MEDI2452 (PB2452) in Cohorts 4, 5, 6, and 7.

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

Interim Analyses:

A formal unblinded interim analysis (IA) of all accumulated safety, PD, and PK data (as needed) will be performed after the last subject in Cohort 6 completes follow-up visit Day 7 to provide an interim assessment of the safety profile of MEDI2452 (PB2452) after the target efficacious dose level has been tested (Cohort 6). Pharmacodynamic and PK data analysis will also be included as needed in the IA to provide an assessment of the likely benefit/risk profile of the study drug. The prespecified IA analyses will be a subset of the final study analyses. The detailed scope of interim analyses will be outlined in a separate document, the statistical analysis plan (SAP). An independent statistical group will produce the interim analysis.

DATE OF PROTOCOL: 01 Feb 2018

LIST OF ABBREVIATIONS

Abbreviation	Definition
ACS	acute coronary syndrome
ADA	anti-drug antibodies
ADP	adenosine diphosphate
Ae	total amount of drug excreted in urine
$Ae_{t1\text{-}t2}$	total amount of drug excreted in urine from time t1 to t2 hours where the values of t1 to t2 are 0 to 6, 6 to 12, and 12 to 24
AE	adverse event
ALT	alanine aminotransferase
ASA	acetylsalicylic acid
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-}12}$	AUC from time 0 to 12 hours after dosing
$AUC_{0\text{-}24}$	AUC from time 0 to 24 hours after dosing
$AUC_{0\text{-}inf}$	area under the plasma concentration versus time curve from time 0 extrapolated to infinity
$AUC_{0\text{-}t}$	area under the concentration versus time curve from time 0 to the time of the last quantifiable concentration
AUEC	area under the effect curve
AV	atrioventricular
BLQ	below the limit of quantification
CFR	Code of Federal Regulations
CL	apparent clearance
CLr	renal clearance
C_{max}	observed maximum plasma concentration
CV	coefficient of variation
DAPT	dual antiplatelet therapy
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
E_{max}	maximum observed concentrations or activity levels
EOS	end-of-study
FDA	Food and Drug Administration
Fe	fraction excreted in urine from 1 to 24 hours after dosing
IA	interim analyses

Abbreviation	Definition
ICF	informed consent form
ICH	International Council for Harmonisation
IPA	inhibition of platelet aggregation
IPA_{max}	inhibition of maximal platelet aggregation
IRB	institutional review board
IV	intravenous
IVSS	intravenous stabilizing solution
LTA	light transmittance aggregometry
Millisecond	msec
MTD	maximum tolerated dose
NOAEL	no-observed-adverse-effect level
PD	pharmacodynamic
PK	pharmacokinetic
PRI	platelet reactivity index
PRU	$P2Y_{12}$ reaction units
QTc	corrected QT interval
QTcF	Fridericia-corrected QT interval
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SRC	safety review committee
$t_{1/2}$	terminal elimination half-life
TEAE	Treatment-emergent adverse event
$TIPA_{max}$	time to inhibition of maximal platelet aggregation
T_{max}	time to reach the observed maximum (peak) concentration
ULN	upper limit of normal
VASP	vasodilator stimulated phosphoprotein

1. INTRODUCTION

1.1 BACKGROUND INFORMATION

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.

Ticagrelor is an orally available, direct-acting cyclopentyltriazolopyrimidine, a selective and reversibly binding $P2Y_{12}$ receptor antagonist (van Giezen et al 2009). AR-C124910XX, the ticagrelor active metabolite (30% to 40% plasma exposure relative to parent in humans (Storey et al 2007), has potency similar to that of ticagrelor versus $P2Y_{12}$. In addition to $P2Y_{12}$, ticagrelor also inhibits the equilibrative nucleoside transporter-1, thereby providing an enhanced adenosine response (Armstrong et al 2014, Cattaneo et al 2014). Ticagrelor in combination with low-dose aspirin (acetylsalicylic acid; ASA) is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction, and stroke) in patients with acute coronary syndrome (ACS) or a history of myocardial infarction. Ticagrelor also reduces the rate of stent thrombosis in patients who have been stented for treatment of ACS. In the management of ACS, ticagrelor treatment is initiated with a 180-mg loading dose, followed by 90 mg twice daily during the first year after an ACS event. After one year the prescribed dosage is 60 mg twice daily.

Therapy with ASA plus an oral antiplatelet agent such as clopidogrel, prasugrel, or ticagrelor is known as dual antiplatelet therapy (DAPT). While DAPT is strongly recommended in the early management of patients experiencing an ACS event, it also increases the risk of bleeding (Storey 2011). Patients with ACS may require urgent or emergent coronary artery bypass graft surgery. In such patients, DAPT is associated with a 2-fold increase in the risk of blood transfusion, a 5-fold increase in the risk of reoperation, and a 50% increased risk of wound infection (Bell et al 2011, Fitchett et al 2011). Consequently, guidelines and guidance statements recommend that the $P2Y_{12}$ receptor antagonist be stopped at least 5 days prior to the procedure, a recommendation that is not possible to follow in patients who require urgent surgery.

There are no approved drugs or biological agents capable of reversing the $P2Y_{12}$ inhibition produced by ticagrelor or other $P2Y_{12}$ inhibitors, and thus if a major bleeding event occurs in a patient on DAPT, there are limited treatment options. Although platelet transfusion restores platelet function in patients on ASA (Taylor et al 2013), it does not reverse the antiplatelet

effect of ticagrelor in healthy volunteers and is unlikely to be of clinical benefit in patients with bleeding (Teng et al 2016). The lack of an effective therapy to mitigate ticagrelor-induced platelet inhibition in patients who have life-threatening bleeding or require urgent surgery or intervention therefore represents a significant unmet need.

MEDI2452 (PB2452) (molecular weight 47.4 kDa) is a recombinant human IgG1λ monoclonal fragment antigen-binding antibody that binds specifically to ticagrelor and AR-C124910XX. It is expressed in *Escherichia* coli cells.

1.1.1 Non-clinical Pharmacology

Detailed descriptions of the non-clinical pharmacology of MEDI2452 (PB2452) may be found in the Investigator Brochure for MEDI2452 (PB2452). The key non-clinical pharmacology study findings for MEDI2452 (PB2452) are as follows:

- MEDI2452 (PB2452) binds ticagrelor and its active metabolite, AR-C124910XX, selectively and with a high affinity (equilibrium dissociation constant [K_D] 20 pmol/L).
- MEDI2452 (PB2452) rapidly neutralizes the unbound plasma fraction of ticagrelor and AR-C124910XX and thereby reverses ticagrelor- and AR-C124910XX-mediated inhibition of adenosine diphosphate (ADP)-induced platelet aggregation in a concentration- and dose-dependent manner in vitro (in human platelet-rich plasma) and in vivo (mouse and pig, dose-dependency data in mouse only).
- In mice dosed with ticagrelor to a supratherapeutic plasma exposure, MEDI2452 (PB2452) dosed before a tail cut reduced bleeding to a level that was not statistically different from that observed in mice not treated with ticagrelor.
- In pigs dosed to a supratherapeutic ticagrelor exposure on a background of ASA, MEDI2452 (PB2452) dosed after liver injury induced an elimination of free ticagrelor and AR-C124910XX in plasma within 5 minutes. The elimination translated into a gradual reversal of ticagrelor-mediated inhibition of ADP-induced platelet aggregation and numerical, but nonsignificant, improvements in mean arterial pressure, blood loss, and survival.

Non-clinical pharmacology studies have demonstrated that MEDI2452 (PB2452) binds with high affinity and selectivity to the $P2Y_{12}$ receptor antagonist ticagrelor and its active metabolite AR-C124910XX. MEDI2452 (PB2452) produces concentration (dose)-dependent reversal of ticagrelor- and AR-C124910XX-mediated inhibition of ADP-induced platelet aggregation. The activity in vitro and the rapid onset of effect observed in vivo translated to a

reduction of bleeding in ticagrelor-treated mice to a level that was not statistically different from that observed in mice not treated with ticagrelor.

1.1.2 Benefit/Risk Assessment

Healthy volunteers are not expected to receive any benefit from administration of MEDI2452 (PB2452). In patients who are taking ticagrelor and who experience serious bleeding or who require emergency or urgent surgical procedures, MEDI2452 (PB2452) may provide significant clinical benefit by reversing the ticagrelor antiplatelet effect and thereby promoting hemostasis.

The potential risks of infusion site reactions and hypersensitivity-type reactions are generic for recombinant protein drugs administered intravenously. These risks can be mitigated by predefined exclusion criteria and by close monitoring during and after administration.

In patients taking ticagrelor for therapeutic benefit, the potential risk of thrombosis upon reversal of the antiplatelet effect of ticagrelor will be evaluated in future clinical studies and by thorough monitoring of hemostasis parameters.

Based on available information regarding the risks of MEDI2452 (PB2452) and the precautions included in this first clinical study, the risks are considered acceptable.

1.2 RATIONALE FOR STUDY

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

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

The availability of an agent that reduces the inhibition of platelet aggregation associated with ticagrelor and AR-C124910XX would fulfill an important unmet clinical need for the following patient populations:

- Patients with major bleeding where ticagrelor may be contributing
- Patients taking ticagrelor who require urgent surgery or intervention associated with a high risk of bleeding
- Patients taking ticagrelor for conditions with a high risk of thrombosis who require major surgery and for whom it is deemed important to minimize the time during which they are not using ticagrelor

1.3 RATIONALE FOR DOSE SELECTION

There were no adverse effects following a single dose of MEDI2452 (PB2452) given intravenously to rats, alone or in combination with oral ticagrelor (20 mg/kg), at doses up to 2000 mg/kg. Therefore, 2000 mg/kg of MEDI2452 (PB2452) was considered to be the no adverse effect level (NOAEL) (systemic exposures C_{max} 18100 µg/mL, $AUC_{(0\text{-inf})}$ 23100 µg*h/mL).

