PHASE 2A, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE-DOSE, 2-PART STUDY TO ASSESS THE SAFETY, TOLERABILITY AND PHARMACOKINETIC RESPONSE AND EXPLORE THE PHARMACODYNAMIC RESPONSE FOLLOWING 4 WEEKS OF ONCE WEEKLY SUBCUTANEOUS INJECTIONS OF PB1046 IN ADULT SUBJECTS WITH STABLE HEART FAILURE WITH REDUCED EJECTION FRACTION (HFREF) (PART 1) AND IN SUBJECTS WITH CARDIAC DYSFUNCTION SECONDARY TO DUCHENNE OR BECKER MUSCULAR DYSTROPHY (PART 2)

Compound:	PB1046 (Vasomera) Injection
US IND Number:	112,431
Clinical Protocol Number:	PB1046-PT-CL-0003-P1
Phase:	2a
Version and Date:	Version 0, 15 March 2016
Sponsor:	PhaseBio Pharmaceuticals Inc. 1 Great Valley Parkway, Suite 30 Malvern, PA 19355
Medical Monitor:	Poul Strange, MD, PhD Integrated Medical Development Windsor Business Park, Building 3B, 2th Floor 186 Princeton-Hightstown Road Princeton Junction, NJ 08550 Phone: 609-897-0505 Ext. 113
Clinical Monitoring and Study Management:	PhaseBio Pharmaceuticals Inc. 1 Great Valley Parkway, Suite 30 Malvern, PA 19355
Serious Adverse Event Reporting:	PhaseBio Pharmaceuticals, Inc. Phone: 610-981-6507/Mobile: 610-608-8619 Fax: 1-484-971-5974
Summary of Incorporated Protocol Amendments:	Amendment No. / Effective Date NA / NA

SPONSOR SIGNATURE PAGE

Phase 2a, Randomized, Double-blind, Placebo-controlled, Multiple-dose, 2-Part Study to Assess the Safety, Tolerability and Pharmacokinetic Response and Explore the Pharmacodynamic Response Following 4 Weeks of Once Weekly Subcutaneous Injections of PB1046 in Adult Subjects with Stable Heart Failure with Reduced Ejection Fraction (HFrEF) (Part 1) and in Subjects with Cardiac Dysfunction Secondary to Duchenne or Becker Muscular Dystrophy (Part 2).

We, the undersigned, have read this protocol and agree that it contains all necessary information required to conduct the clinical trial and complies with applicable regulations and Good Clinical Practice (GCP) standards.

Signature	Date
Lynne M. Georgopoulos, RN, BS, RAC Senior Vice President Clinical Development (Author) PhaseBio Pharmaceuticals, Inc.	15 MAR 2016
Poul Strange Digitally signed by Poul Strange DN: cn=Poul Strange, o=Integrated Medical Development, ou=IMD, email=pstrange@imdcro.com, c=US Date: 2016.03.18 12:34:09 -04'00' Poul Strange Medical Monitor Integrated Medical Development	
LEI SHI Digitally signed by LEI SHI DN: cn=LEI SHI, o=Integrated Medical Development, ou, email=lshi@imdcro.com, c=US Date: 2016.03.17 14:10:30 -04'00' Leon Shi, PhD Biostatistics Integrated Medical Development	
William G. Kramer, PhD Pharmacokinetics Kramer Consulting, LLC	03-17-2016
Susan Arnold Preclinical and Assay Development PhaseBio Pharmaceuticals, Inc.	17 Mar 2016
Lauren M. Richardson Lauren Richardson Quality Assurance/Regulatory Affairs PhaseBio Pharmaceuticals, Inc.	17 Mar 2016

AGREEMENT OF INVESTIGATOR FORM

By signing the Agreement of Investigator Form, I the Principal Investigator agree to:

1. Conduct the study in accordance with the protocol and as subsequently amended by the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects;

2. Conduct the study in accordance with applicable federal, state and local laws and regulations, and in accordance with Good Clinical Practice (GCP) standards;

3. Personally conduct or supervise the study;

4. Ensure that all associates, colleagues and employees assisting in the conduct of the study are adequately trained on the requirements of the protocol and informed about their obligations related to the conduct of the clinical study;

5. Delegate only those study tasks to my associates who have appropriate training and experience and provide documentation on training and the tasks to be delegated in the study file;

6. Ensure the investigational drug product is dispensed only to individuals who have signed consent, are enrolled in the referenced clinical study, and in accordance with the protocol;

7. Ensure the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in 21 CFR, § 50 and 56;

8. Report to the Sponsor (or designee) any AEs that occur in the course of the study, in accordance with 21 CFR § 312.64;

9. Maintain adequate and accurate records in accordance with 21 CFR § 312.62 and to make those records available for inspection with the Sponsor (or designee) or other applicable regulatory authorities;

10. Ensure that an Institutional Review Board (IRB) that complies with the requirements of 21 CFR §56 will be responsible for initial and continuing review and approval of the clinical study;

11. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports);

12. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects;

13. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in 21 CFR § 312.

Principal Investigator Name: _____ Site ID: _____

Signature/Date: _____

ABBREVIATIONS

Abbreviations	Definitions
A	Active
ACEI	Angiotensin-converting enzyme inhibitor
ACS	Acute Coronary Syndrome
ADA	Anti-drug antibodies
AE	Adverse Event
ALT	Alanine Amino Transferase
ARB	Angiotensin-receptor blocker
AST	Aspartate Transaminase
AUC	Area under the curve
AUC(0-τ)	Area under serum concentration-time curve to the last time with a concentration ≥ LOQ
AUC(0-tmax)	Area under the serum concentration curve concentration-time profile from 0 to Tmax
AUC(tmax-τ)	Area under the curve concentration-time profile from Tmax to τ
BB	Beta blocker
BMD	Becker muscular dystrophy
BMI	Body mass index
BP	Blood Pressure
BPM	Beats per minute
BSA	Body surface area
BUN	Blood urea nitrogen
C	Centigrade
CBC	Complete Blood Count
CCS	Canadian Cardiovascular Society
CD	Compact disk
CK	Creatinine kinase
CK-MB	Creatinine kinase MB Isoenzyme
CL/F	Clearance uncorrected for bioavailability (F)
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration

ABBREVIATIONS

Abbreviations	Definitions
Cmax	Maximum Serum Concentration
CLIA	Clinical Laboratory Improvement Act
COA	Certificate of Analysis
cm	Centimeter
cm/s	Centimeter per second
CRU	Clinical Research Unit
CT	Computed Tomography
Da	Dalton
DBP	Diastolic Blood Pressure
dL	Deciliter
DLT	Dose Limiting Toxicity
DMD	Duchenne Muscular Dystrophy
ECG	Electrocardiogram
ECHO	Echocardiography
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EF	Ejection Fraction
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
ELP	Elastin-like polypeptide
ET	Early Termination
F	Bioavailability
FDA	Food and Drug Administration
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
GLP	Good Laboratory Practice
GPCRs	G-Protein Coupled Receptors
HbsAg	Hepatitis B surface antigen

ABBREVIATIONS

Abbreviations	Definitions
HCT	Hematocrit
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure
HFrEF	Heart failure with reduced ejection fraction
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart Rate
hs-cTnT	High Sensitivity Cardiac Troponin T Assay
IB	Investigator's Brochure
IC	Informed Consent
ICH	International Conference on Harmonization
ID	Identification
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
kg	Kilogram
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LOQ	Lower limit of the assay
MDRD	Modification of Diet in Renal Disease
m	Meter
mg	Milligram
MI	Myocardial Infarction
mL	Milliliter
mM	Millimolar
MTD	Maximum Tolerated Dose

ABBREVIATIONS

Abbreviations	Definitions
ms	millisecond
NaCl	Sodium Chloride
NT-Pro-BNP	N-terminal fragment of the prohormone brain natriuretic peptide
NYHA	New York Heart Association
OOP	Out of Protocol
PB1046	Vasomera
P	Placebo
PCP	Phencyclidine
PD	Pharmacodynamic
PIF	Protocol Inquiry Form
PK	Pharmacokinetic
PP	Per-Protocol
PRN	As needed
QTcB	QT interval corrected for heart rate
QTcF	QT corrected by Fredericia's formula
r^2	Coefficient of Determination
RBC	Red blood cells
SAE	Serious adverse event
SBP	Systolic blood pressure
SC	Subcutaneous
SD	Standard Deviation
SMBP	Self-monitored blood pressure
SRC	Study Review Committee
t½	Elimination half-life
TC	Total cholesterol
TG	Triglycerides
Tmax	Time to Maximum Concentration
UA	Urinalysis
ULN	Upper limit of normal

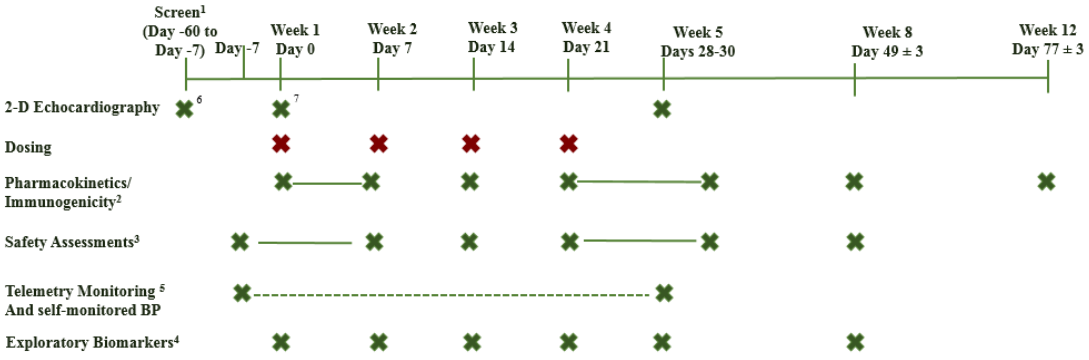
ABBREVIATIONS

Abbreviations	Definitions
US	United States
USP	United States Pharmacopeia
USDD	Unblinded study drug dispenser
V	Visit
VIP	Vasoactive intestinal peptide
Vz/F	Volume of distribution uncorrected for bioavailability (F)
WBC	White Blood Cells
XL-dCMP	X-Linked Dilated Cardiomyopathy
λz	Elimination rate constant

PROTOCOL SYNOPSIS

Study Title	Phase 2a, Randomized, Double-blind, Placebo-controlled, Multiple-dose, 2-Part Study to Assess the Safety, Tolerability and Pharmacokinetic Response and Explore the Pharmacodynamic Response Following 4 Weeks of Once Weekly Subcutaneous Injections of PB1046 in Adult Subjects with Stable Heart Failure with Reduced Ejection Fraction (HFrEF) (Part 1) and in Subjects with Cardiac Dysfunction Secondary to Duchenne or Becker Muscular Dystrophy (Part 2)
Study Number	Part 1: PB1046-PT-CL-0003-P1
Study Objectives	Primary objective: To evaluate the safety and tolerability of escalating doses of PB1046 administered once weekly for 4 weeks in adult subjects with stable NYHA Class II/III heart failure with a reduced ejection fraction (HFrEF). Secondary objectives: • Characterize the pharmacokinetic profile of a subcutaneous dose of PB1046 administered once weekly for 4 weeks; • Evaluate the immunogenicity profile of a subcutaneous dose of PB1046 administered once weekly for 4 weeks. Exploratory: • Characterize the effect of escalating doses of PB1046 on cardiac function as measured by 2-D echocardiography with Doppler following 4 weeks of once weekly dosing with PB1046; • Characterize the effect of PB1046 on cardiac, anti-inflammatory and anti-fibrotic biomarkers.
Study Endpoints	Primary Safety: • Incidence and severity of AEs and their relationship to study drug; • Changes from baseline in vital signs, laboratory parameters, telemetry (e.g., occurrence and frequency of rhythm abnormalities), and the relationship to PB1046 compared to placebo; and • Change from baseline in key ECG parameters (QT, QTcB, QTcF, PR, RR and QRS) and presence or absence of rhythm abnormalities and relationship to exposure of PB1046 compared to placebo. Secondary Pharmacokinetic and Immunogenicity: • Comparison of dose exposures (pharmacokinetic profile) during once weekly administration of various doses of PB1046; and • Incidence of Immunogenicity. Exploratory: • Change from baseline in 2-D echocardiographic parameters following 4 weeks of dosing with PB1046 compared to placebo; and • Change from baseline on exploratory cardiac, anti-inflammatory, and anti-fibrotic biomarkers following 4 weeks of dosing with PB1046 compared to placebo.
Study Population	Part 1: Multiple Dose Escalation Adult male and female subjects 18 years of age and older in stable clinical condition diagnosed with chronic New York Heart Association (NYHA) Class II or III stable HFrEF.
Study Design	This study is a randomized, double-blind, placebo-controlled, study that will assess the safety, tolerability, pharmacokinetics and explore the pharmacodynamics of PB1046 following 4 weeks of once

weekly subcutaneous injections (refer to Figure S1). Part 1 will evaluate 4 escalating dose levels (refer to Figure S2).



[1] Procedures include consent, verification of inclusion/exclusion criteria, medical and medication history, physical exam and laboratory testing.
[2] PK will be collected prior to dosing and at 1, 3 and 6 hours (± 1 hour) post dose on Day 0, Day 1 (24 hours), Day 2 (48 hours), Day 3 (72 hours), Day 5 (120 hours) and Day 7 (168 hours after 1st dose and prior to dose #2), Day 14 (pre dose #3), Day 21 (pre dose #4) and 1, 3, and 6 hours (± 1 hour) post dose on Days 22, 23, 24, 26, 28, 29 and 30. All samples are collected ± 2 hours from previous dose unless otherwise specified. Immunogenicity sampling will also be collected prior to each dose and on Day 49 and Day 77 with additional follow-up if clinically indicated.
[3] Safety assessments include vital signs, ECG, safety laboratory testing, injection site assessments and AE assessment at various time points as applicable.
[4] Biomarkers may include inflammatory markers and micro RNA.
[5] Continuous monitoring that will be captured for approximately 7 days prior to dosing (baseline) through approximately 7 days after the last dose of study drug. Subjects will be provided with an Omron Blood Pressure Monitor with ComFit™ Cuff (Model BP785N) for use of self monitoring of blood pressure at home. An alternative (comparable) automated blood pressure cuff may be used if necessary providing that the CRU ensures the cuff to be used is operating properly. Subjects will be required to collect blood pressure and heart rate on the same arm every morning and every evening.
[6] If subject had a previous echo within 60 days prior to screening with an EF ≤40% and subject qualifies by all other criteria, a screening echo will not be required. However, the baseline echo must be done at least 7 days prior to planned randomization for confirmation of continued study eligibility.
7 Can be done up to 14 days prior to randomization.

Figure S1. Study Schematic

This study will be conducted in two parts. Part 1 will be a sequential multiple-dose escalation study that will enroll (randomize and dose) approximately 28 (3A:1P in Cohort 1 and 6A:2P in subsequent cohorts) subjects. Qualifying subjects will have a diagnosis of NYHA Class II or III heart failure with a reduced ejection fraction (HFrEF), be in stable condition, and be taking clinician-directed appropriate pharmacological therapy (e.g., angiotensin converting enzyme inhibitors, angiotensin receptor blockers or an evidence based beta blocker) for heart failure at stable doses (with the exception of diuretics) for at least 1 month prior to screening. Randomized subjects will receive a fixed dose of study drug throughout the 4 week dosing period (refer to Figure S2). A starting dose of 0.2 mg/kg is selected based on the safety, and minimal to no pharmacodynamic response based on the single dose escalation study [PB1046-PT-CL-0001]. A single dose of 0.2 mg/kg was well tolerated and showed minimal to no reduction in systolic and diastolic seated blood pressure. Model predicted serum exposures covering the planned dose escalation are described in Figure S3 and T1 and are well below nonclinical exposure achieved in the 4 week repeat dose toxicology studies and do not exceed the maximum serum concentration observed in subjects receiving a 30 minute intravenous infusion of PB1046 [PB0146-PT-CL-0002].

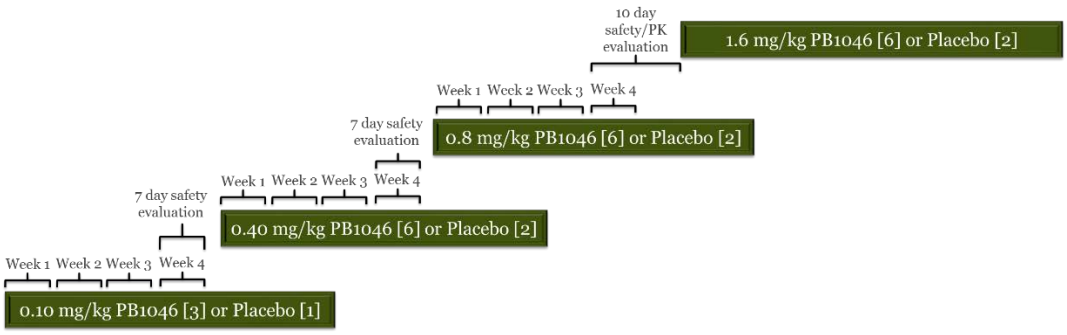


Figure S2. Dose Escalation

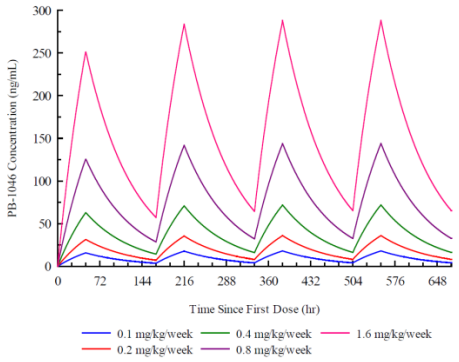


Figure S3. Model-Predicted Serum Concentrations Following Once Weekly Subcutaneous administration

Parameter	Dose (mg/kg/week) 0.1	0.2	0.4	0.8	1.6
Cmin (ng/mL)	4.1	8.2	16.4	32.7	65.5
Cmax (ng/mL)	18.0	36.1	72.1	144.3	288.5
AUC (0-τ) (hr×ng/mL)*	1,693	3,386	6,772	13,544	27,088

*AUC(0-τ) represents the area over the dosing interval, i.e. 7 days (168 hours).

Figure T1. Model-Predicted Pharmacokinetic Parameters Following Once Weekly Subcutaneous administration

Dose escalation will continue if the safety and pharmacokinetic profile are deemed acceptable as assessed by the Medical Monitor, Study Investigators, Clinical/Regulatory, a representative from Preclinical/Assay Development, and a Pharmacokineticist (i.e., the Study Review Committee [SRC]). The SRC may also recommend de-escalation or study discontinuation. All decisions and outcomes related to SRC meetings will be documented and retained as part of the study file. Requested changes (not previously described) to the protocol will be submitted to the Food and Drug Administration (FDA) and to the Institutional Review Board (IRB) prior to implementation as appropriate.

Dose Escalation and Stopping Rules

- More than one subject may be dosed in a 24 hour period up to and including 0.8 mg/kg, which was the maximum dose utilized in the PB1046-PT-CL-0001 study. If dosing exceeds 0.8 mg/kg, no more than one subject will be dosed in a 24 hour period for the first four subjects dosed in a cohort.
- At least 75% of subjects assigned to a cohort must receive at least three weekly doses (e.g., at steady state) with no reported dose limiting toxicities (DLTs) before escalation to the next higher dose level.
- For a dose cohort exceeding 0.8 mg/kg, for which there is no available subcutaneous pharmacokinetic (PK) data, PK data through Day 31 (10 days following the last dose) will be required to be assessed, in addition to safety data, prior to escalating to a higher dose.
- DLTs identified during the study will be assessed as potential indicators of cumulative toxicity and provide rationale for revision of the maximum tolerated dose (MTD).
- Multiple dose escalation will continue until modelling of the PK data indicates that the human AUC (0-168 hours) would exceed currently available nonclinical exposure and/or previous human exposure (PB1046-PT-CL-0001 [SC] or -0002 [IV]), whichever is higher.
- If a subject in a cohort experiences a DLT that is evaluated by the Investigator as related to study drug (PB1046), an additional four subjects (3A and 1P) will be dosed at that dose level. If two or more subjects in a cohort experience a DLT related to PB1046, the MTD will be considered exceeded. The dosing schema may be revised to dose additional subjects below this level to further refine the MTD.
- The decision to temporarily hold or discontinue a subject from study treatment will be based on Investigator discretion regarding reported adverse events or other factors, which may include clinically significant reduction in blood pressure (i.e., hypotension).
- Aggregate assessment of adverse events with specific emphasis on cardiac related events will be assessed on an ongoing basis and will be evaluated for trends related to dose escalation and will be reviewed at each Study Review Committee (SRC) meeting.
- A study subject will be discontinued from study treatment if there is evidence of increased arrhythmia potential or marked prolongation (e.g., QT/QTc > 500 ms or > 60 ms over baseline) of the QT/QTc interval while on treatment.

	• Aggregate evaluation of the risk for arrhythmias or QT/QTc prolongation will be evaluated for trends on an ongoing basis and will reviewed at each Study Review Committee (SRC) meeting. **Study Registration** Upon signing consent, a subject will be registered (status of screened) in the study. Subjects qualifying for participation will be registered (status update) in the study and will be assigned to the next available dosing slot. No subject may participate (receive study drug) in more than one dose cohort. **Run-in/Stabilization Period:** During the period between screening and randomization (planned first dose), the study subject will remain on stable pharmacological therapy for heart failure. Stable therapy is defined as no change in dose or the addition or removal of a therapy with the exception of diuretic dosage. Also the study subject will be in stable health with no hospitalizations or clinically significant acute illnesses between screening and randomization that would put the subject at increased risk for study participation. **Randomization** Subjects will be randomly assigned via a central randomization system to receive either PB1046 or placebo (3:1). Only the study statistician, pharmacokineticist, and the unblinded study drug dispenser (USDD) at the study site will have access to the randomization assignment after enrollment in a cohort has been completed. Activities related to the conduct of Part 2 of the study will be reviewed and approved under a separate Part 2 protocol PB1046-PT-CL-0002-P2.
Description of Study Drug, Dosage, and Storage	Active: Vasomera (PB1046) is a nearly isotonic sterile clear colorless to slight yellow liquid in a 2 mL clear glass vial (approximate fill volume 0.5 ± 0.1 mL) at a concentration of 40 mg/mL. Vials will be stored long term at ≤ -70°C. Short term storage at -20°C (± 10°C) or refrigerated (2 - 8°C) temperatures may be permitted based on ongoing stability analysis. Refer to Certificate of Analysis (COA) for additional drug storage stability information. Placebo: Commercially available 0.9% sodium chloride (NaCl) USP (10 mL single use vials) for injection is a sterile, clear, colorless liquid, that is similar in appearance to active study drug. Although the active compound and placebo are similar in appearance, the study drug will be prepared and administered by a member of the study team not otherwise involved in the evaluation of efficacy or safety.
Study Centers	Up to four (4) investigational sites in the United States (US) will participate in Part 1 of the study.
Main Inclusion Criteria	Subjects will be eligible for inclusion in the study if they meet all of the following criteria at screening and up to the time of randomization as indicated: 1. Willing and able to sign a written informed consent and follow all study-related procedures; 2. Male or female subject ≥ 18 years of age; 3. Male subjects and female subjects of reproductive or childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 30 days after their last dose of study drug. Female subjects of non-childbearing potential are defined as being surgically sterile by bilateral tubal ligation, bilateral oophorectomy, or hysterectomy. A female subject 45 to 60 years of age, inclusive who is post-menopausal for at least 1 year and has a follicle-stimulating hormone level confirmation indicating post-menopausal status will be considered of non-childbearing potential. Female subjects > 60 years of age are considered post-menopausal and of non-childbearing potential; 4. Body mass index ≥ 18 kg/m^2 and ≤ 45 kg/m^2;

	5. Receipt of stable (no change in dose (except diuretics) or addition or removal of a therapy) pharmacological therapy(ies) for heart failure for a minimum of 1 month (30 days) prior to screening and between screening and randomization and are in stable clinical condition; 6. NYHA Class II or III heart failure diagnosis (ischemic or non-ischemic confirmed by medical history) at least (≥) 6 months (180 days) prior to screening; 7. Stable HF defined as no hospitalizations for cardiac related issues within the previous 3 months (90 days) prior to the screening visit or between screening and randomization; 8. A screening Left Ventricular Ejection Fraction ≤ 40% by centralized reading of 2-D echocardiography. 9. Screening hemoglobin ≥ 9.0g/dL secondary to the volume of blood to be collected during the study period. 10. Willing and able to return to the study unit for specified study visits, and be able to self-monitor blood pressure while at home. 11. Live and work in an area with reliable cellular services (e.g., Sprint®) for real time transmission of telemetry data to the core laboratory.
Main Exclusion Criteria	Subjects will be excluded from the study if they meet any of the following criteria up to the time of randomization: 1. Have previously received PB1046 or have a known allergy to the study drug or any of its components; 2. Participating in any other study and have received any other investigational medication or device within 30 days prior to screening or are taking part in a non-medication study which, in the opinion of the Investigator, would interfere with study compliance or outcome assessments; 3. Diagnosed with acute coronary syndrome (ACS) or an acute myocardial infarction (MI) within 3 months (90 days) of screening; 4. Canadian Cardiovascular Society (CCS) Class III or IV angina necessitating frequent use of as needed short acting nitroglycerin (e.g., sublingual); 5. Cardiac surgery or valvuloplasty within 3 months (90 days) prior to screening; 6. Cerebrovascular accident or transient ischemic attack within 3 months (90 days) prior to screening; 7. Sustained systolic blood pressure (SBP) < 100 mmHg and/or diastolic blood pressure (DBP) < 50 mmHg (confirmed by a duplicate seated reading) on at least 3 consecutive readings (self-monitored or office) prior to randomization or overt symptomatic hypotension; 8. Sustained resting heart rate >100 beats per minute (BPM) at screening (V1) or prior to randomization (confirmed on baseline telemetry monitoring); 9. History or evidence (documented on baseline telemetry monitoring) of clinically significant arrhythmias (uncontrolled by drug therapy or use of an implantable defibrillator), long QT syndrome or evidence of QT prolongation demonstrating QTcF > 460 ms (by ECG) prior to randomization; 10. Clinically significant renal dysfunction as measured by the estimated glomerular filtration rate (eGFR) of < 40 mL/min/1.73m^2 as calculated by the CKD-EPI creatinine-cystatin C equation: eGFR = 135 x min (Scr/k, 1)$^{-a}$ × max(Scr/k, 1)$^{-0.601}$ × min(Scys/0.8, 1)$^{-0.375}$ × max(Scys/0.8, 1)$^{-0.711}$ × 0.995^{age} [× 0.969 if female] [× 1.08 if black] at screening, or a clinically significant change in renal function between screening and baseline; 11. Clinically significant liver dysfunction as measured by: alanine aminotransferase >3.0 × the upper limit of normal (ULN), aspartate aminotransferase >3.0 × the ULN, or serum bilirubin ≥ 1.6 mg/dL at screening, or a clinically significant change in liver function between screening and baseline; 12. Pregnant or lactating female subjects;

	13. Known history of or active alcohol abuse or use of illicit drugs within 1 year prior to randomization; 14. Positive screening for human immunodeficiency virus antibodies, hepatitis B surface antigen, or hepatitis C virus antibodies; 15. Any major surgical procedure within 1 month (30 days) prior to screening or planned surgical procedure during the study period; 16. Other medical or psychiatric condition which, in the opinion of the Investigator, would place the subject at increased risk or would preclude obtaining voluntary consent/assent or would confound the secondary objectives of study.

Statistical Analysis	Sample Size The sample size is not driven by inferential statistics. For sequential dose escalation, the sample size for each dose group is set for qualitative investigation of toxicity for which a minimal sample size of 4 (3 active/1 placebo) is adequate at a dose that is considered non-effective, and 6 active/2 placebo for subsequent cohorts. An addition of 4 (3 active and 1 placebo) treated subjects may be dosed in case of potential PB1046 dose limiting toxicity or as otherwise deemed necessary by the Study Review Committee (SRC). Analysis Population The Safety and Intent-to-Treat (ITT) population will be the same and defined as all subjects who receive at least one dose of the study drug. The Per-Protocol (PP) population will be a subset of the ITT population excluding subjects who have any major protocol violations. The pharmacokinetic analysis population will consist of all subjects that are dosed with active study drug and have sufficient data for pharmacokinetic analysis. Safety All safety parameters/data will be analyzed descriptively by the subject and by dose. Safety will be evaluated by analyses of the incidence and severity of treatment emergent adverse events, and change from baseline in vital signs, telemetry monitoring (e.g., rhythm abnormalities), and safety laboratory parameters. Safety parameters will be presented descriptively by treatment group. Additionally, analysis of central tendency and categorical analysis of QT/QTc interval data will be assessed from 12 lead ECGs and relationship to exposure of PB1046 will be evaluated. Other: Pharmacokinetics Pharmacokinetic parameters for PB1046 will be calculated after the first and last doses using non compartmental analysis. Only serum concentrations equal to or greater than the qualified lower limit of the assay (LOQ) will be used in the pharmacokinetic analysis. The following parameters will be evaluated: • Area under the curve over the dosing interval [AUC(0-τ)] • Area under the curve concentration-time profile from 0 to Tmax [AUC(0-tmax)] and from Tmax to τ [AUC(tmax-τ)] • Maximum serum concentration (Cmax) • Time to Cmax (Tmax) • Elimination rate constant (λz) • Elimination half-life (t½) • Clearance (CL/F), uncorrected for bioavailability • Volume of Distribution (Vz/F), uncorrected for bioavailability (F) The parameters λz, t½, CL/F, and Vz/F will be calculated only for the last dose. Compartmental modeling will be done using all of the data from the first through the fourth dose (or last dose). Additional analyses will be conducted as directed by the data. Other: Immunogenicity Serum samples will be screened for the presence of binding anti-drug antibodies (ADA) on an ongoing basis and will be available at the time of the periodic safety review meetings. Samples found to be positive and specific for ADA will be further characterized to determine domain specificity including evaluating if the antibodies cross react with endogenous VIP. Samples testing positive and specific will be titered and further evaluated to determine if the antibodies are capable of neutralizing the response in a cell based assay. Exploratory Endpoints All data will be analyzed descriptively by subject dose group. Inferential statistics may be utilized if driven by the data.

Study Duration	Total anticipated study duration from initiation of screening to the last subject's last visit in Part 1 will be approximately 8-12 months.
Study Oversight	**Study Review Committee** The Study Review Committee (SRC) will review data relating to safety, PK and hemodynamic response after 75% of the subjects in a cohort have completed their 3rd dose and have been followed for minimum of seven (7) days after the 3rd dose prior to dose escalation. The committee will include the Principal Investigators, the Medical Monitor, Clinical/Regulatory Representative (Sponsor), Preclinical/Assay Development Representative (Sponsor), and Pharmacokineticist. The SRC will review the interim safety summaries prepared by the Clinical Representative from safety data entered into the EDC system, safety laboratory data, and pharmacokinetic and immunogenicity (binding ADA) provided by PhaseBio's Assay Development Department. The data will be reviewed in a blinded manner and must be deemed acceptable to the SRC prior to dosing of the next higher single dose group. Additionally, the SRC may recommend additional ECG evaluations or a change in timing of evaluations or additional assessments by holtor monitoring based on the PK profile to further elucidate the relationship of the exposure to PB1046 and the QT/QTc interval. In the case of a Dose Limiting Toxicity (DLT), Serious Adverse Event (SAE), or other significant AE, the SRC may request that the study drug assignment be unblinded. Following review of the interim safety summary, the SRC will decide if dose escalation should continue, recommend de-escalation, or recommend study discontinuation. Provisional SRC recommendations not previously described in the protocol, or any recommendations to discontinue the study will be promptly reported to the IRB and the Food and Drug Administration (FDA). The SRC may recommend evaluation of up to two dose levels to carry forward to Part 2 of the study (PB1046-PT-CL-0003-P2). Activities related to Part 2 of the study will be reviewed and approved under a separate protocol PB1046-PT-CL-0002-P2.