The recommended dose of MEDI2452 (PB2452) for clinical use will be that sufficient to neutralize total body ticagrelor at steady state in a patient using ticagrelor 90 mg twice daily. The doses to be investigated in Phase I were determined using pharmacokinetic (PK)/pharmacodynamic (PD) modeling. In brief, a MEDI2452 (PB2452) dose of 100 mg at 10-fold lower than the expected minimally pharmacologically active dose of 1000 mg is proposed as the starting dose, with a first escalation to 300 mg. Allowing for an escalation of up to 3-fold in each ascending-dose cohort, doses of MEDI2452 (PB2452) to be tested in the presence of ticagrelor are 1000, 3000, and 9000 mg with a higher dose cohort of 18000 mg to provide safety and tolerability and PK/PD information at higher exposures.

The maximum dose that will be administered in this initial Phase 1 study is 18000 mg. The safety margin at the maximum proposed human dose of 18000 mg is 0.6 based on the NOAEL AUC in the pivotal rat Good Laboratory Practice toxicity study in which no adverse effects of single doses of MEDI2452 (PB2452) intravenously administered alone or in combination with oral ticagrelor were observed at the highest dose level tested (2000 mg/kg, NOAEL).

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVES

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 by measuring inhibition of platelet activity (IPA) relative to predose ticagrelor using light transmittance aggregometry (LTA)

2.2 SECONDARY OBJECTIVES

The secondary objectives of the study are:

- To determine the pharmacokinetics of ascending doses of IV MEDI2452 (PB2452) in the presence and absence of ticagrelor
- To determine the pharmacokinetics 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 pharmacokinetics and pharmacodynamics of restarting a single dose of oral ticagrelor 24 hours after MEDI2452 (PB2452) administration
- To evaluate the immunogenicity potential of MEDI2452 (PB2452)

2.3 EXPLORATORY OBJECTIVE

The exploratory objective of the study is:

- To evaluate the effect of MEDI2452 (PB2452) on the PK profile of unbound ticagrelor and unbound AR-C124910XX plasma concentrations

3. INVESTIGATIONAL PLAN

3.1 STUDY DESIGN

This is a Phase 1, first-in-human, randomized, double-blind, placebo-controlled, single ascending dose, sequential group study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of MEDI2452 (PB2452) with and without ticagrelor pretreatment when administered to healthy male and female subjects.

Up to 6 dose levels will be evaluated. This study will have up to 9 cohorts and up to a total of approximately 60 subjects with either 4 or 8 subjects in each cohort depending on the dose. 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.

The study will consist of a screening period (Days –28 to –4), check-in/pretreatment (Day -3 to Day -1), an in-house treatment period (Days 1 through 3), and follow-up visits (Days 4, 7, and 28 [+2 days]). Subjects will receive an IV dose of MEDI2452 (PB2452) or placebo on Day 1.

On Day 1, subjects who meet all of 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 or 6:2 in the following treatment cohorts:

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 MEDI2452 (PB2452) or placebo 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 MEDI2452 (PB2452) or placebo 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 MEDI2452 (PB2452) or placebo over 30 minutes.

Cohorts 4 to 7:

Provided no safety concerns arise in Cohorts 1 through 3, 8 subjects in each of Cohorts 4 through 7 will be randomly assigned in a 6:2 ratio (6A:2P) to receive a single IV dose of MEDI2452 (PB2452) or placebo simultaneous with the 5^{th} 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 MEDI2452 (PB2452) or placebo

simultaneous with the 5th ticagrelor dose (Day 1). Subjects in each of Cohorts 4 through 7 will receive ticagrelor pretreatment, as described above, and a single IV dose of 1000, 3000, 9000, or 18000 mg of MEDI2452 (PB2452), respectively, or placebo over 30 minutes. Cohorts 4 through 7 will be dosed sequentially following the safety and dose-escalation assessment of each preceding dose cohort.

Cohorts 8 and 9:

For the final 2 dose cohorts (Cohorts 8 and 9), following ticagrelor pretreatment, subjects will be randomly assigned (6A:2P) to receive a single IV dose of 9000 or 18000 mg of MEDI2452 (PB2452), respectively, or placebo, and will also receive an additional single oral dose of 180-mg ticagrelor 24 hours after the initiation of the MEDI2452 (PB2452) or placebo infusion. Cohort 8 may be initiated following the safety and dose escalation assessment of Cohort 6 (9000-mg MEDI2452 [PB2452]), and Cohort 9 may be initiated following the safety and dose escalation assessment of Cohort 7 (18000-mg MEDI2452 [PB2452]).

Cohort	Pre-MEDI2452 (PB2452) ticagrelor dosing to steady state (180 mg + 90 mg bid for 5 doses total)	MEDI2452 (PB2452) Dose (mg)	Post-MEDI2452 (PB2452) Ticagrelor (180 mg) 24 hours following MEDI2452 (PB2452) or placebo	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	9000	180 mg	6:2
9	180 mg + 90 mg bid	18000	180 mg	6:2

Abbreviations: BID, twice daily

Dosing for Cohort 1 (first exposure of MEDI2452 [PB2452] in humans) will proceed with two sentinel subjects initially randomly assigned to receive a single IV dose of MEDI2452 (PB2452) or placebo. Blinded safety data from the sentinel subjects up to 24-hours following the MEDI2452 (PB2452) or placebo dose will be reviewed by the investigator before the remaining 2 subjects in Cohort 1 are dosed. The remaining subjects will be dosed at least 24 hours after the sentinel subjects. Additionally, dosing for Cohort 4 (first exposure of the combination of MEDI2452 [PB2452] with ticagrelor in humans) will proceed with 2 sentinel

subjects pre-treated with ticagrelor prior to receiving a single IV dose of MEDI2452 (PB2452) or placebo randomized in a 1:1 ratio of active to placebo. Blinded safety data from the sentinel subjects up to 24 hours following the ticagrelor and MEDI2452 (PB2452) or placebo dose will be reviewed by the investigator before the remaining 6 subjects in Cohort 4 are dosed. The remaining subjects will be dosed at least 24 hours after the sentinel subjects.

Subjects in Cohorts 1 through 3 will check in to the clinical site on Day -1. On Day 1, subjects will receive a single IV infusion of MEDI2452 (PB2452) or placebo in the morning after an overnight fast of approximately 8 hours. Blood samples for PK analysis of MEDI2452 (PB2452) in serum will be collected before dosing (within 10 minutes prior to the initiation of the MEDI2452 [PB2452] infusion) and through 72 hours after initiation of the MEDI2452 (PB2452) infusion. Subjects will undergo end-of-study (EOS) procedures and will be discharged from the clinical site on Day 3. Subjects will return for follow-up visits on Days 4, 7, and 28 (+2 days).

Subjects in Cohorts 4 through 9 will check in to the clinical site on Day -3. On Day -2, subjects will begin pretreatment with ticagrelor in the morning after an overnight fast of approximately 8 hours. On Day 1, subjects will receive a single IV dose of MEDI2452 (PB2452) or placebo in the morning simultaneous with the 5th ticagrelor dose. Plasma samples for PK/PD analysis of MEDI2452 (PB2452), ticagrelor, and its active metabolite AR-C124910XX will be collected before dosing (within 10 minutes prior to the initiation of the MEDI2452 [PB2452] infusion and 5th ticagrelor dose) and up to 72 hours after initiation of the MEDI2452 (PB2452) infusion and the 5th ticagrelor dose. Urine samples for PK analysis of ticagrelor and AR-C124910XX will be collected before dosing (within 60 minutes prior to the first ticagrelor dose on Day -2) and up to 24 hours after the initiation of the MEDI2452 (PB2452) infusion and 5th ticagrelor dose. Subjects in Cohorts 4 through 7 will undergo EOS procedures and will be discharged from the clinical site on Day 3 and will return for follow-up visits on Days 4, 7, and 28 (+2 days).

On Day 2, subjects in Cohorts 8 and 9 will receive an additional ticagrelor dose in the morning 24 hours following the initiation of the MEDI2452 (PB2452) infusion and 5th ticagrelor dose. Additional plasma samples for PK/PD analysis of MEDI2452 (PB2452), ticagrelor, and AR-C124910XX will be collected through 48 hours after the Day 2 post-MEDI2452 (PB2452) 6th ticagrelor dose. Subjects in Cohorts 8 and 9 will undergo EOS procedures and will be discharged from the clinical site on Day 4 and return for follow-up visits on Days 7 and 28 (+2 days).

A safety review committee (SRC) will be formed for a blinded review of safety (eg, clinical laboratory results, adverse events [AEs], 12-lead electrocardiograms [ECGs], vital signs) and available PK data through Day 4 for each dose cohort. The SRC will be minimally composed of the on-site investigator, PPD medical monitor, and clinical pharmacologist, and the PhaseBio study director and clinical operations lead. Dose escalation to successive cohorts will be based upon safety of the preceding cohort. The investigator will make a recommendation on whether to proceed to the next predefined dose level, pause dosing for review of additional safety and/or PK data, or to adjust the dose of the next dose cohort. The decision to adjust or pause the dose or proceed to the next cohort will be made by the SRC. The safety data will be reviewed in a blinded manner and must be deemed acceptable to the SRC prior to dosing of the next higher dose group.