SCHEDULE OF ACTIVITIES

Week/Description	Blood Volume	Screen	Week -1	Week 1/ Dose 1	Week 1/ Daily Visits	Week 2/ Dose 2	Week 3/ Dose 3	Week 4/ Dose 4	Week 4/ Daily Visits	Week 5/ Daily Visits	Week 8/ Safety	Week 12/ Immuno-genicity
Visit Number		**V1**	**V2**	**V3**	**V4-V7**	**V8**	**V9**	**V10**	**V11-V14**	**V15-18**	**V19 or ET**	**V20**
Study Day		**-60**	**-7 (-10 to -7)**	**0**	**1, 2, 3 and 5**	**7**	**14**	**21**	**22, 23, 24 and 26**	**28, 29, 30, and 31**	**49 ± 3 days**	**77 ± 3 days**
Test *Protocol Reference*	**ml/ test**	**Number of Tests**										
Adverse Events *Refer to Section:10.1*			1	1	4	1	1	1	4	4	1	
Concomitant Medications *Refer to Section:6.3*		1	1	1	4	1	1	1	4	4	1	
Consent *Refer to Section 5.1*		1										
Demographics *Refer to Section 5.2*		1										
Directed Physical Examination *Refer to Section 5.6*			*As needed only for Evaluation of Adverse Events*									
Dosing (in office) *Refer to Section 8.5.2*				1		1	1	1				
Dose Preparation (USDD) *Refer to Section 8.5.1*				1		1[k]	1[k]	1[k]				
Echocardiography - 2D with Doppler *Refer to Section 5.12*		1[g]	1[b,d]						1[i]			
Electrocardiogram 12- lead (triplicate) *Refer to Section 5.10*		1		1[b]	3[o,n]	1[b]	1[b]	1[b]	3[o,n]	1[h]	1	
Height/Weight/BMI *Refer to Section 5.7*		1									1	

Week/Description	Blood Volume	Screen	Week -1	Week 1/ Dose 1	Week 1/ Daily Visits	Week 2/ Dose 2	Week 3/ Dose 3	Week 4/ Dose 4	Week 4/ Daily Visits	Week 5/ Daily Visits	Week 8/ Safety	Week 12/ Immuno-genicity
Visit Number		**V1**	**V2**	**V3**	**V4-V7**	**V8**	**V9**	**V10**	**V11-V14**	**V15-18**	**V19 or ET**	**V20**
Study Day		**-60**	**-7 (-10 to -7)**	**0**	**1, 2, 3 and 5**	**7**	**14**	**21**	**22, 23, 24 and 26**	**28, 29, 30, and 31**	**49 ± 3 days**	**77 ± 3 days**
Test *Protocol Reference*	**ml/ test**	**Number of Tests**										
Histories – Medical, Targeted Medical, Surgical, Social and Medications *Refer to Section 5.3*		1										
Inclusion/Exclusion *Refer to Sections 4, 6.1, 6.2, 5.13.4.4, and 5.10.3*		1	1	1[b]								
Injection Site Assessment *Refer to section 5.9*				1[a]	4[f]	1[b]	1[b]	1[b]	4[f]	4[f]	1	
LAB – Alcohol and drug screen (urine)[q] *Refer to Section 5.13.4.2*	NA	1	1	1[b]		1[b]	1[b]	1[b]				
LAB - NT-proBNP and hs-cTnT *Refer to Sections 5.13.4.6 and 5.13.4.7*	4.0			1[b]	3[o]	1[b]	1[b]	1[b]	1[i]	1[h]	1	
LAB - Exploratory Biomarkers: microRNA *Refer to Section 5.13.7*	2.5			1[b]	3[o]	1[b]	1[b]	1[b]	1[i]	1[h]	1	
LAB- Exploratory Biomarkers:Other *Refer to Section 5.13.7*	8			1[b]	3[o]	1[b]	1[b]	1[b]	1[i]	1[h]	1	

Week/Description	Blood Volume	Screen	Week -1	Week 1/ Dose 1	Week 1/ Daily Visits	Week 2/ Dose 2	Week 3/ Dose 3	Week 4/ Dose 4	Week 4/ Daily Visits	Week 5/ Daily Visits	Week 8/ Safety	Week 12/ Immuno-genicity
Visit Number		**V1**	**V2**	**V3**	**V4-V7**	**V8**	**V9**	**V10**	**V11-V14**	**V15-18**	**V19 or ET**	**V20**
Study Day		**-60**	**-7 (-10 to -7)**	**0**	**1, 2, 3 and 5**	**7**	**14**	**21**	**22, 23, 24 and 26**	**28, 29, 30, and 31**	**49 ± 3 days**	**77 ± 3 days**
Test *Protocol Reference*	**ml/ test**	**Number of Tests**										
LAB - Immunogenicity *Refer to Section 5.13.5*	3.5			1[b,s]		1[b]	1[b]	1[b]		1[h]	1	1
LAB – Lipids/FPG *Refer to Sections 5.13.4.5 and 5.13.4.8*	9	1[p]	1[p]								1	
LAB - Pharmacokinetics *Refer to Section 5.13.6*	3.5			4[b,e]	4[o,n]	1[b]	1[b]	4[b,e]	4[o, n]	4[f]		
LAB - Safety Labs *(Hematology, chemistry UA, eGFR calculation) Refer to Sections 5.13.4.8 and 5.13.4.9*	12	1	1			1[b]	1[b]	1[b]		1[h]	1	
LAB - Serology *(HIV, HepB and Hep C) Refer to Section 5.13.4.1*	4	1										
Pregnancy Testing (females of CBP) *Refer to 5.13.4.3*	NA	1	1	1[q,b]		1[b]	1[b]	1[b]				
Physical Examination *Refer to Section 5.4*		1		1[b,j]							1	
Registration *Refer to Section 3.2*			1									

Week/Description	Blood Volume	Screen	Week -1	Week 1/ Dose 1	Week 1/ Daily Visits	Week 2/ Dose 2	Week 3/ Dose 3	Week 4/ Dose 4	Week 4/ Daily Visits	Week 5/ Daily Visits	Week 8/ Safety	Week 12/ Immuno-genicity
Visit Number		**V1**	**V2**	**V3**	**V4-V7**	**V8**	**V9**	**V10**	**V11-V14**	**V15-18**	**V19 or ET**	**V20**
Study Day		**-60**	**-7 (-10 to -7)**	**0**	**1, 2, 3 and 5**	**7**	**14**	**21**	**22, 23, 24 and 26**	**28, 29, 30, and 31**	**49 ± 3 days**	**77 ± 3 days**
Test *Protocol Reference*	**ml/ test**	**Number of Tests**										
Randomization *Refer to Section 8.13.4*				1								
SMBP[m] *Refer to Section 6.6*			●	———	———	———	———	———	———	●		
Telemetry - mobile[l] *Refer to Section 5.11*			●	———	———	———	———	———	———	●		
Telephone contact[r] *Refer to section 5.5*				1		1	1	1				
Vital Signs – Orthostatic *Refer to Section 5.8.1*		1		1[b]	4[f]	1[b]	1[b]	1[b]	4[f]	4[f]	1	
Vital Signs - Seated *Refer to Section 5.8.2*		1		3[b,a]	4[f]	1[b]	1[b]	1[b,a]	4[f]	4[f]	1	
Weight *Refer to Section 5.7*				1[b]		1[b]	1[b]	1[b]			1[b]	
Total Blood Volume 365 mL		25	21	35.5	57.5	33.5	33.5	44	28.5	44	39	3.5

a 1 and 6 hours post dose (± 15 minutes)
b Prior to dosing
c Day 22, 24 and 26
d Can occur up to 2 weeks (14 days) prior to scheduled randomization but should be done before placement of the mobile telemetry device.
e 1, 3 and 6 hours (± 10 minutes)
f Daily ± 2 hours from previous dose time.
g If an historical (routine care) echo was within 60 days prior to screening and EF ≤ 40%, the screening echo will not need to be repeated. However, the baseline echo must be done between Day -14 and Day -7 to confirm final study eligibility by central reader.
h Day 28 only (± 1 hour after last dose)
i Day 24 only ± 1 day (collect biomarker and echo on the same days)
j Abbreviated physical examination
k ± 2 hours from time of day of previously weekly dose
l Continuous monitoring from approximately 7 days prior to dosing (baseline) through 7 days after the last dose of study drug.

m Omron Blood Pressure Monitor with ComFit™ Cuff (Model BP785N) for use of self-monitoring of blood pressure at home starting approximately 7 days prior to randomization. Subjects will be required to collect blood pressure and heart rate using the same arm every morning and every evening.
n 120 hours (± 2 hours) after last dose from previous dose time.
o Completed at 24, 48, and 72 hours (± 1 hour) after last dose. When PK and ECG are required at a given time point, the PK should be done prior to the ECG and the two procedures should be done no more than 30 minutes apart.
p Only performed/analyzed at screening if subject was fasting for at least 8 hours otherwise they will only be reported at Visit 2 when subject was instructed to fast prior to visit.
q Local testing only.
r Should occur in evening (suggested time between 7 and 10 PM).
s Collect 2 x 3.5mL tubes at baseline.

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1 INTRODUCTION

1.1 Background Information

PB1046 (Vasomera) is an investigational compound that comprises the neuropeptide, Vasoactive Intestinal Peptide (VIP) genetically fused to an elastin-like biopolymer (ELP). PB1046 is being developed as an adjunctive therapy for the treatment of heart failure, and cardiomyopathy associated with dystrophinopathies; Duchenne Muscular Dystrophy (DMD), Becker Muscular Dystrophy (BMD), and X-linked dilated cardiomyopathy (XL-dCMP).

VIP is a 28 amino acid neuropeptide and its biological effects are mediated by two receptors, VPAC1 and VPAC2, belonging to the family B of G protein-coupled receptors (GPCRs). VIP positive fibers are distributed throughout the heart and coronary vasculature and VPAC receptors are found on vascular smooth muscle cells within the systemic circulation as well as coronary and myocardial arteries, cardiac myocytes and various immune cells. Since the discovery of VIP almost 50 years ago, the understanding of the function of VIP in human disease has undergone radical transformation from one of vasodilatory and smooth muscle relaxation and inhibitor of smooth muscle proliferation, to new anti-inflammatory and immune-protective properties including upregulation of anti-inflammatory cytokine IL-10 and induction of protective T cells (Szema & Hamidi, 2014).

Several cardiovascular diseases, such as myocardial fibrosis, heart failure, cardiomyopathy and pulmonary hypertension, have been found to be associated with changes in myocardial VIP concentration or with alteration of affinity, density and physiological responsiveness of the VIP receptors (Dvoráková, 2005). Furthermore, a vast body of literature exists that support the therapeutic potential of VIP for cardiopulmonary disease, but the poor stability after systemic administration (half-life of approximately 48 seconds in circulation) has limited its clinical application.

PB1046 is a recombinant fusion protein expressed in *Escherichia coli* (*E. coli*) with a total molecular mass of 50,945 Da. PB1046 is a 634 amino acid polypeptide with vasoactive intestinal peptide (VIP) at the N-terminus and a physiologically inert repeating polymeric elastin-like polypeptide (ELP) at the C-terminus, which results in extended circulatory half-life of the VIP, and provides protection from enzymatic degradation. The VIP moiety comprises mature human VIP with an additional methionine at the N-terminus that reduces activation at the VPAC1 receptor in comparison to activity at the VPAC2 receptor. This profile allows dosing in a range that can elicit the desired therapeutic effects but minimize the potential for negative gastrointestinal effects (GI) associated with over activation of VPAC1 (e.g. profuse watery diarrhea; (Tsutsumi, M., Claus, T. H., Liang, Y., Li, Y., Yang, L., Zhu, J., …Pan, C., 2002)).

Attributes of PB1046 include positive lusitropy (early diastolic relaxation); improved inotropy secondary to changes in intracellular calcium mobilization; peripheral vasorelaxation, which is thought to be due to enhanced nitric oxide synthase activity; and attenuation of inflammation and fibrosis, likely due to modulation of inflammatory cell activity, based on the known mechanisms of VIP. These beneficial effects have been confirmed in several preclinical heart failure (HF) models evaluated with PB1046 (doxorubicin-induced HF model in rats, diastolic

dysfunction triggered by either renoprival hypertension or diabetes in rats, pacing induced systolic dysfunction in dogs and chronic ischemic HF induced via a serial coronary microembolization in sheep as well as an *mdx* mouse model, a murine model of human Duchenne muscular dystrophy. Refer to Investigator's Brochure for additional information.

1.2 Summary of Human Data

At the dose ranges tested (subcutaneous injection - dose range 0.05 to 0.8 mg/kg or 30 minute intravenous infusion - dose range 0.005 to 0.02 mg/kg), PB1046 was not arrhythmogenic nor did it induce QT prolongation. PB1046 tended to reduce both systolic and diastolic blood pressure in a dose dependent/dose exposure manner as expected from the known pharmacological properties of vasoactive intestinal peptide. However, the effect was less pronounced following IV administration compared to subcutaneous administration. None of the subjects exposed experienced a hypotensive episode. Compared to placebo, there was no clinically relevant dose/exposure dependent increases in heart rate following subcutaneous administration. Compared to placebo, mild dose/exposure dependent increases in heart rate were observed following intravenous dosing with PB1046. The mild increases observed were not sustained, not associated with tachycardia nor were they considered clinically relevant and did not result in an appreciable change in the rate pressure product during or for the 3.5 hour period (PB1046 average IV t½ is approximately 2 hours) following intravenous infusion.

Regardless of the route of administration, the most frequent dose/exposure dependent adverse events associated with the use of PB1046 were nausea and headache. Nausea was reported in 10% of patients following subcutaneous administration and 20% following intravenous administration. Although headache was reported (6.7%) in patients receiving subcutaneous dosing with PB1046, 40% of the subjects receiving an intravenous dose of PB1046 reported headache. When PB1046 was administered subcutaneously, it was almost always (90%) associated with mild to moderate injection site erythema that occurred hours to days after injection. This effect is thought to be associated with activation of the VPAC2 receptors around hair follicles causing a localized vasodilatory response. Additionally, the majority (80%) of subjects receiving a subcutaneous injection of PB1046 experienced mild pain at the injection site, which again, occurred hours to days after injection and was often (33%) associated with mild pruritus. When PB1046 was infused intravenously (IV), only about 7% of subjects experienced erythema and about 13% experienced pain at the infusion site which was not reported during the infusion but was reported when the IV site was flushed hours after the infusion had been completed and resolved when the IV catheter was removed. Furthermore, these reported events were not associated with changes in WBC counts. Only one (2%) of the 45 subjects exposed to PB1046 reported mild intermittent generalized pruritus, with an onset approximately 92 hours after infusion of PB1046, which resolved without treatment. The majority of adverse events associated with PB1046 were mild; none were dose limiting or severe.

No serious adverse events or dose limiting toxicities were identified following single SC administration of doses ranging from 0.05mg/kg to 0.8mg/kg and there were no dose limiting toxicities or serious adverse events related to study drug noted following a single 30 minute IV infusion of 0.005mg/kg, 0.01 mg/kg and 0.02mg/kg PB1046.

1.3 Risk / Benefit Assessment

At this stage of development, the risk benefit relationship has not been established. The combined nonclinical and clinical safety data support continued development of PB1046 as a potential adjunctive therapy for heart failure, and cardiomyopathy associated with dystrophinopathies.

1.4 Justification of Starting Dose, Duration of Treatment Exposure and Dose Escalation

A starting subcutaneous dose of 0.2 mg/kg is selected based on the safety, and pharmacodynamic response data from the single dose study [PB1046-PT-CL-0001]. A single dose of 0.2 mg/kg was well tolerated and showed minimal to no reduction in systolic and diastolic seated blood pressure. Model predicted serum exposures covering the planned dose escalation are described in Figure 1 and Table 1 are well below nonclinical exposure achieved in the 4 week repeat dose toxicology studies and do not exceed the maximum serum concentration observed in subjects receiving a 30 minute intravenous infusion of PB1046 [PB1046-PT-CL-0002].

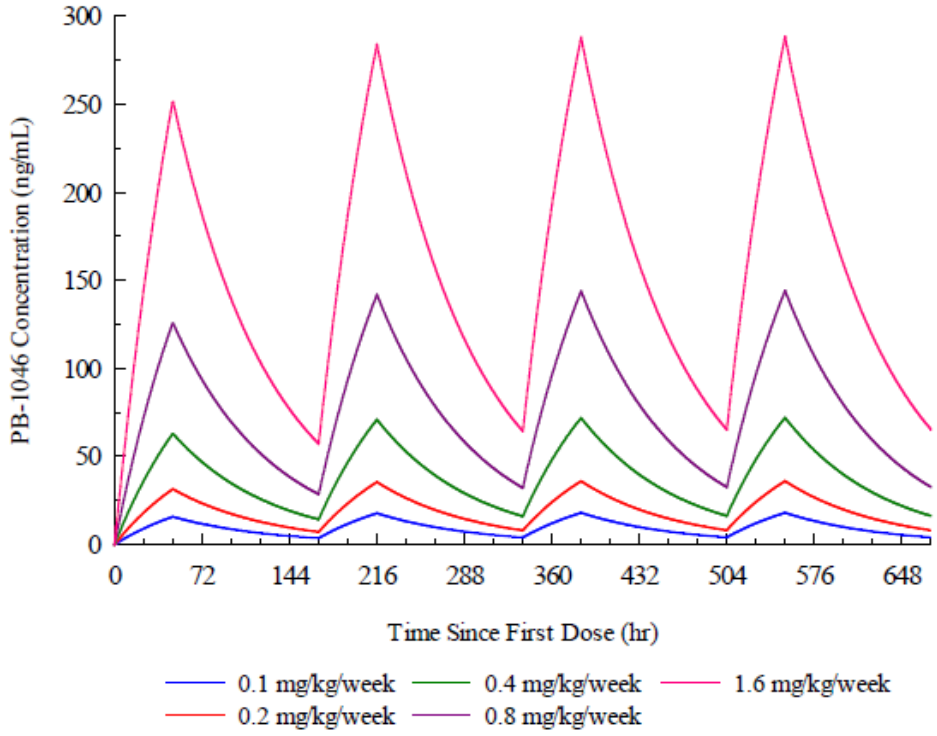


Figure 1 Model-Predicted Serum Concentrations Following Once Weekly Subcutaneous Administration

Parameter	Dose (mg/kg/week)				
	0.1	0.2	0.4	0.8	1.6
Cmin (ng/mL)	4.1	8.2	16.4	32.7	65.5
Cmax (ng/mL)	18.0	36.1	72.1	144.3	288.5
AUC (0-τ) (hr×ng/mL)*	1,693	3,386	6,772	13,544	27,088

*AUC(0-τ) represents the area over the dosing interval, i.e. 7 days (168 hours).