Based on the review of safety and PK data, if available, the SRC may choose to repeat a dose level, administer a dose less than the previous dose, or escalate to a dose lower than the next planned dose.

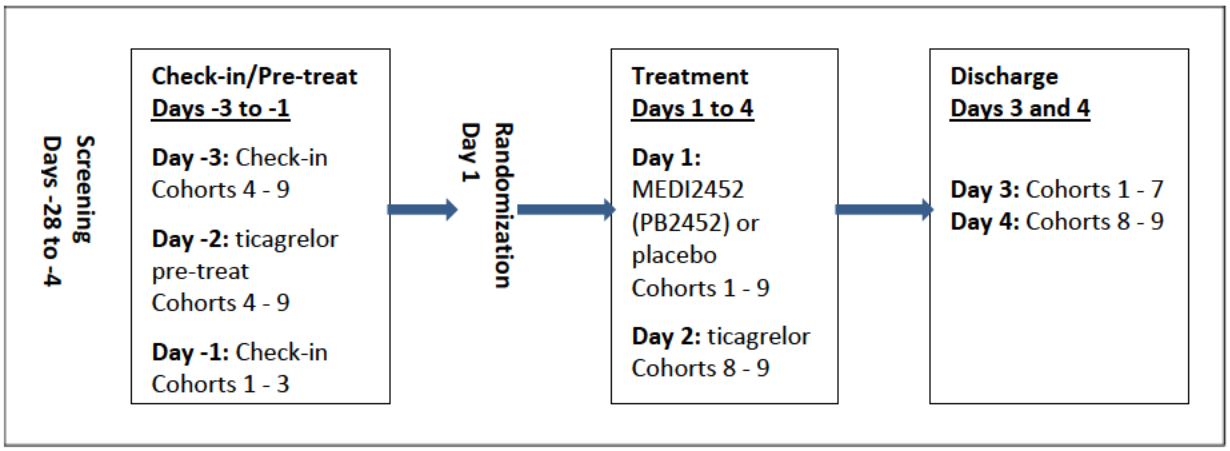
Safety and tolerability will be assessed by monitoring and recording of AEs, clinical laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), vital sign measurements (systolic and diastolic blood pressures, oral body temperature, respiratory rate, and heart rate), ECG results, cardiac telemetry monitoring, immunogenicity results, and physical examination findings.

Plasma samples for PK and PD analysis of MEDI2452 (PB2452), ticagrelor, and its active metabolite, AR-C124910XX, and urine samples for PK analysis of ticagrelor and AR-C124910XX will be collected at specified intervals up to 28 days after dosing.

The estimated duration of the study for each subject, excluding screening, is approximately 30 days.

The overall design of the study is presented in Figure 3–1.

Figure 3–1 Study Flow Diagram



3.2 SELECTION OF STUDY POPULATION

Up to 60 healthy male or female subjects will be enrolled at a single center in the United States. Up to 9 subjects will be dosed with ticagrelor in Cohorts 4 through 9 in order to randomize 8 subjects per cohort.

3.2.1 Inclusion Criteria

Each subject must meet all of the following criteria to be enrolled in this study:

1. The subject is male or female between 18 and 50 years of age, inclusive.

2. The subject has a body mass index between 18 and 35 kg/m^2 and a weight of ≥50 kg but ≤120 kg, inclusive, at screening.

3. The subject is considered by the investigator to be in good general health as determined by medical history, clinical laboratory test results, vital sign measurements, 12 lead ECG results, and physical examination findings at screening.

4. Female subjects of childbearing potential must not be pregnant, lactating, or planning to become pregnant before 3 months after the last dose of study drug, and have a negative serum pregnancy test at screening and check-in. Female subjects of childbearing potential must use 2 effective methods of birth control (ie, oral, implantable, patch, or injectable contraceptives in combination with a condom, hormone-containing intrauterine device that has been in place for at least 2 months prior to screening in combination with a condom, double-barrier method [ie, condoms, sponge, diaphragm, or cervical cap with spermicidal gels or cream], or vasectomy for male subjects or male partners of female subjects) from 30 days before study drug administration through the end of the study.

Women are considered not to be of childbearing potential if they have fulfilled one of the following criteria: documentation of irreversible surgical sterilization (ie, hysterectomy, or bilateral oophorectomy [not tubal ligation]), or postmenopausal (defined as amenorrhea for 12 consecutive months following cessation of all exogenous hormonal treatments, and documented plasma follicle-stimulating hormone level >40 IU/mL). Male subjects with partners of childbearing potential must agree to use appropriate and effective measures of contraception (eg, condom plus diaphragm with spermicide; condom plus spermicide) during the study and for 30 days after the last dose of study drug, and to refrain from donating sperm for at least 7 days prior to the first dose of study drug until at least 90 days following the last dose of study drug.

5. The subject agrees to comply with all protocol requirements.

6. The subject is able to provide written informed consent.

3.2.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

1. History of any clinically significant disease or disorder which, in the opinion of the investigator, may either put the subject at risk because of participation in the study, or influence the results or the subject's ability to participate in the study.

2. History or presence of gastrointestinal, hepatic, or renal disease (with the exception of Gilbert's syndrome) or renal insufficiency (ie, estimated glomerular filtration rate <60 ml/min/1.73m^2), or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.

3. Any clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of study drug.

4. Any clinically relevant abnormal findings in physical examination, vital signs, hematology and coagulation parameters, clinical chemistry, or urinalysis results during screening or check-in, which in the opinion of the investigator or medical monitor may compromise the safety of the subject in the study or interfere with the evaluation of the study drug or reduce the subjects' ability to participate in the study. Specific exclusionary values at screening or check-in blood tests are any of the following:

    - Aspartate transaminase (AST) level >1.5 × upper limit of normal (ULN)

- Alanine transaminase (ALT) level >1.5 × ULN
- Hemoglobin level below the lower limit of normal (hemoglobin levels within 0.5 g/L of the lower cut off point may be acceptable based on the judgment of the investigator and medical monitor)
- Thyroid stimulating hormone level above the ULN at screening
- Prothrombin time or partial thromboplastin time level outside the normal range

5. The subject has an increased risk of bleeding, including the following:
   - Recent history (within 30 days preceding the first dose of study drug) of gastrointestinal bleeding
   - Any history of intracranial, intraocular, retroperitoneal, or spinal bleeding
   - Any recent (within 30 days preceding the first dose of study drug) major trauma
   - History of hemorrhagic disorders that may increase the risk of bleeding (eg, hemophilia, von Willebrand's disease)
   - Inability to discontinue therapy with nonsteroidal anti-inflammatory drugs at screening (must discontinue medication within at least 7 days or 5 half-lives, whichever is longer, prior to first dose of study drug)
   - Subjects who have taken, within 30 days of screening, any oral or parenteral anticoagulant, including low molecular-weight heparin
   - Platelet count < 100,000 mm^3
6. Any clinically important abnormalities in rhythm, conduction, or morphology of the resting 12-lead ECG or any abnormalities that may interfere with the interpretation of serial ECG changes, including corrected QT interval (QTc) interval changes at screening, as judged by the investigator, and also including:
   - Prolonged Fridericia-corrected QT interval (QTcF) >450 milliseconds (msec), shortened QTcF <340 msec, or pause >3 seconds at screening, or family history of long QT syndrome

- Prolonged PR (PQ) interval >240 msec, intermittent second- or third-degree atrioventricular (AV) block or AV dissociation, or shortened PR interval <120 msec at screening

- Incomplete, full, or intermittent bundle branch block (QRS <110 msec with normal QRS and T wave morphology is acceptable if there is no evidence of left ventricular hypertrophy)

7. The subject has a positive test result for hepatitis B surface antigen, hepatitis C virus antibody, or human immunodeficiency virus types 1 or 2 antibodies at screening.

8. Abnormal vital signs after 10 minutes supine rest, defined as any of the following:

   - Systolic blood pressure >140 mm Hg

   - Diastolic blood pressure >90 mmHg

   - Heart rate <50 or >100 beats per minute

   Note: Abnormal results may be repeated once for confirmation, at the discretion of the investigator

9. The subject should not participate in the study if they have any ongoing or recent (ie, during the screening period) minor medical complaints that may interfere with the interpretation of the study data or are considered unlikely to comply with study procedures, restrictions, and requirements as judged by the investigator.

10. History of transient ischemic attack or cardiovascular accident (ischemic or hemorrhagic), severe head trauma, intracranial hemorrhage, intracranial neoplasm, arteriovenous malformation, aneurysm, or proliferative retinopathy.

11. The subject is receiving chronic treatment with nonsteroidal anti-inflammatory drugs (including aspirin [greater than 100 mg daily]), anticoagulants, or other antiplatelet agents that cannot be discontinued (including clopidogrel, prasugrel, ticlopidine, dipyridamole, or cilostazol).

12. The subject is considered to be at risk of bradycardic events (eg, known sick sinus syndrome, atrial fibrillation, or second- or third-degree AV block) unless already treated with a pacemaker.

13. Concomitant oral or IV therapy with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers, which cannot be stopped within at least 5 half-lives, but not shorter than 10 days, before randomization (a list of examples can be found in Section 6.2).

14. The subject has used any prescription (excluding hormonal birth control) or over-the-counter medications (except paracetamol [up to 2 g per day]), including herbal or nutritional supplements, within 14 days before the first dose of study drug.

15. The subject has consumed grapefruit or grapefruit juice, Seville orange or Seville orange-containing products (eg, marmalade), or alcohol-, or xanthine-containing products within 48 hours before dosing with study drug.

16. The subject is participating in any other study or is taking part in a non-medication study which, in the opinion of the investigator, would interfere with the outcome of the study.

17. The subject has received another new chemical entity (defined as a compound which has not been approved for marketing) or any marketed or investigational biologic agent within 30 days of the first administration of study drug in this study. The period of exclusion begins 30 days after the final dose or 5 half-lives of the experimental medication has elapsed, whichever is longer.

18. The subject has involvement with any PhaseBio or study site employee or their close relatives (eg, spouse, parents, siblings, or children whether biological or legally adopted).

19. The subject has previously received MEDI2452 (PB2452).

20. The subject is a smoker or has used nicotine or nicotine-containing products (eg, snuff, nicotine patch, nicotine chewing gum, mock cigarettes, or inhalers) within 3 months before the first dose of study drug.

21. The subject has a known or suspected history of drug abuse (including alcohol) as judged by the investigator.

22. The subject has a positive test result for drugs of abuse, alcohol, or cotinine (nicotine level above 300 ng/mL) at screening or check-in.

23. The subject has a planned surgical procedure that will occur during the study (from screening through EOS).

24. The subject is involved in strenuous activity or contact sports within 24 hours before the first dose of study drug and while confined in the clinical site.

25. The subject has donated blood or plasma within 1 month of screening or any blood donation/loss more than 500 mL during the 3 months prior to the first dose of study drug.

26. The subject has a history of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the investigator or history of hypersensitivity to drugs with a similar chemical structure or class to ticagrelor, any biologic therapeutic agent, or any significant food allergy that could preclude a standard diet in the clinical site.

27. Concern for the inability of the subject to comply with study procedures and/or follow-up, or, in the opinion of the investigator, the subject is not suitable for entry into the study.

3.2.3 Subject Restrictions During the Study

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

- Subjects in Cohorts 1 through 3 must be willing to remain in the clinic from Day -1 through 48 hours following MEDI2452 (PB2452) dosing on Day 1. Subjects in Cohorts 4 through 7 must be willing to remain in the clinic from Day -3 through 48 hours following MEDI2452 (PB2452) dosing on Day 1. Subjects in Cohorts 8 and 9 must be willing to remain in the clinic from Day -3 through 48 hours following ticagrelor dosing on Day 2.

- Subjects in Cohorts 1 through 7 must be willing to return to the clinic for follow-up visits on Days 4, 7, and 28 (+2 days) and subjects in Cohorts 8 and 9 must be willing to return to the clinic for follow-up visits on Days 7 and 28 (+2 days).

- Subjects must refrain from smoking or use of nicotine or nicotine-containing products as specified in Exclusion Criteria #20.

- Consumption of alcohol is not permitted within 48 hours prior to check-in until discharge from the clinical site.

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

3.3 WITHDRAWAL OF SUBJECTS FROM THE STUDY

3.3.1 Reasons for Withdrawal

Subjects can withdraw consent and discontinue from the study at any time, for any reason, without prejudice to further treatment.

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

1. Is non-compliant with the protocol;
2. Experiences a serious AE (SAE) or intolerable AE(s) that, in the investigator's opinion, requires withdrawal from the study;
3. Has laboratory safety assessments that reveal clinically significant hematological or biochemical changes from baseline values;
4. Develops symptoms or conditions listed in the exclusion criteria during the course of the study and through EOS;
5. Requires a medication prohibited by the protocol; or
6. Requests an early discontinuation for any reason.

The investigator can also withdraw a subject upon the request of the sponsor (PhaseBio Pharmaceuticals, Inc) or if the sponsor terminates the study. Upon occurrence of a SAE or intolerable AE, the investigator will confer with the sponsor. If a subject is discontinued because of an AE, the event will be followed until it is resolved or until stable.

3.3.2 Handling of Withdrawals

Subjects are free to withdraw from the study at any time upon request. Subject participation in the study may be stopped at any time at the discretion of the investigator or at the request of the sponsor.

When a subject withdraws from the study, the reason(s) for withdrawal will be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Whenever

possible, any subject who withdraws from the study prematurely will undergo all EOS assessments. Any subject who fails to return for final assessments will be contacted by the site in an attempt to have them comply with the protocol. The status of subjects who fail to complete final assessments will be documented in the eCRF.

3.3.3 Replacements

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

3.4 STUDY TREATMENTS

3.4.1 Method of Assigning Subjects to Treatment Groups

PPD will generate the randomization schedule. Eligible subjects will be randomly assigned to treatment on Day 1 before dosing. Within each cohort, subjects will be randomly assigned to receive either MEDI2452 (PB2452) (100, 300, 1000, 3000, 9000, or 18000 mg of MEDI2452 [PB2452]) or matching placebo in a ratio of 3:1 or 6:2 depending on the cohort. In Cohorts 1 and 4, 2 subjects will initially receive MEDI2452 (PB2452) or placebo. There will be a safety evaluation of at least 24 hours before the remaining subjects in Cohorts 1 and 4 will be dosed (Section 3.4.2.1).

3.4.2 Treatments Administered

Subjects will receive one of the following treatments based on the cohort in which they are enrolled and the treatment to which they are randomly assigned:

- 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: single oral dose of 180 mg ticagrelor (2 × 90-mg tablet) in the morning on Day -2 followed by 90 mg ticagrelor orally every 12 hours for 4 additional doses;

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: single oral dose of 180 mg ticagrelor (2 × 90-mg tablet) in the morning on Day -2 followed by 90 mg ticagrelor orally every 12 hours for 4 additional doses; 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: single oral dose of 180 mg ticagrelor (2 × 90-mg tablet) in the morning on Day -2 followed by 90 mg ticagrelor orally every 12 hours for 4 additional doses; 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: single oral dose of 180 mg ticagrelor (2 × 90-mg tablet) in the morning on Day -2 followed by 90 mg ticagrelor orally every 12 hours for 4 additional doses; simultaneous with the 5th ticagrelor dose, a single 30-minute IV infusion of 18000 mg MEDI2452 (PB2452) or matching placebo on Day 1

- Cohort 8: single oral dose of 180 mg ticagrelor (2 × 90-mg tablet) in the morning on Day -2 followed by 90 mg ticagrelor orally every 12 hours for 4 additional doses; simultaneous with the 5th ticagrelor dose, a single 30-minute IV infusion of 9000 mg MEDI2452 (PB2452) or matching placebo on Day 1, followed by a single oral dose of 180 mg ticagrelor (2 × 90-mg tablet) in the morning on Day 2 (24 hours after initiation of the MEDI2452 [PB2452] infusion and 5th ticagrelor dose)

- Cohort 9: single oral dose of 180 mg ticagrelor (2 × 90-mg tablet) in the morning on Day -2 followed by 90 mg ticagrelor orally every 12 hours for 4 additional doses; simultaneous with the 5th ticagrelor dose, a single 30-minute IV infusion of 18000 mg MEDI2452 (PB2452) or matching placebo on Day 1, followed by a single oral dose of 180 mg ticagrelor (2 × 90-mg tablet) in the morning on Day 2 (24 hours after initiation of the MEDI2452 [PB2452] infusion and 5th ticagrelor dose)

The assigned study drug (MEDI2452 [PB2452]) or matching placebo will be administered by clinical site staff as an IV infusion to subjects in all cohorts in the morning on Day 1 after an overnight fast of approximately 8 hours. Study drug will be infused over a 30-minute period. Subjects will remain fasted for 2 hours following administration of study drug.

Treatment with oral ticagrelor will be administered by the clinical site staff to subjects in Cohorts 4 through 9 beginning in the morning on Day -2 after an overnight fast of

approximately 8 hours. Subjects will fast for 2 hours prior to receiving the 4 additional doses of ticagrelor. For subjects in Cohorts 8 and 9, the 24-hour post-MEDI2452 (PB2452) infusion 6th ticagrelor dose will be administered by clinical site staff in the morning on Day 2 after an overnight fast of approximately 8 hours. All doses of ticagrelor will be administered with 240 mL of water.

During fasting periods subjects will restrict their consumption of water to small amounts as needed for thirst. At all other times during the study, subjects may consume water ad libitum.

3.4.2.1 Dose Escalation

A SRC will be formed for a blinded review of safety (eg, clinical laboratory results, AEs, ECGs, vital signs) and available PK data through Day 4 for each dose cohort. The SRC will be minimally composed of the on-site investigator, PPD medical monitor, and clinical pharmacologist, and the PhaseBio study director and clinical operations lead. Dose escalation to successive cohorts will be based upon safety of the preceding cohort. The investigator will make a recommendation on whether to proceed to the next predefined dose level, pause dosing for review of additional safety and/or PK data, or to adjust the dose of the next dose cohort. The decision to adjust or pause the dose or proceed to the next cohort will be made by the SRC. The safety data will be reviewed in a blinded manner and must be deemed acceptable to the SRC prior to dosing of the next higher dose group.

This study is designed such that dose escalation for Cohorts 1 through 7 is allowed only after a safety data review of each dose cohort by the SRC. Administration at the next dose level will only proceed after the safety data obtained from the previous dose cohort and available PK data have been evaluated and approved by the SRC. If the dose level for Cohort 6 is determined to be safe and well-tolerated, dosing for Cohort 8 may occur in parallel with Cohort 7.