Table 1 Model-Predicted Pharmacokinetic Parameters Following Once Weekly Subcutaneous administration

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

To evaluate the safety and tolerability of escalating doses of PB1046 administered once weekly for 4 weeks in adult subjects with stable NYHA Class II/III heart failure with a reduced ejection fraction (HFrEF).

2.1.2 Secondary Objectives

- Characterize the pharmacokinetic profile of a subcutaneous dose of PB1046 administered once weekly for 4 weeks;
- Evaluate the immunogenicity profile of a subcutaneous dose of PB1046 administered once weekly for 4 weeks.

2.1.3 Exploratory

- Characterize the effect of escalating doses of PB1046 on cardiac function as measured by 2-D echocardiography with Doppler following 4 weeks of once weekly dosing with PB1046;
- Characterize the effect of PB1046 on cardiac, anti-inflammatory and anti-fibrotic biomarkers.

2.2 Criteria for Evaluation

2.2.1 Safety Endpoints

- Incidence and severity of AEs and their relationship to study drug;
- Changes from baseline in vital signs, laboratory parameters, telemetry (e.g., occurrence and frequency of rhythm abnormalities), and the relationship to PB1046 compared to placebo; and

- Change from baseline in key ECG parameters (QT, QTcB, QTcF, PR, RR and QRS) and presence or absence of rhythm abnormalities and relationship to exposure of PB1046 compared to placebo.

2.2.2 Other Endpoints

2.2.2.1 Pharmacokinetic and Immunogenicity

- Comparison of dose exposures (pharmacokinetic profile) during once weekly administration of various doses of PB1046;

- Incidence of Immunogenicity.

2.2.2.2 Exploratory

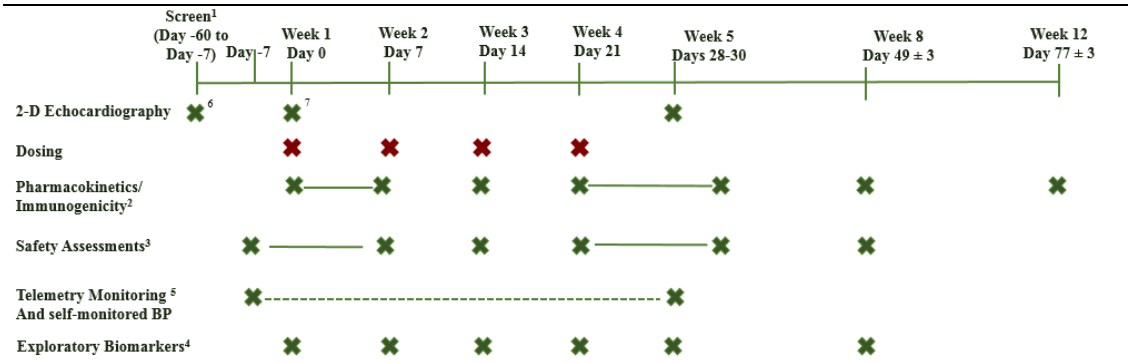
- Change from baseline in 2-D echocardiographic parameters following 4 weeks of dosing with PB1046 compared to placebo;

- Change from baseline on exploratory cardiac, anti-inflammatory, and anti-fibrotic biomarkers following 4 weeks of dosing with PB1046 compared to placebo.

3 STUDY DESIGN

3.1 General Description

This study is a randomized, double-blind, placebo-controlled study that will assess the safety, tolerability, pharmacokinetics and explore the pharmacodynamics of PB1046 following 4 weeks of once weekly subcutaneous injections. Subjects will be followed for safety for 4 weeks following the last dose with an additional visit 8 weeks following the last dose for collection of an immunogenicity sample (refer to Figure 2). This study will be conducted in two parts. Part 1 will be a sequential multiple-dose escalation study that will enroll (randomize and dose) approximately 28 (3A:1P in Cohort 1 and 6A:2P in subsequent cohorts) subjects. Qualifying subjects will have a diagnosis of NYHA Class II or III heart failure (ischemic or non-ischemic) with a reduced ejection fraction (HFrEF), be in stable condition, and be taking clinician-directed appropriate pharmacological therapy (e.g., angiotensin converting enzyme inhibitors, angiotensin receptor blockers or an evidenced based beta blocker) for heart failure at stable doses (with the exception of diuretics) for at least 1 month prior to screening. Randomized subjects will receive a fixed dose of study drug throughout the 4 week dosing period. The data from Part 1 of the study will direct the dose(s) selected for Part 2. Part 2 of the study will be further described and conducted under a separate Part 2 protocol (PB1046-PT-CL-0003-P2) that will evaluate the safety/tolerability, pharmacokinetics and will explore the pharmacodynamics of PB1406 following 4 weeks of once weekly dosing in up to 21 male subjects with dystrophic cardiomyopathy.



[1] Procedures include consent, verification of inclusion/exclusion criteria, medical and medication history, physical exam and laboratory testing.
[2] PK will be collected prior to dosing and at 1, 3 and 6 hours (± 1 hour) post dose on Day 0, Day 1 (24 hours), Day 2 (48 hours), Day 3 (72 hours), Day 5 (120 hours) and Day 7 (168 hours after 1st dose and prior to dose #2), Day 14 (pre dose #3), Day 21 (pre dose #4) and 1, 3, and 6 hours (± 1 hour) post dose on Days 22, 23, 24, 26, 28, 29 and 30. All samples are collected ± 2 hours from previous dose unless otherwise specified. Immunogenicity sampling will also be collected prior to each dose and on Day 49 and Day 77 with additional follow-up if clinically indicated.
[3] Safety assessments include vital signs, ECG, safety laboratory testing, injection site assessments and AE assessment at various time points as applicable.
[4] Biomarkers may include inflammatory markers and micro RNA.
[5] Continuous monitoring that will be captured for approximately 7 days prior to dosing (baseline) through approximately 7 days after the last dose of study drug. Subjects will be provided with an Omron Blood Pressure Monitor with ComFit™ Cuff (Model BP785N) for use of self monitoring of blood pressure at home. An alternative (comparable) automated blood pressure cuff may be used if necessary providing that the CRU ensures the cuff to be used is operating properly. Subjects will be required to collect blood pressure and heart rate on the same arm every morning and every evening.
[6] If subject had a previous echo within 60 days prior to screening with an EF ≤40% and subject qualifies by all other criteria, a screening echo will not be required. However, the baseline echo must be done at least 7 days prior to planned randomization for confirmation of continued study eligibility.
7 Can be done up to 14 days prior to randomization.

Figure 2 Study Schematic

3.2 Study Registration

Upon signing consent, a subject will be screened (status set to "screened" in the electronic case report form [eCRF]). Subjects qualifying for participation will be registered (status update to "registered" in the eCRF) in the study and will be assigned to the next available dosing slot. No subject may participate (receive study drug) in more than one dose cohort.

3.3 Run-in/Stabilization Period

During the period between screening and randomization (planned first dose), the study subject will remain on stable pharmacological therapy for heart failure. Stable therapy is defined as no change in dose or the addition or removal of a therapy. Adjustment of diuretic dosage if applicable, will be permitted. Also the study subject will be in stable health with no hospitalizations or acute illness between screening and randomization that would put the subject at increased risk for study participation. Approximately 7 days prior (Day -10 to Day -7) to planned randomization, subjects will return to the study unit for placement of mobile telemetry and collection of baseline safety laboratory tests. Within 14 days prior to randomization, subjects will undergo a baseline echocardiogram. Subjects will be instructed to monitor their blood pressure twice daily (morning and evening) starting at least 7 days prior to dosing.

3.4 Randomization

Qualifying subjects will be randomly assigned via a central randomization system to receive either PB1046 or placebo. Only the unblinded study drug dispenser (USDD) at the study site will have access to the randomization assignment. However, at the completion of each dose cohort, the study statistician and pharmacokineticist (including PK analytical lab) will have access to the randomization codes for that cohort in order to prepare data summaries required

for the study review meetings to assist in decisions regarding dose escalation. All displays will be provided to the committee in a blinded manner.

3.5 Planned Dose Escalation

A starting dose of 0.2 mg/kg is selected based on the safety, and minimal to no pharmacodynamic response in the single dose escalation study in subjects with essential hypertension [PB1046-PT-CL-0001]. Model predicted serum exposures covering the planned dose escalation are outlined in Figure 3 are described in Figure 1 and Table 1. The model predicted exposures are well below nonclinical exposure (area under the curve) achieved in the 4 week repeat dose toxicology studies (rats and monkeys) and do not exceed the maximum serum concentration observed in subjects receiving a 30 minute intravenous infusion of PB1046 [PB0146-PT-CL-0002].

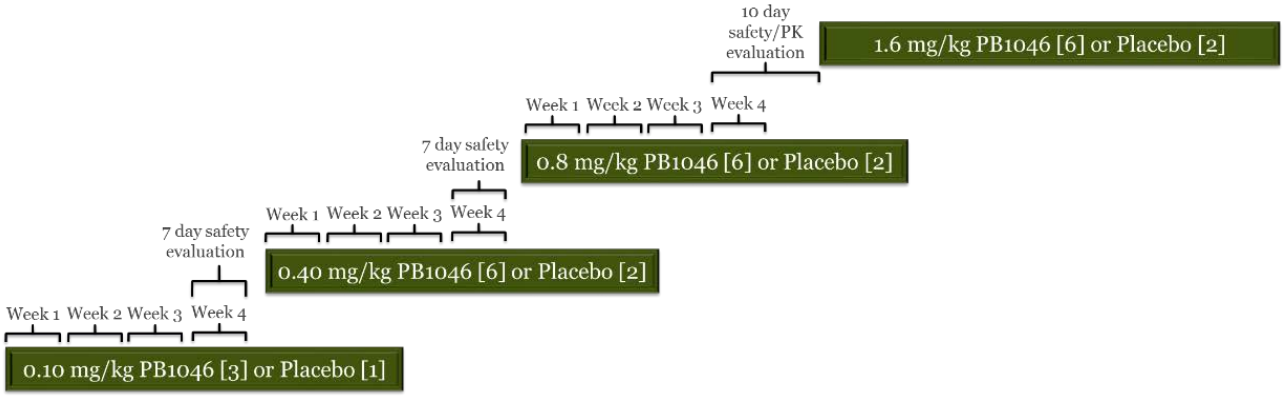


Figure 3 Dose Escalation

3.5.1 Dose Escalation Rules

- More than one subject may be dosed in a 24 hour period up to and including 0.8 mg/kg, which was the maximum dose utilized in the PB1046-PT-CL-0001. If dosing exceeds 0.8 mg/kg, no more than one subject will be dosed in a 24 hour period for the four three subjects dosed in a cohort.

- At least 75% of subjects assigned to a cohort must receive at least three weekly doses (e.g., at steady state) with no reported dose limiting toxicities (DLTs) before escalation to the next higher dose level.

- For a dose cohort exceeding 0.8 mg/kg, for which there is no available subcutaneous pharmacokinetic (PK) data, PK data through Day 31 (10 days following the last dose) will be required to be assessed in addition to safety data prior to escalating to a higher dose.

- DLTs identified during the study will be assessed as potential indicators of cumulative toxicity and provide rationale for revision of the maximum tolerated dose (MTD).

- Multiple dose escalation will continue until modelling of the PK data indicates that the human AUC (0-168 hours) would exceed currently available nonclinical exposure and/or previous human exposure (PB1046-PT-CL-0001 [SC] or -0002 [IV]), whichever is higher.

- If a subject in a cohort experiences a DLT that is evaluated by the Investigator as related to study drug (PB1046), an additional four subjects (3A and 1P) will be dosed at that dose level. If two or more subjects in a cohort experience a DLT related to PB1046, the MTD will be considered exceeded. The dosing schema may be revised to dose additional subjects below this level to further refine the MTD.

- The decision to temporarily hold or discontinue a subject from study treatment will be based on Investigator discretion regarding reported adverse events or other factors, which may include clinically significant reduction in blood pressure (i.e., hypotension).

- Aggregate assessment of adverse events with specific emphasis on cardiac related events will be assessed on an ongoing basis and will be evaluated for trends related to dose escalation and will be reviewed at each Study Review Committee (SRC) meeting.

- A study subject will be discontinued from study treatment if there is evidence of increased arrhythmia potential or marked prolongation (e.g., QT/QTc > 500 ms or > 60 ms over baseline) of the QT/QTc interval while on treatment.

- Aggregate evaluation of the risk for arrhythmias or QT/QTc prolongation will be evaluated for trends on an ongoing basis and will reviewed at each Study Review Committee (SRC) meeting.

Dose escalation will continue if the safety and pharmacokinetic profile are deemed acceptable as assessed by the Medical Monitor, Principal Investigators, Clinical/Regulatory and a representative from Preclinical/Assay Development (i.e., the Study Review Committee [SRC]). The SRC may also recommend de-escalation or study discontinuation. All decisions and outcomes related to SRC meeting will be documented and retained as part of the study file. Updates will be made to the Food and Drug Administration (FDA) and to the Institutional Review Board (IRB) as appropriate.

3.6 Safety Oversight

3.6.1 Study Review Committee

The Study Review Committee (SRC) will review data relating to safety, PK and hemodynamic response after 75% of the subjects in a cohort have completed their 3rd dose and have been followed for seven (7) days after the 3rd dose prior to dose escalation. The committee will include the Principal Investigators, the Medical Monitor, Clinical/Regulatory Representative (Sponsor), Preclinical/Assay Development Representative (Sponsor) and a Pharmacokineticist. The SRC will review the interim safety summaries prepared by the Clinical Representative from safety data entered into the EDC system, safety laboratory data, and pharmacokinetic and immunogenicity (binding ADA) data provided by PhaseBio's Assay

Development Department, as applicable. The safety data will be reviewed in a blinded manner and must will be deemed acceptable to the SRC prior to dosing of the next higher dose group. The SRC may recommend additional ECG evaluations or a change to the scheduled evaluations based on the PK profile, to further elucidate the relation of exposure to PB1046 and the QT/QTc interval.

In the case of a Dose Limiting Toxicity (DLT), Serious Adverse Event (SAE), or other significant AE, the SRC may request that the study drug assignment be unblinded. Following review of the interim safety summary, the SRC will decide if dose escalation should continue, recommend de-escalation, or recommend study discontinuation. SRC recommendations not previously described in the protocol, or any recommendations to discontinue the study will be promptly reported to the IRB and the Food and Drug Administration (FDA).

The SRC amy recommend up to two dose levels to carry forward to Part 2 of the study (PB1046-PT-CL-0003-P2). Activities related to Part 2 of the study will be reviewed and approved under a separate protocol PB1046-PT-CL-0002-P2.

3.6.2 Investigator

The Investigator (Principal or physician Sub-Investigator) must have access and be available to promptly review the results of all safety assessments (i.e., clinical laboratory testing), electrocardiogram (ECG) results, vital signs and adverse events (AEs) including injection site assessment information throughout the study. Safety assessments must be promptly (should be within 48 hours of notification of event) entered into the Electronic Data Capture (EDC) system and clinical laboratory data should be available within about 48 hours from date of receipt of samples at the central laboratory.

Clinical laboratory data will be evaluated by the Investigator (Principal or physician Sub investigator) and clinical relevance will be assessed for abnormal values and the assessment will be documented on the laboratory report. A copy of the reports will be maintained as part of the source documentation.

3.6.3 Definitions

3.6.3.1 Dose Limiting Toxicity (DLT)

A dose limiting toxicity is defined as any Grade 3 or greater toxicity excluding injection site reactions as further described, that is evaluated by the Investigator as related to study drug. For injection site reactions a DLT is defined as a Grade 3 toxicity in 2 or more injection site assessment categories (e.g., pain, tenderness, erythema/redness, and/or induration/swelling; refer to Appendix A), or a Grade 4 injection site reaction in any one assessment category and is evaluated by the Investigator as related to study drug. The treatment assignment will be unblinded to confirm relationship to PB1046. An additional four subjects (3A and 1P) may be dosed with PB1046 at that dose level if deemed appropriate by the Study Review Committee (SRC).

3.6.3.2 Maximum Tolerated Dose (MTD)

Although this study is not designed to dose to a MTD, the MTD may be reached if two or more subjects in a cohort experience a DLT as defined in section 3.6.3.1. No further dosing will occur above the MTD.

GRADE	Clinical Description of Severity
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING OR DISABLING Adverse Event
5	DEATH RELATED TO Adverse Event

4 SUBJECT SELECTION

4.1 Inclusion Criteria

Subjects will be eligible for inclusion in the study if they meet all of the following criteria:

1. Willing and able to sign a written informed consent and follow all study-related procedures;

2. Male or female subject ≥ 18 years of age;

3. Male subjects and female subjects of reproductive or childbearing potential must practice effective contraception during the study and be willing and able to continue contraception for 30 days after their last dose of study drug. Female subjects of non-childbearing potential are defined as being surgically sterile by bilateral tubal ligation, bilateral oophorectomy, or hysterectomy. A female subject 45 to 60 years of age, inclusive who is post-menopausal for at least 1 year and has a follicle-stimulating hormone level confirmation indicating post-menopausal status will be considered of non-childbearing potential. Female subjects > 60 years of age are considered post-menopausal and of non-childbearing potential;

4. Body mass index ≥ 18 kg/m2 and ≤ 45 kg/m^2;

5. Receipt of stable (no change in dose (except diuretics) or addition or removal of a therapy) pharmacological therapy(ies) for heart failure for a minimum of 1 month (30 days) prior to screening and between screening and randomization and are in stable clinical condition;

6. NYHA Class II or III heart failure diagnosis (ischemic or non-ischemic confirmed by medical history) at least (≥) 6 months (180 days) prior to screening;

7. Stable HF defined as no hospitalizations for cardiac related issues within the previous 3 months (90 days) prior to the screening visit or between screening and randomization;

8. A screening Left Ventricular Ejection Fraction ≤ 40% by centralized reading of 2-D echocardiography.

9. Screening hemoglobin ≥ 9.0g/dL secondary to the volume of blood to be collected during the study period.

10. Willing and able to return to the study unit for specified study visits, and be able to self-monitor blood pressure while at home.

11. Live and work in an area with reliable cellular services (e.g., Sprint®) for real time transmission of telemetry data to the core laboratory.

4.2 Exclusion Criteria

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

1. Have previously received PB1046 or have a known allergy to the study drug or any of its components;

2. Participating in any other study and have received any other investigational medication or device within 30 days prior to screening or are taking part in a non-medication study which, in the opinion of the Investigator, would interfere with study compliance or outcome assessments;

3. Diagnosed with acute coronary syndrome (ACS) or an acute myocardial infarction (MI) within 3 months (90 days) of screening;

4. Canadian Cardiovascular Society (CCS) Class III or IV angina necessitating frequent use of as needed short acting nitroglycerin (e.g., sublingual);

5. Cardiac surgery or valvuloplasty within 3 months (90 days) prior to screening;

6. Cerebrovascular accident or transient ischemic attack within 3 months (90 days) prior to screening;

7. Sustained systolic blood pressure (SBP) < 100 mmHg and/or diastolic blood pressure (DBP) < 50 mmHg (confirmed by a duplicate seated reading) on at least 3 consecutive readings (self-monitored or office) prior to randomization or overt symptomatic hypotension;

8. Sustained resting heart rate >100 beats per minute (BPM) at screening (V1) or prior to randomization (confirmed on baseline telemetry monitoring);

9. History or evidence (documented on baseline telemetry monitoring) of clinically significant arrhythmias (uncontrolled by drug therapy or use of an implantable defibrillator), long QT syndrome or evidence of QT prolongation demonstrating QTcF > 460 ms (by ECG) prior to randomization;

10. Clinically significant renal dysfunction as measured by the estimated glomerular filtration rate (eGFR) of < 40 mL/min/1.73m^2 as calculated by the CKD-EPI creatinine-cystatin C equation: eGFR = 135 x min (Scr/k, 1)$^{-a}$ × max(Scr/k, 1)$^{-0.601}$ × min(Scys/0.8, 1)$^{-0.375}$ × max(Scys/0.8, 1)$^{-0.711}$ × 0.995^{age} [× 0.969 if female] [× 1.08 if black] at screening, or a significant change in renal function between screening and baseline;

11. Clinically significant liver dysfunction as measured by: alanine aminotransferase >3.0 × the upper limit of normal (ULN), aspartate aminotransferase >3.0 × the ULN, or serum bilirubin ≥ 1.6 mg/dL at screening, or a significant change in liver function between screening and baseline;

12. Pregnant or lactating female subjects;

13. Known history of or active alcohol abuse or use of illicit drugs within 1 year prior to randomization;

14. Positive screening for human immunodeficiency virus antibodies, hepatitis B surface antigen, or hepatitis C virus antibodies;

15. Any major surgical procedure within 1 month (30 days) prior to screening or planned surgical procedure during the study period;

16. Other medical or psychiatric condition which, in the opinion of the Investigator, would place the subject at increased risk or would preclude obtaining voluntary consent/assent or would confound the secondary objectives of study.

5 DESCRIPTION OF STUDY PROCEDURES

A description of study procedures listed in the Schedule of Activities is provided within the content of this protocol. Refer to the **Schedule of Activities** for additional information on the frequency of each procedure.

5.1 Informed Consent

All subjects must provide written informed consent prior to participating in any screening evaluations or any other study activities. The Investigator or his/her approved designee (as documented on the Delegation of Authority Log) must explain the nature of the study protocol and associated risks to the potential study participant. The potential participant must be allowed sufficient time to review the information and to ask questions. The date that the informed consent form is signed, a brief description of the consent process (e.g., questions asked by the subject) and the name of the individual who obtained the consent will be recorded in the subject's source documentation. A copy of the signed informed consent should be provided to each subject. The date and confirmation that informed consent was obtained and consent form version will be recorded in the eCRF.

During a subject's participation in the study should an updated informed consent become available, it is the site's responsibility to re-consent those subjects as directed by the Institutional Review Board following the same procedures as in the previous paragraph. The date and confirmation that a revised informed consent was obtained will be recorded in the subject's source documentation as well as the eCRF.

5.2 Demographics

Subject demographic information will be recorded at screening. Demographic information will include date of birth, gender (at the time of birth), race, and ethnicity. Findings will be documented in the source documentation and the eCRF.

5.3 Histories

5.3.1 General Medical/Surgical and Social History

Relevant medical and surgical history will be recorded at screening and will include medical diagnoses, major surgical procedures within the last 3 years. Social history (tobacco, drug, and alcohol use) as well as dietary habits (e.g., unrestricted, vegetarian, gluten-free, vegan, other) and allergies (food, medications and environmental) will also be recorded at screening. Findings will be documented in the source documentation and the eCRF.

5.3.2 Targeted Medical History

Subjects who qualify for this study, must have been diagnosed with heart failure. Date of initial diagnosis, New York Heart Association Classification, type: ischemic or non-ischemic, and date of and ejection fraction (EF) from the most recent echocardiogram and treatments for heart failure as well as other relevant cardiac history will be recorded in the eCRF and documented in the source documentation.

5.3.3 Medications

Chronic medications used to treated a relevant medical diagnosis that has taken within the last 3 months (90 days) prior to screening or acute (e.g., antibiotics) as needed medications (e.g., TUMS®, acetominophen) taken at the time of screening will be recorded in the source document and on the eCRF. Also refer to Section 6.3 Concomitant Medications for additional information.

5.4 Physical Examination

A general physical examination will include at minimum an examination of general appearance, skin, eyes, ears, nose, throat, neck/thyroid, lungs, heart, upper/lower extremities, lymph nodes, abdomen, musculoskeletal system and neurological system. Additional systems will be evaluated as needed. Physical exam findings must be recorded in the source documentation and include the date and name of the individual conducting the examination. Physical examinations must be performed by an individual licensed to conduct standard physical examinations. An abbreviated physical examination will include an examination of general appearance, lungs, heart, lower extremities and abdomen.

Significant findings that are present prior to dosing with study drug will be recorded in the eCRF as pre-treatment adverse events. Clinically significant findings present after dosing will be recorded as an adverse event in the eCRF.

5.5 Telephone Contact

The Investigator or designee will contact the subject by phone the evening of each dosing day (recommended to occur between 7 and 10 PM) to assess their status. All subject contacts will be documented in the source records.

5.6 Directed Physical Exam

A directed physical exam will be done as necessary during the study based upon signs and/ or symptoms that may have presented or reported adverse events that may have presented during a subject's participation in the study. If no signs or symptoms or an adverse event are present then no directed physical exam is necessary.

5.7 Height/Weight and Calculation of BMI and BSA

Height and weight will be measured and will be used for calculation of body mass index (BMI) and Body Surface Area (BSA). The calculation for study drug administration will be based upon the weight taken on Day 0 and will remain the same throughout the subject's participation in the study, unless there is a greater than 10% change in the subject's weight between Day 0 and subsequent dosing days. If this were to occur sites are instructed to notify the Sponsor for instructions.

Weight should be measured with shoes off and light clothing only. A digital scale should be used and, for consistency, the same scale should be used for all weight measurements for a given subject.

5.8 Vital Signs - General

Blood pressure and heart rate will be measured using an Omron automated blood pressure (BP) monitor (Model BP785N) provided by the Sponsor. This monitor is able to measure triplicate measurements one minute apart (as applicable). Vital signs should be measured on the SAME arm (location should be documented) throughout the study (including subject self-monitored blood pressure; refer to Section 6.6) for accurate comparison of readings over time.

Position is critical for accurate BP measurements. Therefore, when the BP is measured, the arm (cuff) should be at the level of the heart. In the supine position, the arm should be kept at the side at the level of the body. When standing, the cuff should be at the level of the heart with the arm supported. Do not allow the arm to hang down. When sitting, feet should be flat on the floor with back supported and arm supported at the level of the heart (e.g., resting on a table). Additionally respiratory rate and temperature (oral or oral equivalent) will be captured once at each designated time point per the Schedule of Activities.

It is important that vital signs be taken either before a meal, or at least 30 minutes after a meal or consuming caffeine. If the subject is a smoker, the subjects must not be permitted to smoke within 30 minutes prior to scheduled study activities.

5.8.1 Orthostatic Blood Pressure

Systolic and diastolic blood pressure and heart rate will be measured in the supine position after resting for at least ten (10) minutes (+ 2 minutes) (times to be recorded in the source document), followed by the standing position (time at standing position will be documented in the source record). The first measurement beginning immediately upon standing and the second measurement will be taken at 3 minutes after standing (Irvin & White, 2004). The

subject should indicate if they experienced dizziness or other symptomatology upon standing. Findings will be recorded in the source document and in the eCRF.

5.8.2 Seated Blood Pressure

Blood pressure (systolic/diastolic) and heart rate will be assessed approximately one minute apart in triplicate per the Schedule of Activities after the subject has rested in a seated position for at least five (5) minutes. Each of these blood pressure readings and heart rate readings will be recorded in the eCRF along with the time they were taken. Temperature (oral or oral equivalent) and respiratory rate will be recorded once at each scheduled time point. Findings will be recorded in the source documentation and in the eCRF.

5.9 Injection Site Assessment

The injection site(s) will be examined periodically for the absence/presence of pain, tenderness, erythema/redness (including size), induration/swelling (including size) and will be recorded in the source document. Injection site findings (with reference to injection site number; refer to Section 8.5.2) will also be recorded as an adverse event in the eCRF. Each injection site will be examined for a minimum of 7 days following injection or until any treatment-emergent skin lesions have resolved or stabilized. Refer to Schedule of Activities for frequency of assessments. Refer to Appendix A for toxicity grading.

5.10 12 Lead Electrocardiogram

All investigative sites will be provided with an identical make/model calibrated portable ECG machine. Site personnel must assess the quality of the ECG while the subject is still at the investigative site in the event that additional ECGs need to be performed (i.e., if artifact is present). QT intervals will be reported uncorrected as well as corrected for heart rate according to the Frederica Formula. All ECG's will be read (confirmed report) by a central ECG core laboratory (BioTelemetry Research).

5.10.1 Subject Preparation Procedure

In accordance with the standards for collection of vital signs, it is suggested that the 12 lead ECG be collected either before a meal or at least 30 minutes after a meal or consuming caffeine. If the subject is a smoker, the subjects must not be permitted to smoke within 30 minutes prior to scheduled test.

To ensure good electrode contact, dry shave any site containing excess hair. Lightly abrade each electrode site.

- ECGs need to be recorded with subjects in a supine position and resting for at least 10 minutes before recording.

- With the subject at rest in the supine position, attach the electrodes to the lead wires and then to the subject (refer to Figure 4).

5.10.2 ECG Measurement and Printouts

The investigative site will print one original of each triplicate ECG performed at each time point for the source document file. The Investigator will review and sign the unconfirmed ECG (site source file copy) for initial evaluation of safety. ECGs will be electronically transmitted to the core laboratory (BioTelemetry Research) and read (confirmed). The Investigator will be notified of any clinically significant abnormal ECG findings. A confirmed ECG will be provided to the clinical site for their records. Refer to ECG manual for additional details regarding data transmission.

5.10.2.1 Electrode Placement

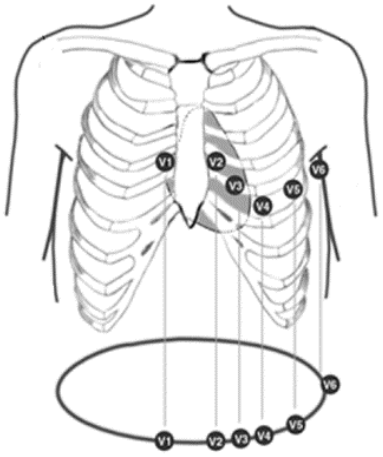


Figure 4: 12 Lead ECG Electrode Placement Diagram

Precordial electrodes

V1: Placed on the fourth intercostal space at the right sternal border.
V2: Placed on the fourth intercostal space at the left sternal border.
V3: Placed midway between V2 and V4.
V4: Placed at the midclavicular line in the fifth intercostal space.
V5: Placed at the anterior axillary line on the same horizontal level as V4 or if the anterior axillary line is ambiguous, midway between V4 and V6.
V6: Placed at the mid-axillary line on the same horizontal level as V4 and V5.

Limb electrodes

Limb electrodes can be placed anywhere on the limbs. However, the following placement is recommended:

RA and LA: Place on the wrist.
RL and LL: Place approximately 7cm (or 3 inches) above the ankle.

5.10.3 Verification of Qualifying QTcF at Randomization

The Investigator will be required to verify the baseline (pre-dose) ECG findings with interpretation (should be documented on the third ECG in the pre-dose series) and will enter (or designee) the triplicated ECG measurements into the eCRF for calculation of mean triplicate QTcF and verification of study qualification prior to randomization.

5.11 Remote 24/7 Mobile Telemetry Monitoring

5.11.1 Device

The Mobile Cardiac Outpatient Telemetry (MCOT™) monitoring device (Cardionet, Malvern, PA) will be used in this study. The device received FDA marketing clearance in February 2002. Each device is tested, programmed, and validated at Cardionet prior to shipment to the investigative site. This will ensure that the equipment is functioning properly and transmits successfully to the receiving center.

A study subject will wear a sensor on a lanyard with 3 electrodes (Figure 5) as they continue their normal daily routine for approximately 5 weeks (starting 7 days (may be started as early as Day -10 if necessary) prior to randomization and first dose of study drug for 7 days following the last dose of study drug). Two leads of ECG data are monitored continuously. The algorithm uses rate, rhythm, QRS morphology and P wave recognition for arrhythmia detection. The subject will carry a PDA size monitor that has cellular capabilities. After acquiring ECG data, the sensor transmits the full disclosure data to the hand-held monitor unit with a range up to approximately 150 feet. The hand-held monitor device contains a proprietary algorithm which analyzes the ECG data for arrhythmias. If an arrhythmia is detected, the monitor transmits an ECG strip of the arrhythmia over the cellular network to an Independent Diagnostic Testing Facility which is staffed 24/7/365. Note: Wireless ECG transferred data is completely recoverable while the patient is being monitored. If the subject is out of cellular range, no data will be lost. No action is required by the subject or study personnel to transmit the ECG data. Customer Support-available 24 hours /7 days a week via phone at 866-326-1936 or via email: ClinicalStudies@cardionet.com.