Based on the review of safety and PK data, if available, the SRC may choose to repeat a dose level, administer a dose less than the previous dose, or escalate to a dose lower than the next planned dose. In the case of a DLT, SAE, or other significant AE, the SRC may request that the study drug assignment be unblinded.

3.4.2.2 Infusion or Allergic Reactions

The administration of study drug must be performed under supervision of trained medical staff and where facilities to handle allergic reactions are available. Should a subject experience multiple relevant symptoms typical of infusion reactions seen with some

recombinant protein drugs (eg, lightheadedness, nausea, chills, fever) (Doesseger et al 2015), the study drug infusion may be stopped or slowed at the discretion of the investigator and/or the medical monitor. Once symptoms resolve, re-infusion may be attempted. Should a subject experience symptoms typical of an allergic reaction (eg, shortness of breath, anaphylaxis, urticaria, angioedema), then study drug administration should be discontinued immediately and permanently.

Suspected anaphylaxis should be assessed according to the clinical diagnostic criteria outlined by the National Institute of Allergy and Infectious Diseases, which are provided in Appendix 6.4.

For these and other circumstances, subjects will receive appropriate medical treatment at the discretion of the investigator.

3.4.2.3 Dose-Limiting Toxicities

1. A DLT is defined as any AE judged by the investigator to be study drug related (ie, causality rated as possible or greater) that is assessed as severe or higher.

2. A DLT is defined as an SAE or any other medically important AE that impacts subject safety experienced by 1 or more subjects in a cohort who, after unblinded safety review, are confirmed to have received MEDI2452 (PB2452). Serious AEs that are determined by the investigator as related to study drug will be reviewed by the SRC to determine if they are DLTs.

3. A DLT is defined as a clinically significant laboratory abnormality (according to the investigator) experienced by 2 or more subjects in a cohort who, after unblinded safety review, are confirmed to have received MEDI2452 (PB2452).

4. A DLT may be considered for a subject who withdraws because of intolerable treatment-emergent AE (TEAE). The investigator must use his or her judgment in determining whether any event is a DLT.

3.4.2.4 Stopping Criteria

After completion of Day 4 for each dose cohort, the SRC (see Section 3.4.2.1) will review and assess all available safety (eg, clinical laboratory results, AEs, ECGs, vital signs), tolerability, and available PK data to make a decision on the dose for next dose cohort. Dose escalation may be suspended if any of the following scenarios occur with a reasonable possibility of causal relationship with MEDI2452 (PB2452):

- Events that, in the opinion of the medical monitor and sponsor SRC, contraindicate further dosing of additional subjects
- Any serious AE with a suspected relationship to MEDI2452 (PB2452) in a dose cohort
- Data from the previous dose cohort indicating safety concerns for the next cohort to be dosed at a higher level, such as unanticipated responses (eg, clinically significant changes in clinical laboratory data, ECGs, cardiac telemetry, vital signs, or physical examinations)
- More than 50% of the subjects in a given dose cohort are withdrawn due to poor tolerability of MEDI2452 (PB2452)
- Two or more subjects experiencing severe AEs assessed at least possibly related to MEDI2452 (PB2452), or 1 or more subjects experiencing severe AEs assessed at least possibly related to MEDI2452 (PB2452) at the discretion of the investigator
- Two or more subjects have >3 × ULN of either ALT or AST, or > 2 × ULN for bilirubin or alkaline phosphatase where no other reason can be found to explain the combination of increases
- Two or more subjects experiencing a severe infusion reaction

Dose escalation may also be suspended if, in the opinion of the investigator or sponsor, any other significant safety or tolerability issues are identified in the comprehensive review of available data that warrant further evaluation before additional subjects are dosed. This may include emerging nonclinical data, clinically relevant AEs, or relevant data from other sources indicating safety concerns even if the event(s) per se does not meet the protocol-specified definition of a DLT.

Dose-limiting toxicities identified during the study will be assessed as potential indicators of cumulative toxicity and provide rationale for revision of the maximum tolerated dose (MTD). Although this study is not designed to dose to a MTD, the MTD may be reached if 3 or more

subjects in a dose cohort experience a DLT as defined in Section 3.4.2.3. No further dosing will occur above the MTD.

3.4.3 Identity of Investigational Product

The study drug (MEDI2452 [PB2452]) is supplied as a sterile white to off-white lyophilized cake, free from visible foreign particles in a 20R glass vial at a nominal fill volume of 7.5 mL. MEDI2452 (PB2452) (reconstituted state) is [redacted]

The following drug supplies will be used in the study:

Product	Supplied as:
MEDI2452 (PB2452)	10 gram (g) single dose vial
Placebo (sterile 0.9% sodium chloride)	1 liter IV bag
IV stabilizing solution	3 mL vial
Ticagrelor	90-mg immediate release tablets

In addition to the study drug, an IV stabilizing solution (IVSS) is supplied to prevent adsorption and aggregation of MEDI2452 (PB2452) or placebo to the IV infusion system. The IVSS is supplied as a sterile colorless-to-yellow, clear-to-slightly opalescent liquid in a 3-mL glass vial at a nominal fill of 1 mL. The IVSS vial contains a nominal 1-mL solution of [redacted]

It should be noted that the lyophilized MEDI2452 (PB2452) study drug must not be reconstituted with the IVSS.

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

Ticagrelor 90-mg tablets are supplied as a round, biconvex, yellow, film-coated tablet with a "90" above "T" on one side.

3.4.4 Management of Clinical Supplies

3.4.4.1 Study Drug Packaging and Storage

PhaseBio Pharmaceuticals, Inc will provide the investigator and clinical site with adequate quantities of MEDI2452 (PB2452) and IVSS. Ticagrelor and placebo (0.9% sterile sodium

chloride for injection) will be commercially obtained and supplied by PPD and stored in accordance with the manufacturer's label recommendations.

MEDI2452 (PB2452) will be supplied in a 20R glass vial at a nominal fill volume of 7.5 mL, stoppered with siliconized 20 mm chlorobutyl elastomer, Flurotec-coated, single vent lyophilization stopper, and sealed with flip-off cap overseal. Following reconstitution with water for injection MEDI2452 (PB2452) is further diluted into 0.9% saline for IV infusion. The clinical site pharmacy will prepare a single dose for each subject based on the dosing cohort and randomization assignment. The concentration will vary between 0.4 mg/mL up to 72 mg/mL. Separate instructions will be provided to the clinic for dose dilution, preparation, storage, and administration.

The IVSS will be supplied in a 3-mL glass vial at a nominal fill of 1 mL, stoppered with siliconized 13-mm chlorobutyl rubber stopper, and sealed with flip-off cap overseal.

The study drug (MEDI2452 [PB2452]) must be stored in a secure area (eg, a locked, temperature-controlled unit), protected from moisture and light, and be stored at 2°C to 8°C (36°F to 46°F). The clinical site will be required to keep a temperature log to establish a record of compliance with these storage conditions. All study drugs will be kept in a secure cabinet or room with access restricted to necessary clinic personnel.

3.4.4.2 Study Drug Accountability

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

3.4.5 Blinding

This is a double-blind study. Neither the subjects nor the investigator will be aware of the treatment assignment. Blinding will be maintained throughout the study by use of active and placebo 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. 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 who are not part of the study team may be unblinded during the conduct of the study (study director, a single biostatistician, and a bioanalytical scientist[s]) before data is more generally unblinded. These summaries will not reveal individual subjects' treatment assignments. Except as noted above, all other members of PhaseBio Research and Development will remain blinded. Access to the randomization code will be strictly controlled according to PPD and PhaseBio standard operating procedures.

3.4.6 Breaking the Blind

A subject may be unblinded in the event of a DLT, 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.

A formal unblinded interim analysis (IA) of all accumulated safety, PD, and PK data (as needed) will be performed after the last patient in Cohort 6 completes follow-up visit Day 7 to provide an interim assessment of the safety profile of MEDI2452 (PB2452) after the target efficacious dose level has been tested (Cohort 6). Pharmacodynamic and PK data analysis will also be included as needed in the IA to provide an assessment of the likely benefit/risk profile of the study drug. The prespecified IA analyses will be a subset of the final study analyses. The detailed scope of interim analyses will be outlined in a separate document, the statistical analysis plan (SAP). An independent statistical group will produce the interim analysis.

3.4.7 Treatment Compliance

All doses of study drug will be administered at the clinical site under direct observation of clinic personnel and recorded in the eCRF. Clinic personnel will confirm that the subject has received the entire dose of study drug.

The date and time of study drug dosing will be recorded on the appropriate page of the eCRF. If a subject does not receive study drug, the reason for the missed dose will be recorded.

3.4.8 Prior and Concomitant Medications

3.4.8.1 Prior Medications and Therapies

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.

3.4.8.2 Concomitant Medications and Therapies

Subjects are prohibited from taking any prescription or over-the-counter medications or supplements as described in Section 3.2.2. Paracetamol/acetaminophen may be administered at the discretion of the investigator at doses of <2 g/day.

Subjects are prohibited from therapy with strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers as described in Section 3.2.2. A list of example inhibitors and inducers of CYP3A4 is presented in Section 6.2.

Subjects are prohibited from taking nonsteroidal anti-inflammatory drugs, anticoagulants, or other antiplatelet agents as described in Section 3.2.2.

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

3.5 STUDY PROCEDURES

After signing the informed consent form (ICF) (Section 4.3), subjects will undergo study procedures at the time points specified in the schedule of events (Table 6−1).