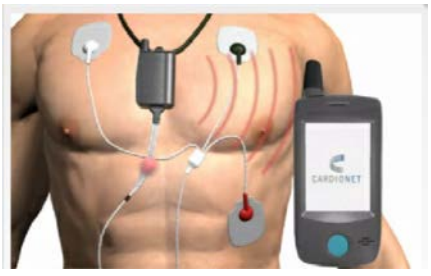


Figure 5. MCOT Monitoring Device

5.11.2 Notifications and Reporting

5.11.2.1 Notifications

When an arrhythmia is detected, the ECG is automatically transmitted to Cardionet where the ECG is immediately interpreted. Results will be called or sent via e-mail and/or fax to the Investigator. Additionally the report will be sent to the Sponsor's Adverse Event Reporting fax line for automatic distribution to the Medical Monitor. All alert reports will be stored with the subject records.

The Investigator and subject will be notified immediately by Cardionet for the following rhythm issues:

Emergent Criteria	Rate	Duration
Pause	All Events	≥8 Seconds
Severe Tachycardia (All rhythms)	≥220 BPM	Any
Severe Bradycardia (All rhythms)	<25 BPM	Any
Ventricular Tachycardia (symptomatic)	>100 BPM	≥25 Beats
Sustained VTach	>150 BPM	>30 Seconds
Rapid VTach	≥190 BPM	>6 Beats

The Investigator will be notified immediately by Cardionet for the following rhythm issues:

Urgent Criteria	Rate	Duration
Pause/Asystole	All Events	≥3 Seconds
Syncope	All Events	All Events
Severe Tachycardia (All rhythms) - Asymptomatic	>190 BPM	>30 Seconds
Severe Tachycardia (All rhythms) - Symptomatic	>170 BPM	>30 Seconds
Severe Bradycardia	<35 BPM	> 30 Seconds
Atrial Fibrillation/Flutter	New Onset	>10 Seconds Notify 9A-5P, 7 Days a Week
NSVT	>100 BPM	>3 Beats w/ symptoms
2nd Degree AVB – Mobitz Type II	All Events	All Events
3rd Degree AV Block – Complete HB/AV Dissociation	All Events	All Events
Defibrillator/Pacemaker – Failure to Capture/Sense	All Events	All Events

If the subject reports an adverse event during the monitoring period, the "event" should be marked on the hand held transmitter.

5.11.2.2 Reporting

Daily reports will be available to the Investigator through Cardionet access portal at https://access.cardionet.com/Login.aspx?ReturnUrl=%2fMarketing%2fDefault.aspx. Prior to

dosing, the Investigator (or designee) will need to confirm that the subject has not experienced an episode(s) of sustained resting tachycardia (100 bpm +) during baseline period (Day -7 to Day 0 prior to dosing) that would exclude the subject from continued study participation.
At the completion of the monitoring period, a final report will be generated by Cardionet and will be sent to the Investigator. This report should be maintained with the subject record.

5.12 2-D Echocardiography with Doppler

Two-dimensional echocardiography (2D-echo) will be performed utilizing the site's echocardiography machine and will be performed by a qualified echocardiographer. It is preferable that the same technician perform all 2D-echo evaluations for a given subject whenever possible. An Informational questionnaire which pertains to the system as well as participating echocardiographers will be collected by BioTelemetry Research who will be responsible for training and centralized 2D-echo readings. Each echocardiographer will be required to submit a test echocardiogram for certification purposes. Certification echocardiogram is to be performed on a volunteer who is not participating in the study. Upon acceptable certification echo, BioTelemetry Research will send a Certification Echo certificate to the site. Certification must be received prior to performing a study echo.

All echocardiograms will be reviewed by two independent blinded reviewers, one of whom is a Board Certified Cardiologist. The echocardiography technician will not be required to perform or record any measurements on the echo screen.

It is anticipated that it will take approximately 20 minutes to complete a resting echo evaluation for each subject at each time-point. A detailed Echocardiography Procedure Manual will provide supplemental information to that contained in the protocol.

The following parameters may be assessed:

- Blood pressure (BP) and heart rate (HR) (arterial peak, mean and diastolic blood pressure)
- Left ventricular internal diameter in diastole (cm)
- Left ventricular internal diameter in systole (cm)
- Left ventricular wall thickness in diastole (cm; both septum and posterior wall)
- Left ventricular outflow tract diameter in mid-systole (cm)
- Left ventricular volumes (end-diastole and end-systole, in mL; apical views)
- Left ventricular outflow tract flow-time velocity integral (by pulsed Doppler; in cm)
- Ascending aorta peak flow velocity (by Continuous Wave Doppler; in m/s)
- Transmitral flow velocity pattern (both by pulsed and Continuous Wave Doppler)

- Doppler tissue imaging of tricuspid, septal and mitral annulus (velocity; in cm/s)
- Left atrial volume (in mL/M2)
- Derivation of: Left ventricular (LV) Ejection Fraction, Strain Rate (SR)/Strain Rate Image (SRI), LV Stroke Volume and Index, LV Cardiac Output and Index, Ejection Time, Systemic Vascular Resistance, Mitral E and A velocities, LV and index, Myocardial tissue velocities S' and e'.

5.12.1 System Requirements

- System must undergo routine maintenance check as recommend by the manufacturer and documentation of such maintenance will be made available upon request.
- Harmonic imaging capable
- Tissue Doppler capable
- Digital (DICOM) acquisition is preferred
- For all echocardiograms, if using a digital system, the files should be able to be burned as DICOM or AVI / JPEG format. Biotelemetry Research can NOT accept WMV, MP4, RAW or MPEG formats. Files will be sent to Biotelemetry Research for analysis. The echo images must be labelled with the subject ID, initials, date and time of evaluation.
- Have the ability to keep a copy of all echocardiograms for the subject source records.

5.13 Laboratory Testing

5.13.1 Testing Facilities

Blood samples for screening and routine safety laboratory testing will be analyzed by a centralized laboratory (Medpace Reference Laboratory, Cincinnati, OH) that is certified under the Clinical Laboratory Improvement Act (CLIA). Pharmacokinetic and immunogenicity testing will be performed by PhaseBio Pharmaceuticals, Inc., Malvern, PA utilizing methods that are validated as appropriate for the stage of development that will be done in accordance with Good Laboratory Practice (GLP) standards. Additional exploratory sample analysis for various biomarkers will be conducted under a protocol for research purposes only and analysis may be done at PhaseBio Pharmaceuticals, Inc., or a specialty and/or academic facility in direct support of this study.

5.13.2 Blood Volumes

It is anticipated that approximately 365 mL of blood will be collected over the study period (screening, which can occur up to 60 days prior to randomization and through 12 weeks after randomization). Assuming that the majority of subjects will weigh at least 60 kg, it is

estimated that no more than 2.5% total blood volume (mL) will be collected in a 24 hour period and no more than 5% of total blood volume (mL) will be collected over a 30 day period.

5.13.3 Sample Identification and Sample Banking

Blood samples will be labeled with the 5-digit subject ID and initials and sample collection date/time and sample type. The Sponsor will not have any information that would identify the subject.

Blood samples may be retained indefinitely by the Sponsor for future testing for the purpose of investigating the study drug's safety and effectiveness in support of future clinical research and/or to answer regulatory authority questions related to safety and effectiveness at the time of registration. Blood samples will not be shared with other research institutions for purposes outside of the stated purposes noted above.

5.13.4 Screening and Safety Laboratory Testing

5.13.4.1 Serology for HIV, Hepatitis B, and Hepatitis C

All subjects will be screened for HIV, HBsAg, and HCV. Evaluation for HIV seropositivity will consist of enzyme-linked immunosorbent assay (ELISA) and, if positive, will be confirmed by the Bio Rad Multispot HIV-1/2 antibody differential test. Appropriate counseling will be made available to the subject in the event of a positive finding. Notification of state and federal authorities, as required by law, will be the responsibility of the Investigator. Samples will be analyzed by Medpace Reference Laboratory.

5.13.4.2 Drug and Alcohol Testing

A drug screen (urine) to test for the presence of amphetamines, benzodiazepines, cocaine metabolites, phencyclidine (PCP), barbiturates, cannabinoids, and opiates as well as an alcohol test (i.e., breath test, urine or serum) will be performed at screening and prior to dosing utilizing CLIA waived methodology. Testing supplies will be provided by the Sponsor to be tested locally at the site.

5.13.4.3 Pregnancy Test

A pregnancy test is required for female subjects of childbearing potential. Results must be negative (serum) in order for subjects to be randomized in the study. Samples will be analyzed by Medpace Reference Laboratory.

Note: Women of childbearing potential who were not following an acceptable method of birth control and who were sexually active at the time of screening must have two negative serum pregnancy tests approximately 15 days apart to confirm that the subject is not pregnant prior to dosing with study drug.

Additionally, a urine pregnancy test (local CLIA waived) will be done prior to each dose of study drug. Testing supplies will be provided by the Sponsor to be tested locally at the site.

5.13.4.4 Follicle-Stimulating Hormone Level

Medpace Reference laboratory will conduct and analysis of follicle-stimulating hormone levels in women 45 to 60 years of age for confirmation of postmenopausal status if not previously available. This testing will only be done as requested by the study site.

5.13.4.5 Lipid Profile

A fasting lipid profile includes (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein-cholesterol [LDL-C], low-density lipoprotein/high-density lipoprotein (LDL/HDL) ratio, and triglycerides [TG]). Samples will be analyzed by Medpace Reference Laboratory.

5.13.4.6 N-terminal Pro-B Type Natriuretic Peptide (NT-ProBNP)

N-terminal pro-B type natriuretic peptide (NT-proBNP), is an indicator of myocardial stretch and is recognized as a robust prognostic marker at all stages of HF and related clinical outcomes (de Antonio, Lupon, Galan, Vila, Urrutia, & Bayes-Genis, 2012). Samples will be analyzed using an inmmuno-electrochemiluminescence assay on the Modular Analytics E 170 (Roche Diagnostics) with a sensitivity of 5 pg/mL. Results lower than 5 pg/mL are reported as <5 pg/mL. Samples will be analyzed by Medpace Reference Laboratory.

5.13.4.7 High Sensitivity Cardiac Troponin T Assay (hs-cTnT)

Cardiac troponin is a marker of myocyte injury which may be able to predict adverse clinical outcomes in acute and chronic HF (de Antonio, et al, 2012; Sherwood, & Newby, 2014). A high-sensitivity assay for cardiac troponin T (hs-cTnT) is able to detect low troponin concentrations and improves precision at the lower limit of detection. Furthermore, some reports suggest that hs-cTnT also provides relevant prognostic information in HF. Troponin levels will be measured by an electrochemiluminescence immunoassay using an hs-cTnT assay on the Modular Analytics E 170 (Roche Diagnostics) with a sensitivity of 0.003 ng/mL. Results lower than 0.003 ng/mL are reported as <0.003 ng/mL. Samples will be analyzed by Medpace Reference Laboratory.

5.13.4.8 Routine Safety Laboratory Testing

The following safety laboratory panel will be analyzed by Medpace Reference Laboratory. For fasting samples, the subject must have fasted (no food or drink except for water) for at least 8 hours prior to collection of sample.

Test Group	Parameter
Serum Chemistry	Alanine Amino Transferase (ALT)
	Aspartate Transaminase (AST)
	Albumin
	Alkaline phosphatase
	Amylase
	Anion gap
	Bilirubin (total, direct and indirect)
	Blood urea nitrogen (BUN)

Test Group	Parameter
	Calcium
	Carbon dioxide
	Chloride
	Creatinine, serum
	Cystatin C
	Creatinine kinase (CK)
	Creatinine kinase MB Isoenzyme (CK-MB)
	Gamma glutamyl transferase (GGT)
	Lactate dehydrogenase (LDH)
	Lipase
	Magnesium
	Phosphorous
	Potassium
	Sodium
	Total protein
	Urea-N
Plasma Chemistry	Fasting plasma glucose (FPG)
Hematology	Complete blood count [red blood cells (RBC), hematocrit (HCT), hemoglobin (Hgb), white blood cells (WBC), platelets] (reported as % and absolute values)
	Differential (Automated)
Urinalysis/Microscopy	Appearance
	Bilirubin
	Blood
	Color
	Glucose
	Ketones
	Microscopic examination [bacteria, casts, red blood cells (RBC), white blood cells (WBC), crystals]
	pH
	Protein
	Protein/creatinine ratio
	Urobilinogen

5.13.4.9 Calculation of Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate (eGFR) will be calculated by Medpace Reference Laboratory by the following methods:

- CKD-EPI creatinine-cystatin C equation: eGFR = 135 x min (Scr/k, 1)-a × max(Scr/k, 1)$^{-0.601}$ × min(Scys/0.8, 1)$^{-0.375}$ x max(Scys/0.8, 1)$^{-0.711}$ × 0.995^{age} [× 0.969 if female] [× 1.08 if black]

- IDMS-Traceable MDRD Study Equation: eGFR (mL/min/1.73 m^2) = 175 × (S_{cr} in mg/dL)$^{-1.154}$ × (Age)$^{-0.203}$ × (0.742 if female) × (1.212 African American) (conventional units)

- Cockcroft-Gault (C-G) Equation: CLcr in mL/min is estimated from a spot serum creatinine (mg/dL) determination using the following formula:

$$\text{CLcr (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg / dL)}} \quad \{\times 0.85 \text{ for female patients}\}$$

5.13.5 Immunogenicity (Antibody) Testing

For details regarding collection, collection schedule, specimen processing, and shipping, see Schedule of Activities and Appendix B. Samples will be screened for the presence of binding anti-drug antibodies. Samples testing positive and specific for antibodies against PB1046 will be further characterized to determine the domain specificity including whether the antibodies cross react with native VIP. Additional characterization of the antibody response may be performed as warranted. Samples testing positive and specific for anti-drug antibodies will be titered and further evaluated for their neutralizing potential using a cell based assay. Immunogenicity samples may be tested to measure PB1046 serum concentrations if necessary. Additional out of protocol (OOP) samples may be collected if clinically necessary (e.g., if last sample is positive for antibodies additional samples may be requested).

5.13.6 Pharmacokinetic Testing

Samples will be analyzed at PhaseBio Pharmaceuticals Inc. For details regarding collection, collection schedule, specimen processing, and shipping, see Schedule of Activities and Appendix B.

5.13.7 Exploratory Biomarkers

The exploratory biomarkers listed below may be considered for evaluation. Additional biomarkers may be evaluated as directed by the data. Exploratory biomarkers will be analyzed at PhaseBio Pharmaceuticals Inc. or a PhaseBio designated testing facility, using good scientific principles and commercially available kits (validated or non-validated). This analysis will be done for research and development purposes. Additionally MicroRNA samples will be analyzed at a secondary research facility using the PAXgene® Blood RNA System (PreAnalytiX®, a Qiagen/BD Company). Test will be done on a research and development basis only.

Exploratory Biomarkers	
	CCD2+ (T cell % and number)
	CD2+DR
	CD3+ (T cells)
	CD3+/CD4+
	CD4+ DR
	CD3+/CD8+
	CD8+DR
	CD19+ (B cells)
	MMP-9
	CD25+
	FOXP3+
	TGF-B
	IL-10
	IL-4
	IL-6

	IL-1beta
	IFN-gamma
	TNF alpha
microRNA	miRs related to cardiac remodeling/heart failure: miR-1,-23a, -26b, -27a, -133, -195, -199b, -208b, -423 and -499
	miRs related to cardiac fibrosis miR-21, -29b, and -30c
	miRs related to muscle atrophy miR-23a, -96, and -182)
	miRs related to oxidative stress/apoptosis: miR-361 and miR-1187

6 STUDY GUIDELINES

6.1 New York Heart Association (NYHA) Classification for Heart Failure Symptoms

The following description should be considered when assessing Inclusion Criteria No. 6.

Class	Description
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.
Source: American Heart Association. Retrieved on 09FEB2016 from: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp	

6.2 Canadian Cardiovascular Society (CCS) Classification for Angina

The following description should be considered when assessing Exclusion Criteria No. 4.