3.5.1 Pharmacokinetic Assessments

Plasma:

Blood samples for PK analysis of MEDI2452 (PB2452) in serum will be collected from all subjects at the following time points: before dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours, and 7 and 28 days after initiation of the infusion.

Plasma samples for determining total concentrations of ticagrelor and its active metabolite AR-C124910XX, will be collected from subjects in Cohorts 4 through 9 at the following timepoints: before dosing (within 10 minutes prior to the initiation of the MEDI2452 [PB2452] infusion and 5th ticagrelor dose [Hour 0]), and at 0.5, 1, 2, 3, 6, 12, and 24 hours after the initiation of the MEDI2452 (PB2452) infusion and 5th ticagrelor dose. Additional samples will be collected from subjects in Cohorts 8 and 9 at the following timepoints: 0.5, 1, 2, 3, 6, 12, 24, and 48 hours after the Day 2 post-MEDI2452 (PB2452) 6th ticagrelor dose.

Plasma samples for determining unbound concentrations of ticagrelor and AR-C124910XX will be collected from subjects in Cohorts 4 through 9 at the following timepoints: before dosing (within 10 minutes prior to the initiation of MEDI2452 [PB2452] infusion and 5th ticagrelor dose [Hour 0]), and at 0.5, 1, 2, 3, 6, 12, and 24 hours after the initiation of the MEDI2452 (PB2452) infusion and 5th ticagrelor dose. Additional samples will be collected from subjects in Cohorts 8 and 9 at the following timepoints: 0.5, 1, 2, 3, 6, 12, and 24 hours after the Day 2 post-MEDI2452 (PB2452) 6th ticagrelor dose.

The following plasma PK parameters will be calculated for MEDI2452 (PB2452) using actual sampling times rather than scheduled sampling times:

- Area under the plasma concentration versus time curve (AUC) from time 0 to the time of last quantifiable concentration (AUC_{0-t})
- Observed maximum plasma concentration (C_{max})
- Time to reach the observed maximum plasma concentration (T_{max})
- AUC from time 0 extrapolated to infinity (AUC_{0-inf}) (if data permit)
- Terminal elimination half-life ($t_{½}$) (if data permit)
- Apparent clearance (CL) (if data permit)

The following plasma PK parameters will be calculated for ticagrelor and AR-C124910XX using actual sampling times rather than scheduled sampling times:

- C_{max}
- T_{max}
- AUC from time 0 to 12 hours after dosing (AUC_{0-12})

- AUC from time 0 to 24 hours after dosing (AUC_{0-24})
- AUC_{0-inf} (if data permit)
- t½ (if data permit)

The following plasma PK parameters will be calculated for AR-C124910XX using actual sampling times rather than scheduled sampling times:

- C_{max} ratio (metabolite:parent)
- AUC_{0-24} ratio (metabolite:parent)

Urine:

Pooled urine samples to assess urine ticagrelor and AR-C124910XX concentrations will be collected from subjects in Cohorts 4 through 9 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 after the initiation of the MEDI2452 (PB2452) infusion and 5th ticagrelor dose.

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

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

Additional PK parameters may be generated, if needed.

3.5.1.1 Pharmacokinetic Sample Collection

Details on the collection, preparation, and handling of PK blood and urine samples and sample shipping instructions will be provided separately to the clinical site in the form of a laboratory manual. The clinical site will store all urine and plasma/serum samples at the designated temperatures until shipped to the appropriate laboratories for analysis. Back-up samples will be maintained by the clinical site under the same conditions, or at a designated

storage facility, until PhaseBio Pharmaceuticals indicates that the back-up samples should be shipped to the sponsor.

MEDI2452 (PB2452) and immunogenicity analysis will be performed by:

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

Ticagrelor and AR-C124910XX concentration analysis will be performed by:

Covance
1121 East 3900 South, Suite C-110
Salt Lake City, UT 84124
[redacted]

3.5.1.2 Bioanalytical Methods

Pharmacokinetic samples for total and free ticagrelor and AR-C124910XX will be analyzed using a validated liquid chromatography coupled with tandem mass spectrometry assay in human plasma. Pharmacokinetic samples for MEDI2452 (PB2452) will be analyzed using an immunoassay. The methods will be validated as per International Council for Harmonisation (ICH) standards and fit for purpose. Details of the bioanalytical methods and validation will be available in a separate bioanalytical report.

3.5.2 Pharmacodynamic Assessments

Blood samples for PD analysis will be collected from subjects in Cohorts 4 through 9 at the following time points: before dosing (within 60 minutes prior to first ticagrelor dose on Day -2) and again before dosing (within 10 minutes prior to the initiation of the MEDI2452 [PB2452] infusion and 5th ticagrelor dose [Hour 0]) and at 0.5, 1, 2, 3, 6, 12, 24, and 48 hours after the initiation of the MEDI2452 (PB2452) infusion and 5th ticagrelor dose. Additional blood samples for PD analysis from subjects in Cohorts 8 and 9 will be collected at the following time points: 1, 2, 6, and 12 hours after the Day 2 post-MEDI2452 (PB2452) 6th ticagrelor dose. Subjects will be scheduled to provide adequate time for performance of PD sample handling and processing within the stated guidelines outlined in Section 3.5.2.1.

The following PD parameters will be calculated using the data generated by LTA, $P2Y_{12}$ reaction units (PRU), and platelet reactivity index (PRI) assays:

LTA:

- inhibition of platelet aggregation (IPA) (max and final extent) induced by 20µM adenosine diphosphate (ADP) at each assessment point
- inhibition of maximal platelet aggregation (IPA_{max})
- time to IPA_{max} ($TIPA_{max}$)

VerifyNow™$P2Y_{12}$:

- PRU at each assessment point

VASP by ELISA:

- PRI at each assessment point

Additional PD parameters may be generated, if needed.

3.5.2.1 Pharmacodynamic Sample Collection

Blood samples will be collected in blood collection tubes specific for each of the 3 assays:

- LTA: 3.2% sodium citrate (blue-top) (2 tubes, 4.5 mL blood each)
- VerifyNow™$P2Y_{12}$: Greiner Bio-One Vacuette® partial fill blood collection tube containing 3.2% sodium citrate (approximately 3 mL blood)
- VASP: 3.2% sodium citrate (blue-top) (1.8 mL blood)

The LTA assays must be completed within 3 hours of venipuncture and the VerifyNow test must be completed within 4 hours of venipuncture. Results from these assays will be forwarded to CirQuest Labs for ongoing evaluation of testing and data adjudication. The PRI assay must be completed within 48 hours of venipuncture and will be shipped overnight to CirQuest Labs, LLC at 140 Collins Avenue, Memphis, TN 38112[redacted]

Instructions for sample collection, preparation, and shipping will be provided separately to the clinical site.

3.5.2.2 Bioanalytical Methods

Details of the bioanalytical methods and validation will be available in a separate bioanalytical report.

3.5.3 Safety Assessments

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), 12-lead ECG results, cardiac telemetry, and physical examination findings.

3.5.4 Adverse Events

3.5.4.1 Adverse Event Definitions

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

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

A TEAE is defined as any event not present before exposure to study drug (MEDI2452 [PB2452]) or any event already present that worsens in intensity or frequency after exposure.

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

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

An AE or suspected adverse reaction is considered “unexpected” if it is not listed in the investigator brochure or at the specificity or severity that has been observed with the study drug being tested; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the

current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

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

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

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

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

Special attention will be given to DLTs and the MTD, if applicable. Dose-limiting toxicity is defined in Section 3.4.2.3. Dose escalation to the next dose level is described in Section 3.4.2.1.

The overall safety profile, including but not limited to DLT and MTD will be used in the selection of the starting dose(s) in future studies of MEDI2452 (PB2452) administered by infusion.

3.5.4.2 Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to PhaseBio Pharmaceuticals, Inc. Adverse events will be assessed from the time of pretreatment dosing with ticagrelor on Day -2 until completion of all study procedures and EOS assessments (Day 28).

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

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

3.5.4.3 Reporting Adverse Events

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

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

Any AE considered serious by the investigator or which meets SAE criteria (Section 3.5.4.1) must be reported to the sponsor immediately (after the investigator has confirmed the occurrence of the SAE). The investigator will assess whether there is a reasonable possibility that the study drug caused the SAE. The sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the US Title 21 Code of Federal Regulations (CFR) Parts 312 and 320. The investigator is responsible for notifying the institutional review board (IRB) directly.

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

PPD Medical Monitor: Rahul Bhatnagar, MD
PPD
7551 Metro Center Drive, Suite 300
Austin, TX 78744
[redacted]

3.5.4.4 Assessment of 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 using the following criteria:

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

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

3.5.4.5 Assessment of Causality

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

The investigator will assess causality (ie, whether there is a reasonable possibility that the study drug caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

- Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

- Possible: This relationship is based on evidence suggesting a causal relationship between the study drug and the AE, ie, there is a reasonable possibility that the drug caused the event. The event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

- Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely.

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

3.5.4.6 Follow-up of Adverse Events

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

3.5.5 Clinical Laboratory Testing

Clinical laboratory tests will be performed by PPD Central Laboratory. Blood will be collected at the time points indicated in the schedule of events (Table 6−1) and will be prepared using standard procedures. Repeat clinical laboratory tests may be performed at the

discretion of the investigator, if necessary, to evaluate inclusion and exclusion criteria or clinical laboratory abnormalities. The clinical laboratory that will perform the tests will provide the reference ranges for all clinical laboratory parameters.

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, carbon dioxide, 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 (screening only)
Other analyses	Urine drug screen (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, cotinine, methylenedioxymethamphetamine [MDMA], opiates, phencyclidine, propoxyphene, and tetrahydrocannabinol) (screening and check-in only) Urine Alcohol (check-in only) Female subjects: Follicle-stimulating hormone, serum pregnancy test (human chorionic gonadotropin [at screening, check-in, and Day 28 only])
Immunogenicity	Anti-drug antibodies (ADA)

When procedures are overlapping and occurring at the same time point, the order of priority for procedures should be PK blood collection, 12-lead ECG, vital sign measurements, and then clinical laboratory tests.

Abnormal clinical laboratory values will be flagged as either high or low (or normal or abnormal) based on the reference ranges for each laboratory parameter. The investigator will determine whether any of the abnormally high or low results are clinically significant or not clinically significant. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from the screening value is noted, the clinically significant value and reason for clinical significance will be documented on the AE page of the eCRF. The investigator will continue to monitor the subject with additional assessments until the values have reached the reference range or the values at screening or until the investigator determines that follow-up is no longer medically necessary.

3.5.6 Vital Sign Measurements

Vital signs will be measured at the time points indicated in the schedule of events (Table 6−1). Vital sign measurements will include systolic and diastolic blood pressures, oral body temperature, respiratory rate, and heart rate. The subject will be seated for at least 10 minutes before all measurements are taken.

The investigator will determine whether any of the vital sign measurements are clinically significant or not clinically significant. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from the screening values is noted, the clinically significant value and reason for clinical significance will be documented on the AE page of the subject's eCRF. The investigator will continue to monitor the subject with additional assessments until the value has reached the reference range or the value at screening or until the investigator determines that follow-up is no longer medically necessary.

3.5.7 Twelve-Lead Electrocardiogram

Triplicate 12-lead ECGs will be obtained after the subject has been in the supine position for at least 10 minutes at the time points indicated in the schedule of events (Table 6−1) and as indicated by AEs or telemetry findings. The investigator should review and sign the ECG for any immediate issues. 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 QTcF.

The investigator will determine whether any of the 12-lead ECG results are clinically significant or not clinically significant. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from screening is noted, the clinically significant value and reason for clinical significance will be documented on the AE page of the subject's eCRF. The investigator will continue to monitor the subject with additional assessments until either the values have reached reference range or the values at screening or until the investigator determines that follow-up is no longer medically necessary.

3.5.8 Physical Examinations

A standard physical examination will be performed at the time points indicated in the schedule of events (Table 6−1). The examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. A brief physical examination will include assessment of skin (including any signs for cutaneous erythema), lungs, cardiovascular system, and abdomen (liver, spleen).

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

Height and weight will be measured and body mass index will be calculated at screening only.

3.5.9 Infusion Site Assessments

The infusion site will be examined by the investigator or designee periodically for pain, tenderness, erythema/redness, and induration/swelling as indicated in the schedule of events (Table 6−1). Any infusion site reactions observed will be monitored and recorded as AEs.

See Appendix 6.3 for infusion site assessment scales.

3.5.10 Telemetry Monitoring

Cardiac telemetry will be performed at the time points indicated in the schedule of events (Table 6−1) to monitor heart rate and rhythm activity as real-time safety measurements. The clinical research site will be responsible for providing trained study personnel for monitoring of telemetry. The telemetry monitoring system utilized will be maintained in accordance with the clinical research site's standard operating procedures.

The investigator will determine if any of the telemetry findings are clinically significant. Clinical significance is defined as any variation in results that has medical relevance and may result in an alteration in medical care (eg, active observation, diagnostic measures, or therapeutic measures).

If a clinically significant change from the telemetry findings on Day -1 (approximately 12 hours before the start of infusion) is noted, the clinically significant value and reason for clinical significance will be documented in the AE page of the subject's eCRF. Clinically significant abnormalities should be followed up by performing a 12-lead ECG. The investigator will continue to monitor the subject with additional assessments until the investigator determines that follow-up is no longer medically necessary.

3.5.11 Immunogenicity

Immunogenicity (antibody) samples will be screened for the presence of binding ADA at the time points indicated in the schedule of events (Table 6−1).

3.6 STATISTICAL ANALYSIS PLAN

3.6.1 Sample Size Calculations

The sample size (N = 60) 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.

3.6.2 Analysis Populations

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

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

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

3.6.3 Statistical Analysis

Details of all statistical analyses will be described in a separate SAP. All data collected will be presented in data 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.

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

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

3.6.3.1 Safety Analyses

Adverse events will be coded by preferred term and system organ class using the latest version of the Medical Dictionary for Regulatory Activities. All AE data will be presented in a data listing. Treatment-emergent AEs will be summarized by treatment and overall, as well as by severity and relationship to study drug. Serious AEs and AEs leading to discontinuation of study drug will be presented in the data listings.

Actual values and changes from baseline for clinical laboratory test results, vital sign measurements, and 12-lead ECG results will be summarized by treatment at each time point using descriptive statistics (number of subjects, mean, SD, median, minimum, and maximum). Shift tables will be generated for clinical laboratory test results. Clinical laboratory test results, vital sign measurements, 12-lead ECG results, and physical examination findings will be presented in data listings.

3.6.3.2 Pharmacokinetic Analyses

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

The PK parameters of MEDI2452 (PB2452), ticagrelor, and AR-C124910XX will be determined using noncompartmental methods using Phoenix® WinNonlin® (Certara, L.P., Princeton, NJ) Version 6.4 or higher or SAS® Version 9.3 or higher (SAS Institute Inc., Cary, NC). Pharmacokinetic parameters will be summarized for each dose level using descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum). Geometric means will be reported for AUCs and C_{max}. Actual sampling times, rather than scheduled

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

Dose proportionality will be tested using the power regression model for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, and C_{max} of MEDI2452 (PB2452) in Cohorts 4, 5, 6, and 7.

3.6.3.3 Pharmacodynamic Analyses

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

3.6.4 Handling of Missing Data

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 CV will be reported as not applicable. Missing concentrations will be excluded from the calculations.

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

3.6.5 Interim Analyses

A formal unblinded IA of all accumulated safety, PD, and PK data (as needed) will be performed after the last patient in Cohort 6 completes follow-up visit Day 7 to provide an interim assessment of the safety profile of MEDI2452 (PB2452) after the target efficacious dose level has been tested (Cohort 6). Pharmacodynamic and PK data analysis will also be included as needed in the interim analysis to provide an assessment of the likely benefit/risk profile of the study drug. The prespecified IA analyses will be a subset of the final study analyses. The detailed scope of IA will be outlined in a separate document, the SAP. An independent statistical group will produce the interim analysis.

Separate from the IA, blinded safety data review for each dose cohort will be performed before dosing in the next cohort is allowed (Section 3.4.2.1).

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

3.7 DATA QUALITY ASSURANCE

This study will be conducted using quality processes described in applicable procedural documents. The quality management approach to be implemented will be documented and will comply with the current ICH guidance on quality and risk management. All aspects of the study will be monitored for compliance with applicable government regulatory requirements, current Good Clinical Practice, the protocol, and standard operating procedures. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff. Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

4. INVESTIGATOR OBLIGATIONS

The following administrative items are meant to guide the investigator in the conduct of the study and may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB but will not result in protocol amendments.

4.1 CONFIDENTIALITY

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

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

4.2 INSTITUTIONAL REVIEW

Federal regulations and the ICH guidelines require that approval be obtained from an IRB before participation of human subjects in research studies. Before study onset, the protocol, ICF, advertisements to be used for the recruitment of study subjects, and any other written information regarding this study to be provided to the subject or the subject's legal guardian must be approved by the IRB. Documentation of all IRB approvals and of the IRB compliance with the ICH harmonised tripartite guideline E6(R2): Good Clinical Practice will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB approvals should be signed by the IRB chairman or designee and must identify the IRB name and address, the clinical protocol by title or protocol number or both and the date approval or a favorable opinion was granted.

4.3 SUBJECT CONSENT

Written informed consent in compliance with US Title 21 CFR Part 50 shall be obtained from each subject before he or she enters the study or before performing any unusual or nonroutine

procedure that involves risk to the subject. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB submission. Once reviewed, the investigator will submit the ICF to the IRB for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating subjects must sign the revised form.

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

4.4 STUDY REPORTING REQUIREMENTS

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

4.5 FINANCIAL DISCLOSURE AND OBLIGATIONS

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

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

4.6 INVESTIGATOR DOCUMENTATION

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

- IRB approval,

- An original investigator-signed investigator agreement page of the protocol,
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572,
- Curriculum vitae for the principal investigator and each subinvestigator listed on Form FDA 1572. Current licensure must be noted on the curriculum vitae. Curriculum vitae will be signed and dated by the principal investigators and subinvestigators at study start-up, indicating that they are accurate and current.
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under US Title 21 CFR Part 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- An IRB-approved ICF, samples of site advertisements for recruitment for this study, and any other written information about this study that is to be provided to the subject or legal guardians, and
- Laboratory certifications and reference ranges for any local laboratories used by the site, in accordance with US Title 42 CFR Part 493.

4.7 STUDY CONDUCT

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

4.8 DATA COLLECTION

4.8.1 Case Report Forms and Source Documents

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

Electronic CRFs and electronic data capture will be utilized. The electronic data capture system is validated and compliant with US Title 21 CFR Part 11. Each person involved with the study will have an individual identification code and password that allows for record traceability. Thus, the system, and subsequently any investigative reviews, can identify

coordinators, investigators, and individuals who have entered or modified records, as well as the time and date of any modifications. There may be an internal quality review audit of the data and additional reviews by the clinical monitor.