Classification	Description
I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation.
II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, in wind or under emotional stress, or only during the few hours after awakening. Walking more than two level blocks and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
III	Marked limitation of ordinary physical activity. Walking one or two level blocks and climbing one flight of stairs in normal conditions and at normal pace.
IV	Inability to carry out any physical activity without discomfort; angina may be present at rest.
Source: Campeau Lucien. Grading of Angina Pectoris. Circulation 1976; 54:522–3	

6.3 Concomitant Medications

6.3.1 General

Use of chronic medications or as-needed medications (e.g., TUMS®, acetominophen) will be permitted during the screening and active study period (unless otherwise restricted, refer to Section 6.3.3) and should be recorded in the source document and on the eCRF. Any changes in concomitant medication usage will be recorded in the source documents and on the eCRF. If the reason for change is related to an adverse event, the event should be recorded in the source documents and as an adverse event in the eCRF.

6.3.2 Concomitant Heart Failure Medications

Concomitant evidence-based heart failure medications are permitted by the protocol and should be maintained at stable doses (with the exception of diuretics) for at least 1 month (30 days) prior to screening and throughout the study period. Evidence-based medical therapy may include but is not limited to use of an angiotensin-converting enzyme inhibitor (ACEI), angiotensin-receptor blocker (ARB), beta blocker (BB), aldosterone receptor antagonists (or mineralocorticoid receptor antagonists) and/or hydralazine and isosorbide dinitrate.

Although heart failure medications should be maintained at stable doses, dose will be permitted if deemed medically necessary (e.g., increase risk of hypotension) by the Investigator. Any changes in concomitant medication usage and reason for dose adjustment will be recorded in the source documents and on the eCRF.

6.3.3 Medication Restrictions

- PDE5 inhibitors are known to potentiate the effects of antihypertensives. Therefore it is recommended that subjects taking PDE5 inhibitors on an as needed basis (e.g., for erectile dysfunction), refrain from taking these medications while receiving study drug, and for a period of 14 days (approximately 5 half-lives of PB1046) following the last dose.

- It is not known if fast acting nitrates taken in combination with PB1046 will cause an unsafe drop in blood pressure. Therefore, until more information is known, if it recommended that if a subject requires frequent use of as needed (PRN) nitrates (e.g., sublingual) to control angina (refer to Exclusion Criteria 4), they should not be included in the study.

6.4 Prevention of Pregnancy during the Study

6.4.1 Instructions for Female Subjects

Women who are pregnant or breastfeeding will not be allowed to participate in this study. If a female subject of childbearing potential is sexually active and has not been using an accepted method of birth control, two negative serum pregnancy tests performed approximately 15 days apart are required to check for possible early pregnancy prior to initial dosing with study drug.

Prior to administration of subsequent doses of study drug, a urine pregnancy test will be completed prior to dosing.

Due to unknown risks and potential harm to the unborn fetus, female subjects must use a reliable method of birth control while participating in this study and for 30 days after the last dose of study drug. Reliable methods of birth control include the following: abstinence (not having sex), oral contraceptives, intrauterine device, Depo-Provera, Norplant®, surgically sterile (tubal ligation, bilateral oophorectomy or hysterectomy), vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship, or careful use of condoms and a spermicidal foam or gel and/or a cervical cap or sponge.

6.4.2 Instructions for Male Subjects

Due to unknown risks and potential harm to the unborn fetus, male subjects of reproductive potential (capable of impregnating their partner) who are sexually active with a women of childbearing potential must use a reliable method of birth control while participating in this study and for 30 days after the last dose of study drug. Reliable methods of birth control include the following: abstinence (not having sex), vasectomy (with confirmed negative sperm counts), careful use of condoms and a spermicidal foam or gel and/or a cervical cap or sponge. For the female partner, oral contraceptives, intrauterine device, Depo-Provera, Norplant or be surgically sterile (tubal ligation, bilateral oophorectomy or hysterectomy).

6.5 Diet and Exercise

Study subjects should maintain their usual caloric intake and exercise regimen during study participation.

6.6 Self-Monitored Blood Pressure (SBMP)

Study subjects will be provided with a diary (refer to Appendix D) and will be asked to monitor their blood pressure (set to automatically measure in triplicate, 1 minute apart and will report the mean value) twice daily (morning and evening) starting approximately 1 week prior to randomization through 1 week following the last dose of study drug. An automated blood pressure cuff (Omron Blood Pressure Monitor with ComFit™ Cuff (Model BP785N) as shown in Figure 6 will be provided to subjects as needed for this assessment. Study personnel will provide training (and document in the source documents) to subjects on the use of the blood pressure monitoring unit. The subject should bring the monitor and diary with them to each study visit.

Figure 6 Omron ComFit™ Blood Pressure Cuff Model BP785N

7 STUDY VISITS

The procedures and assessments to be performed at each visit are indicated in the Schedule of Activities. An estimated time for the conduct of each visit is provided as a guide only to the study site personnel and study subject for planning purposes. Note: it will not be considered a departure from the protocol if the visit length is shorter or longer than anticipated.

7.1 Screening (Visit 1)

The screening visit can occur up to 60 days prior to randomization. It is estimated that this visit will take approximately 4 hours to complete.

- Informed Consent Process
    - **The subject must provide written informed consent** PRIOR to any study procedures being done.
    - Once signed, proceed with the following study procedures in the recommended sequence:
- Subject Interview
    - Review and record prior medications (those taken within the last 3 months (90 days)) and current concomitant medications;
    - Review and record prior histories; medical, targeted cardiac history; surgical and social history (smoking, dietary restrictions/habits and alcohol consumption)
    - Record demographic information; and
    - Evaluate inclusion/exclusion criteria against responses obtained during the subject interview.
- Assessments
    - Measure and record height and weight and calculate BMI and BSA;
    - 12 lead ECG (in triplicate 1 minute apart). ECG will be electronically transmitted to BioTelemetry, the ECG core laboratory;
    - Obtain and record vital sign measurements:
        - Temperature (oral or oral equivalent) and respiratory rate
        - Orthostatic - BP and heart rate
        - Seated - BP and heart rate in triplicate (1 minute apart); and

- Perform a complete physical examination and record results.

- Sample Collection

  - Collect urine sample for local testing:

    - Alcohol and drug testing using CLIA waived testing supplies provided by Medpace Reference Laboratory.

    - Retain remaining urine sample for urinalysis that will be shipped to, and analyzed by, Medpace Reference Laboratory.

  - Obtain Medpace Reference Laboratory requisition booklet matched to Subject ID and collect the following samples:

    - Pregnancy testing (serum) for female subjects of childbearing potential.

    - If female is reported to be postmenopausal and is between the ages of 45 and 60, they may be required to have an FSH level to confirm postmenopausal status unless they have other documented criteria to verify that they are not of childbearing potential.

    - Collect blood samples for the following testing: serology panel for HIV, HepB, HepC; safety laboratory assessments (hematology, chemistry). If the subject is fasting, a fasting lipid profile and fasting plasma glucose will be analyzed. If the subject is not fasting, this should be noted on the laboratory requisition form and these tests will not be done at this visit (not required for confirmation of study eligibility) but will be done at baseline (Visit 2, 7 days prior to scheduled randomization). All samples will be shipped to and analyzed by Medpace Reference Laboratory.

- Schedule 2-D Echocardiogram

  - If the subject has had a 2-D echocardiogram within the last 60 days that confirms the subject has an ejection fraction (EF) ≤40%, this will be sufficient for confirmation of study eligibility for initial screening. However, the subject must be scheduled for their baseline evaluation 7-14 days before scheduled randomization for final confirmation of qualifying EF by BioTelemetry (core laboratory)

  - If no recent 2-D echocardiogram is available, schedule screening test.

- Instructions to Subject

  - Inform the subject that they will be notified (within about 2 weeks) whether or not they qualify for the study participation.

7.2 Run In Period (Visit 2, Day -10 to Day -7)

Subjects who qualify for the study will meet all entry criteria at Visit 1 will be scheduled to return for Visit 2.

7.2.1 Scheduling the Visit and Baseline Echocardiogram

- Visit 2 can occur as early as 10 days before dosing but should be done at least 7 days prior to randomization/first dose. This visit should take approximately 1.5 hours.
- The 2D echocardiogram may be done up to 14 days prior to randomization.
- Inform the subject that they will need to fast for a minimum of 8 hours (no food or drink except water) prior to the study visit.

7.2.2 Visit 2

- Subject Interview
    - Confirm that the subject has had/is schedule for their baseline 2-D echocardiogram completed. When echocardiogram complete, send electronically sent to BioTelemetry, the Echo core laboratory;
    - Review concomitant medications and record;
    - Review changes in the subject's health (pre-treatment adverse events) since the last visit; and
    - Evaluate inclusion/exclusion criteria (to ensure the subject still qualifies for participation).
- Sample Collection
    - Collect urine sample for local testing:
        - Pregnancy testing for female subjects of childbearing potential using the CLIA waiver testing supplies provided by Medpace Reference Laboratory;
        - Alcohol and drug testing using CLIA waived testing supplies provided by Medpace Reference Laboratory; and
        - Retain remaining urine sample for urinalysis that will be shipped to, and analyzed by, Medpace Reference Laboratory.
    - Obtain Medpace Reference Laboratory requisition booklet matched to Subject ID and collect the following samples:

- Blood samples for safety laboratory assessments; hematology, chemistry, fasting lipid profile and fasting plasma glucose.
- All samples will be shipped to and analyzed by Medpace Reference Laboratory.

- Mobile Telemetry
  - Set up mobile telemetry and instruct subject on its use, marking "events", and how to change electrodes; and
  - Ensure that the data is capturing prior to subject leaving the study site.
- Self-monitored Blood Pressure (SMBP) Training
  - Instruct subject on the use of the Omron ComFit™ Blood Pressure Cuff Model BP785N; and
  - Review blood pressure measuring requirements (morning and evening using the SAME arm) and completion of diary.
- Instructions to Subject
  - Schedule Visit 3 and discharge from study site.
  - Remind subject to bring Omron blood pressure cuff and diary to next visit.

7.3 Visit 3 (Day 0)

Subjects should be scheduled to return to the study in the morning, at around 07:30. This time is suggested as subsequent visits will need to occur ± 2 hours from dosing at this visit and to allow dosing to occur by 10:00. This visit should take approximately 7.5 hours (about 1.5 hours for pre-dose assessments and dosing, and 6 hours after dosing for blood sample collection).

- Pre-dose Subject Interview
  - Review concomitant medications and record;
  - Review changes in the subject's health (pre-treatment adverse events) since the last visit; and
  - Evaluate self-monitored blood pressure diary; and
  - Evaluate inclusion/exclusion criteria (to ensure the subject still qualifies for participation.

- Pre-dose Assessments

    - Measure and record weight (needed for calculation of study drug dose);

    - Reset mobility telemetry for 30 day monitoring interval and ensure it is functioning and recording properly;

    - 12 lead ECG (in triplicate 1 minute apart). ECG will be electronically transmitted to BioTelemetry, the ECG core laboratory. Refer to protocol Section 5.10.3 regarding verification of qualifying ECG (QTcF) by Investigator;

    - Obtain and record vital sign measurements (using subject's Omron blood pressure cuff. If not available use another Omron cuff and note in source documents):

        - Temperature (oral or oral equivalent) and respiratory rate

        - Orthostatic - BP and heart rate

        - Seated - BP and heart rate in triplicate (1 minute apart); and

    - Perform an abbreviated physical exam (at minimum to include general appearance, lungs, heart, lower extremities, and abdomen) and record results.

- Pre-dose Sample Collection

    - Collect urine sample for local testing:

        - Pregnancy testing for female subjects of childbearing potential using the CLIA waiver testing supplies provided by Medpace Reference Laboratory.

        - Alcohol and drug testing using CLIA waived testing supplies provided by Medpace Reference Laboratory.

    - Obtain Medpace Reference Laboratory requisition booklet matched to Subject ID and collect the following samples:

        - Blood samples for pharmacokinetics, immunogenicity, exploratory biomarkers, NT-Pro-BNP and hs-cTnT.

        - Samples will be shipped to Medpace Reference Laboratory and PhaseBio Pharmaceuticals Inc. as directed per the laboratory procedure manual.

- Randomization

    - The Study Coordinator or designee will complete the Randomization Module and update status to Randomized in the eCRF system. The information to be entered, Study Part, subject weight, Cohort and dose level (Cohort 1 will be dosed at 0.2 mg/kg. and subsequent dosing for cohorts will be assigned after each SRC meeting).

    - Once completed, the Unblinded Study Drug Dispenser (USDD) will view the Randomization Module and treatment allocation (active or placebo) for the subject via the eCRF page (a central randomization system). Only the USDD has read access to the treatment allocation via the eCRF. A subject will be assigned, in the order randomized into the study, the next corresponding treatment assignment per the randomization schedule generated by the study statistician.

    - The study drug will be prepared in accordance with the procedures outlined in Protocol Section 8.5. and as further described in the study specific pharmacy procedure manual.

- Dosing

    - A subject will be dosed by a member of the study team in accordance with protocol Section 8.5.2.

    - Document the date and time of dosing and location of dosing (quadrant on the abdomen). It is suggested that dosing site be rotated in a clockwise fashion (e.g., first dose RUQ, second dose will be in the LUQ, etc.).

- Post Dose Assessments

    - Obtain and record vital sign measurements at 1 and 6 hours (± 15 minutes) post dose using subject's Omron blood pressure cuff:

        - Temperature (oral or oral equivalent) and respiratory rate

        - Seated - BP and heart rate in triplicate (1 minute apart)

    - Assess injection site at 1 and 6 hours (± 15 minutes) post dose.

- Post-dose Sample Collection

    - Obtain Medpace Reference Laboratory requisition booklet matched to Subject ID and collect the following samples:

        - Pharmacokinetic sample at 1, 3 and 6 hours (± 1 hour) post dose.

        - All samples will be shipped to Medpace Reference Laboratory.

- Subject Instructions

    - Subject will be instructed to return to the study unit on Day 1 (24 hours), Day 2 (48 hours), Day 3 (72 hours) ± 1 hour after the dosing (injection) time and Day 5 (120 hours) ± 2 hours after the dosing time. The subject does not need to be fasting for these visits.

    - Subject should bring with them their diary and blood pressure cuff at each visit.

- Telephone Contact

    - Subject will be contacted by the Investigator or designee in the evening (between approximately 7:00 and 10:00 PM) to check on the status of the study subject. Contacts will be recorded in the source documents.

7.4 Visit 4 through 7 (Days 1, 2, 3 and 5)

Each visit should take approximately 1 hour.

- Subject Interview – at each visit

    - Review concomitant medications and record;

    - Review changes in the subject's health (adverse events) since the last visit; and

    - Evaluate self-monitored blood pressure diary.

- Assessments – at each visit unless otherwise noted

    - Ensure telemetry it is functioning and recording properly;

    - Assess injection site (± 2 hours) post the time of day of the last dose;

    - 12 lead ECG (in triplicate 1 minute apart) at 24 (Day 1), 48 (Day 2) and 72 (Day 3) hours (± 1 hour) post the time of day of the last dose. Note: should be done within 30 minutes of collection of PK sample at each time point;

    - Obtain (± 2 hours) post the time of day of the last dose and record vital sign measurements using subject's Omron blood pressure cuff. (If not available, use another Omron cuff and note in source document):

        - Temperature (oral or oral equivalent) and respiratory rate

        - Orthostatic - BP and heart rate

        - Seated - BP and heart rate in triplicate (1 minute apart)

- Directed physical examination – done only as needed to evaluate adverse events. Record results.

- Sample Collection – at each visit unless otherwise noted

  - Obtain Medpace Reference Laboratory requisition booklet matched to Subject ID and collect the following samples:

    - Pharmacokinetics, NT-Pro BNP, hs-cTnT and exploratory biomarkers, at 24 (Day 1), 48 (Day 2) and 72 (Day 3) hours (± 1 hour) post the time of day of the last dose and prior to but within 30 minutes of collection of the 12 lead ECG.

    - Pharmacokinetics at Day 5 (± 2 hours) after the last dose.

    - Samples will be shipped to Medpace Reference Laboratory and PhaseBio Pharmaceuticals Inc. as directed.

- Subject Instructions

  - Subject will be instructed to return to the study unit on Day 7, 14 and 21 for dosing; and

  - Subject should bring with them their diary and blood pressure cuff at each visit.

7.5 Visit 8 (Day 7), Visit 9 (Day 14) and Visit 10 (Day 21)

It is estimated that each visit should take approximately 1.5 hours to complete.

- Pre-dose Subject Interview – at each visit

  - Review concomitant medications and record;

  - Review changes in the subject's health (adverse events) since the last visit; and

  - Evaluate self-monitored blood pressure diary.