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

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

4.9 ADHERENCE TO PROTOCOL

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

4.10 REPORTING ADVERSE EVENTS

By participating in this study, the investigator agrees to submit reports of SAEs according to the timeline and method outlined in this protocol. In addition, the investigator agrees to submit annual reports to his or her IRB as appropriate. The investigator also agrees to provide the sponsor with an adequate report, if applicable, shortly after completion of the investigator's participation in the study.

4.11 INVESTIGATOR'S FINAL REPORT

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

4.12 RECORDS RETENTION

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements

or by an agreement with the sponsor. It is the sponsor's responsibility to inform the investigator/institution as to when these documents no longer need to be retained.

4.13 PUBLICATIONS

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

Data are the property of the sponsor and cannot be published without their prior authorization, but data and any publication thereof will not be unduly withheld.

5. STUDY MANAGEMENT

5.1 MONITORING

5.1.1 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, is obligated to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals in addition to maintaining necessary telephone and email contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and staff.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current ICH E6(R2) guidelines and standard operating procedures.

5.1.2 Inspection of Records

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

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

5.2 MANAGEMENT OF PROTOCOL AMENDMENTS AND DEVIATIONS

5.2.1 Modification of the Protocol

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

5.2.2 Protocol Deviations

The investigator or designee must document and explain in the subject's source documentation any deviation from the approved protocol. The investigator may implement a

deviation from, or a change to, the protocol to eliminate an immediate hazard to study subjects without prior IRB approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

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

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

5.3 STUDY TERMINATION

Although the sponsor has every intention of completing the study, they reserve the right to discontinue it at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last subject completes the last visit (includes the EOS visit and any additional long-term follow-up). Any additional long-term follow-up that is required for monitoring of the resolution of an AE or finding may be appended to the clinical study report.

5.4 FINAL REPORT

Whether the study is completed or prematurely terminated, the sponsor will ensure that clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that clinical study reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

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

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

6. APPENDICES

6.1 APPENDIX 1: SCHEDULE OF EVENTS

Table 6−1 Schedule of Events

Procedure	Screening	Check-in/ Pretreatment			Treatment				EOS/ Follow-up[a]	
Study Day(s)	−28 to −4	−3	-2	−1	1	2	3	4/FU[b]	7	28 (+2 days)
Informed consent	X									
Inclusion/exclusion criteria	X									
Demographics	X									
Medical history	X									
Urine drug screen (includes cotinine)	X	X[c]		X[d]						
Urine alcohol		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		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				
Clinical laboratory testing	X	X[c]		X[d]			X[d]	X[c]	X	X
Randomization					X					
Study drug administration										
Ticagrelor			X[i]	X[i]	X[i]	X[j]				
MEDI2452 (PB2452)[k]					X					
PK blood sampling										
Serum MEDI2452 (PB2452)[l]					X	X	X	X	X	X
Plasma ticagrelor/AR-C124910XX					X[m]	X[m] / X[n]	X[n]	X[n]		
Free plasma ticagrelor/AR-C124910XX					X[o]	X[o] / X[p]	X[p]			
PK urine sampling[q]					X	X				
PD sampling (LTA/PRU/VASP)			X		X[r]	X[r] / X[s]	X[s]			
Infusion site assessment[t]					X	X	X	X	X	
Serum immunogenicity		X[c]		X[d]					X	X
Adverse events		X[c]	X[c]	X	X	X	X	X	X	X
Discharge from clinic							X[u]	X[v]		

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.

[b] For Cohorts 1 through 7 only: Day 4 will be a follow-up visit.

[c] Cohorts 4 through 9 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 MEDI2452 [PB2452] infusion) and at 1, 2, 4, 8, and 24 hours after the initiation of the MEDI2452 (PB2452) infusion, and at 30, 36, 42, and 48 hours after the initiation of the MEDI2452 (PB2452) infusion and on Days 4, 7, and

28. During the MEDI2452 (PB2452) 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 MEDI2452 [PB2452] infusion) and at 1, 4 (±30 minutes), 5 (±10 minutes), 24, and 48 hours (±30 minutes) after the initiation of the MEDI2452 (PB2452) 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 MEDI2452 (PB2452) infusion (Hour 0) and will continue until subject is discharged from the clinical site.

[i] For Cohorts 4 through 9 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 (ie, 5 total doses of ticagrelor with the 5th dose occurring simultaneously with the initiation of the MEDI2452 [PB2452] infusion).

[j] For Cohorts 8 and 9 only: On Day 2, ticagrelor will be administered as an additional single dose of 180 mg, 24 hours after the initiation of the MEDI2452 (PB2452) infusion on Day 1 (6th ticagrelor dose).

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

[l] For all cohorts: Blood samples for determination of serum MEDI2452 (PB2452) will be collected within 10 minutes prior to the initiation of MEDI2452 (PB2452) infusion (Hour 0), and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, and 72 hours; and 7 and 28 days after the initiation of the MEDI2452 (PB2452) infusion.

[m] For Cohorts 4 through 9 only: Blood samples for determination of plasma ticagrelor and AR-C124910XX will be collected within 10 minutes prior to the initiation of MEDI2452 (PB2452) infusion and 5th ticagrelor dose (Hour 0) and at 0.5, 1, 2, 3, 6, 12, and 24 hours after initiation of MEDI2452 (PB2452) infusion and 5th ticagrelor dose.

[n] For Cohorts 8 and 9 only: Additional blood samples for determination of plasma ticagrelor and AR-C124910XX will be collected at 0.5, 1, 2, 3, 6, 12, 24, and 48 hours after Day 2 administration of ticagrelor (6th ticagrelor dose).

[o] For Cohorts 4 through 9 only: Blood samples for determination of unbound plasma ticagrelor and AR-C124910XX will be collected before dosing (within 10 minutes prior to the initiation of MEDI2452 [PB2452] infusion and 5th ticagrelor dose [Hour 0]), and at 0.5, 1, 2, 3, 6, 12, and 24 hours after initiation of MEDI2452 (PB2452) infusion and 5th ticagrelor dose.

[p] For Cohorts 8 and 9 only: Additional blood samples for determination of unbound plasma ticagrelor and AR-C124910XX will be collected at 0.5, 1, 2, 3, 6, 12, and 24 hours after Day 2 administration of ticagrelor (6th ticagrelor dose).

[q] For Cohorts 4 through 9 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, and 12 to 24 hours after the initiation of the MEDI2452 (PB2452) infusion and the 5th ticagrelor dose.

[r] For Cohorts 4 through 9 only: Blood samples for PD analysis (LTA/PRU/VASP testing) will be collected before dosing (within 60 minutes prior to first ticagrelor dose on Day -2) and again within 10 minutes prior to initiation of MEDI2452 (PB2452) infusion and 5th ticagrelor dose (Hour 0), and at 0.5, 1, 2, 3, 6, 12, 24, and 48 hours after initiation of MEDI2452 (PB2452) infusion and 5th ticagrelor dose.

[s] For Cohorts 8 and 9 only: Additional blood samples for PD analysis (LTA/PRU/VASP testing) will be collected at 1, 2, 6, and 12 hours after Day 2 administration of ticagrelor (6th ticagrelor dose).

[t] Infusion site assessments will be performed for all subjects within 15 minutes prior to the initiation of the MEDI2452 (PB2452) infusion (Hour 0), and at 1, 3, 24, 48, and 72 hours after initiation of the MEDI2452 (PB2452) infusion and on Day 7.

[u] For Cohorts 1 through 7 only.

[v] For Cohorts 8 and 9 only.

6.2 APPENDIX 2 - LIST OF EXAMPLE INHIBITORS AND INDUCERS OF CYP3A4

Strong Inhibitors (≥5-fold increase in AUC or >80% decrease in oral clearance):

Boceprevir
Clarithromycin
Conivaptan
Grapefruit juice
Indinavir
Itraconazole
Ketoconazole
Lopinavir/ritonavir
Mibefradil
Nefazodone
Nelfinavir
Posaconazole
Ritonavir
Saquinavir
Telaprevir
Telithromycin
Voriconazole

Strong Inducers (≥80% decrease in AUC):

Avasimibe
Carbamazepine
Phenytoin
Rifampin
St John's wort

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

6.3 APPENDIX 3 - INFUSION SITE ASSESSMENT

The investigator will assess the degree of reaction at the infusion site at scheduled time points during the study using the following rating scale:

Adverse Events of Interest	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Injection site adverse events				
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever for >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema/redness*	2.5 – 5 cm	5.1 – 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/swelling**	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/swelling should be evaluated and graded using the functional scale as well as the actual measurement.

6.4 APPENDIX 4: SECOND SYMPOSIUM ON THE DEFINITION AND MANAGEMENT OF ANAPHYLAXIS: SUMMARY REPORT—SECOND NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASE/FOOD ALLERGY AND ANAPHYLAXIS NETWORK SYMPOSIUM

Second symposium on the definition and management of anaphylaxis: Summary report-Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium can be accessed at the following website link:

http://www.jacionline.org/article/S0091-6749%2805%2902723-5/pdf

Clinical criteria for diagnosing anaphylaxis are presented in Table 6.4.

Table 6-4 Clinical Criteria for Diagnosing Anaphylaxis

Anaphylaxis is highly likely when any <u>one</u> of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING: a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a <u>likely</u> allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula) b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia) c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours): a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP[1] b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

Abbreviations: BP, blood pressure; PEF, peak expiratory flow.

[1] Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 × age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

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