- Pre-dose Assessments – at each visit

  - Measure and record weight (Note: if weight increase or decreases greater than 10% from Day 0, contact the Sponsor prior to dosing);

  - Ensure telemetry is functioning and recording properly;

  - Assess injection site (± 2 hours) post the time of day of the last dose;

  - 12 lead ECG (in triplicate 1 minute apart). ECG will be electronically transmitted to BioTelemetry, the ECG core laboratory;

- Obtain and record vital sign measurements using subject's Omron blood pressure cuff. (If not available, use another Omron cuff and note in source document):
  - Temperature (oral or oral equivalent) and respiratory rate
  - Orthostatic - BP and heart rate
  - Seated - BP and heart rate in triplicate (1 minute apart)
- Directed physical examination – done only as needed to evaluate adverse events. Record results.

- Pre-dose Sample Collection – at each visit
  - Collect urine sample for local testing:
    - Pregnancy testing for female subjects of childbearing potential using the CLIA waiver testing supplies provided by Medpace Reference Laboratory.
    - Alcohol and drug testing using CLIA waived testing supplies provided by Medpace Reference Laboratory.
    - Retain remaining urine sample for urinalysis that will be shipped to, and analyzed by, Medpace Reference Laboratory.
  - Obtain Medpace Reference Laboratory requisition booklet matched to Subject ID and collect the following samples:
    - Blood samples for safety laboratory assessments; hematology, and chemistry;
    - Blood samples for pharmacokinetics, immunogenicity, exploratory biomarkers, NT-Pro-BNP and hs-cTnT.
    - Samples will be shipped to Medpace Reference Laboratory and to PhaseBio Pharmaceuticals Inc. as directed.

- Dosing at each visit
  - A subject will be dosed by a member of the study team ± 2 hours from time of the previous weekly dose in accordance with protocol Section 8.5.2.
  - Document the date and time of dosing and location of dosing (quadrant on the abdomen). It is suggested that dosing site be rotated in a clockwise fashion (e.g., first dose RUQ, second dose will be in the LUQ, etc.).

- Post-dose Sample Collection - Day 21 only

- Obtain Medpace Reference Laboratory requisition booklet matched to Subject ID and collect the following samples:
    - Blood sample for pharmacokinetics at 1, 3 and 6 hours (± 10 minutes) post dose.
    - Samples will be shipped to Medpace Reference Laboratory and PhaseBio Pharmaceuticals Inc. as directed.

- Subject Instructions
    - Subject will be instructed to return to the study for Visits 11 through 14 (Days 22, 23, 24 and 26).
    - Subject should bring with them their diary and blood pressure cuff at each visit.

- Telephone Contact
    - Subject will be contacted by the Investigator or designee in the evening (between approximately 7:00 and 10:00 PM) of each dosing day check on the status of the study subject. Contacts will be recorded in the source documents.

7.6 Visit 11 through 14 (Days 22, 23, 24 and 26)

It is estimated that each visit should take approximately 1.5 hours to complete.

- Schedule 2-D Echocardiogram – Day 24 ± 1 day
    - Ensure examination complete.
    - Echo will be electronically sent to BioTelemetry, the Echo core laboratory.

- Subject Interview – at each visit
    - Review concomitant medications and record;
    - Review changes in the subject's health (adverse events) since the last visit; and
    - Evaluate self-monitored blood pressure diary.

- Assessments – at each visit unless otherwise noted
    - Ensure telemetry it is functioning and recording properly;
    - Assess injection site (± 2 hours) post the time of day of the last weekly dose;
    - 12 lead ECG (in triplicate 1 minute apart) at 24 (Day 22), 48 (Day 23) and 72 (Day 24) hours (± 1 hour) after the time of the last weekly dose and at 120 hours

(Day 26) ± 2 hours after the last dose. ECG will be electronically transmitted to BioTelemetry, the ECG core laboratory. ECG should be done within 30 minutes of collection of the PK sample;

- Obtain (± 2 hours from the time of the last weekly dose) and record vital sign measurements (using subject's Omron blood pressure cuff. If not available use another Omron cuff and note in source document):
  - Temperature (oral or oral equivalent) and respiratory rate
  - Orthostatic - BP and heart rate
  - Seated - BP and heart rate in triplicate (1 minute apart)
- Directed physical examination – done only as needed to evaluate adverse events. Record results.

- Sample Collection – at each visit unless otherwise noted
  - Obtain Medpace Reference Laboratory test booklet matched to Subject ID and collect the following samples:
    - Pharmacokinetics at 24 (Day 22), 48 (Day 23) and 72 (Day 24) hours (± 1 hour) post dose and prior to but within 30 minutes of collection of the 12 lead ECG.
    - Pharmacokinetics at Day 26 (± 2 hours) for time of dosing.
    - On Day 24 ± 1 day only, Biomarkers, NT-pro BNP and hs-cTnT should be done on the same day as the 2-D echocardiogram due.
    - Samples will be shipped to Medpace Reference Laboratory and PhaseBio Pharmaceuticals Inc. as directed.

- Subject Instructions
  - Subject should be reminded to fast (no food or drink except water) for a minimum of 8 hours prior to Day 28 visit.
  - Subject should bring with them their diary and blood pressure cuff at each visit.

7.7 Visit 15 through 18 (Days 28, 29, 30 and 31)

It is estimated that each visit should take approximately 1.5 hours to complete.

- Subject Interview – at each visit
  - Review changes in the subject's health (adverse events) since the last visit;

- Review concomitant medications; and
- Evaluate self-monitored blood pressure diary.

- Assessments – at each visit unless otherwise noted
  - Remove telemetry on Day 28;
  - Assess injection site (± 2 hours) post the time of day of the last weekly dose;
  - 12 lead ECG (in triplicate 1 minute apart) on Day 28 (± 1 hour) after the time of the last weekly dose. ECG will be electronically transmitted to BioTelemetry, the ECG core laboratory. Should be done within 30 minutes of collection of the PK sample;
  - Obtain (± 2 hours from the time of the last weekly dose) and record vital sign measurements (using subject's Omron blood pressure cuff. If not available use another Omron cuff and note in source document):
    - Temperature (oral or oral equivalent) and respiratory rate
    - Orthostatic - BP and heart rate
    - Seated - BP and heart rate in triplicate (1 minute apart)
  - Directed physical examination – done only as needed to evaluate adverse events. Record results.

- Sample Collection – at each visit unless otherwise noted
  - Obtain Medpace Reference Laboratory requisition booklet matched to Subject ID and collect the following samples:
    - Pharmacokinetics, ± 2 hours from the time of day of the last dose. Sample collection on day 28 only should be within 30 minutes of collection of the 12 lead ECG.
    - Collect urine sample for urinalysis that will be shipped to, and analyzed by, Medpace Reference Laboratory on Day 28 only.
    - Blood samples for immunogenicity, safety laboratory assessments; hematology, chemistry, fasting lipid profile and fasting plasma, exploratory biomarkers, NT-Pro-BNP and hs-cTnT on Day 28 only.
    - All samples will be shipped to Medpace Reference Laboratory and PhaseBio Pharmaceuticals Inc. as directed.

- Subject Instructions

- Remind subject to bring with them their diary and blood pressure cuff at each visit.
- Instruct subject to discontinue monitoring blood pressure at home on Day 31.
- Inform the subject that they will need to fast for a minimum of 8 hours (no food or drink except water) prior to the study visit.

7.8 Visit 19 (Day 49 +/- 3 days) or Early Termination [ET]

It is estimated that this visit should take approximately 2 hours.

- Subject Interview
  - Review concomitant medications and record;
  - Review changes in the subject's health (adverse events) since the last visit.
- Assessments
  - Measure and record weight;
  - Assess injection site and record findings;
  - 12 lead ECG (in triplicate 1 minute apart). ECG will be electronically transmitted to BioTelemetry, the ECG core laboratory;
  - Obtain and record vital sign measurements using subject's Omron blood pressure cuff. (If not available use another Omron cuff and note in source document.):
    - Temperature (oral or oral equivalent) and respiratory rate
    - Orthostatic - BP and heart rate
    - Seated - BP and heart rate in triplicate (1 minute apart)
  - Physical examination - complete
- Sample Collection
  - Obtain Medpace Reference Laboratory test requisition booklet matched to Subject ID and collect the following samples:
    - Blood samples for immunogenicity, safety laboratory assessments; hematology, chemistry, fasting lipid profile and fasting plasma, exploratory biomarkers, NT-Pro-BNP and hs-cTnT.

- Samples will be shipped to Medpace Reference Laboratory and PhaseBio Pharmaceuticals Inc. as directed.

7.9 Visit 20 (Day 77 +/- 3 days)

7.9.1 Final Immunogenicity Visit

It is estimated that this visit will take approximately 15 minutes.

- Sample Collection

  - Obtain Medpace Reference Laboratory test booklet matched to Subject ID and collect immunogenicity lab sample.

  - Remind subject that they will be required to return for additional immunogenicity sampling if the sample collected at this visit is positive for antibody development.

7.10 Unscheduled Visit(s)

In the event that additional immunogenicity testing is required, the subject may be asked to return for additional visits. This may also be the case to follow up on open adverse events or to follow clinical significant abnormal laboratory results.

7.11 Unscheduled Procedures

It may be necessary to collect additional 12 lead ECGs as directed by the pharmacokinetic data and as recommend by the SRC. Other unscheduled procedures may be performed as clinically indicated for evaluation of subject safety.

7.12 Subject Withdrawal and Early Termination (ET)

7.12.1 General

Subjects may withdraw from treatment or from the study at any time at their own request or they may be withdrawn at any time at the discretion of the Investigator or Sponsor for safety, behavioral, or administrative reasons. For safety reasons, a subject will also be discontinued from the study treatment if they test positive for alcohol or illicit drugs (tested prior to each dose) during the study. However these subjects will continue to be followed per the protocol.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document subject outcome, if possible. The Investigator should inquire about the reason for withdrawal and request that the subject return for the ET (complete procedures at final safety visit) and follow up with the subject regarding any unresolved adverse events.

7.12.2 Discontinuation from Treatment

If a subject experiences an adverse event and the Investigator determines that the subject should be discontinued from study treatment, subjects should continue to be followed in the study as per the protocol.

7.12.3 Discontinuation from the Study

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

8 STUDY TREATMENT

8.1 Method for Assigning Treatment/Randomization

A central randomization code for each cohort in the study is generated by the study statistician in a ratio of 3 active to 1 placebo and is uploaded into the secured eCRF randomization module. The assigned treatment (active or placebo), can only be viewed within the eCRF system by the USDD. A subject will be assigned, in the order randomized into the study to the next corresponding treatment assignment per the randomization schedule.

8.1.1 Study Coordinator (or designee)

At Visit 3 (Day 0), the Study Coordinator or designee will complete the Randomization Module and update status to Randomized in the eCRF system. The information to be entered, Study Part, subject weight, Cohort and dose level (Cohort 1 will be dosed at 0.2 mg/kg. and subsequent dosing for cohorts will be assigned after each SRC meeting).

8.1.2 Unblinded Study Drug Dispenser (USDD)

Once completed, the Unblinded Study Drug Dispenser (USDD) will view the Randomization Module and Dosing and Treatment Allocation (active or placebo) for the subject via the eCRF page. The Dosing module will provide an auto-calculated dosing volume based on the assigned dose, subject weight (entered by the Study Coordinator or designee) and the study drug concentration (PB1046 at 40 mg/mL). Additional detailed instructions on access and the randomization procedure are provided in the pharmacy procedure manual.

8.2 Drug Supplies

8.3 Formulation, Packaging and Labelling of Vasomera (PB1046) Injection

Vasomera™ (PB1046) Injection
0.5 mL (40 mg/mL)
Lot No.: 1-FIN-1047 Mfg. Date: 04Mar11
Recommended Storage at ≤ -70°C
(Short Term Excursions Permitted. Refer to COA)
Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use
Manufactured for PhaseBio Pharmaceuticals, Inc by
Althea Technologies, Inc.
11040 Roselle St., San Diego, CA 92121

Investigational Drug Product for Use Only with Protocol <insert>

This box contains ____ single use vials of
Vasomera (PB1046) Injection 0.5 mL (40 mg/mL)

Refer to above referenced protocol for detailed dosing instructions
Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use

Lot No. 1-FIN-1047 Mfg. Date: 04Mar11
Recommended Storage at ≤ -70°C (Short Term Excursions Permitted. Refer to COA)
Manufactured for PhaseBio Pharmaceuticals Inc. by
Althea Technologies, Inc.
11040 Roselle St., San Diego, CA 92121

8.3.1 Formulation and Packaging of Placebo

Sterile 0.9% sodium chloride (NaCl) USP for Injection will provided by the Sponsor to the study site and will be stored in accordance with the manufacturer's labeled recommendations. A manufacturer's COA will be provided and will be kept in the study file.

8.4 Study Drug Storage

Vials will be stored long term at ≤ -70°C and, if necessary, may be stored frozen (-10 to -30°C) or refrigerated (2 to 8°C) at the clinical research site based on stability data and Certificate of Analysis (COA). The study drug must be stored in a secure locked area under the responsibility of the Principal Investigator or designee. All unused study drug will be returned to PhaseBio Pharmaceuticals Inc.

8.5 Preparation and Dispensing

Since the active study drug is supplied as open labeled bulk vials and placebo may not be identical in appearance, randomization, preparation of syringes, and blinding will be performed by an Investigator-designated USDD (see Appendix C) who is not otherwise involved in the assessment of study subjects. As an additional precaution to maintain the study blind, study drug will be administered by a qualified care giver who will not perform any study assessments.

8.5.1 Dose Preparation

1. The study drug (PB1046) is provided at a concentration of 40 mg/mL with each vial containing 0.5 mL (20 mg per vial). Calculate the total dose (mg) for administration

based on weight and assigned Cohort/dose level (calculated in the eCRF) and retrieve the appropriate number of vials from storage.

2. Remove the vial(s) from the freezer/refrigerator. Note: If stored frozen, allow to thaw at room temperature for approximately 15-30 minutes. Invert, tap and swirl the vials to ensure that the material is free flowing and homogeneous.

3. The mixed solution should be clear and essentially free from particulate matter.

4. The USSD will immediately draw up the study drug (Vasomera or equal volume of placebo) in either a 0.5 or 1.0 mL polypropylene syringe(s) with a 28 gauge 1/2 inch needle. Note: If the total volume to be delivered is >1mL, the volume should be split evenly between syringes.

5. The barrel of the syringe(s) will be wrapped with a clear yellow covering and will also be labeled with the study number, subject ID, subject initials and date and time of dose preparation. Labeling should be placed so as not to obscure verification of the injection volume.

6. Study drug will be administered at room temperature. Note: From the time the vials are removed from storage to the time of administration should not be less than 30 minutes but should not be more than 4 hours. The time the vial(s) are removed from storage and the time the drug is prepared should be recorded on the inventory log.

8.5.2 Administration

Dosing should occur in the morning between approximately 8:00 and 10:00. The subject does not need to be fasting prior to injection. The study drug (PB1046 [Vasomera] or equal volume of placebo) will be injected into the subcutaneous layer of the abdomen. Do not inject in an area where tissue is compromised (i.e., scarring, tattoos, broken or irritated skin). If more than one injection is required to deliver the complete dose, injections should be given in close proximity (approximately 2 inches) in one quadrant (refer to Figure 7). It is suggested that the dosing site be rotated in a clockwise fashion (e.g., first dose RUQ, second dose will be in the LUQ, etc.). The location of injection(s) must be recorded in the source document records in order to perform accurate injection site assessments.

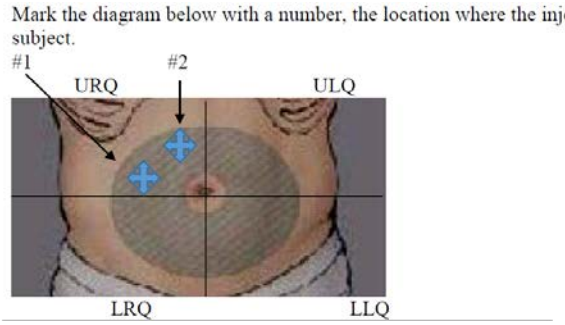


Figure 7 Documenting Location of Injection Sites

8.6 Restricted Use of Cold or Heat Applications to Site of Injection

PB1046 is comprised of VIP fused to an elastin-like polypeptide (ELP) biopolymer to extend the half-life and slow the rate of absorption. Direct application of a heat or cold source to the site of injection may alter the rate of absorption. Therefore, use of cold or heat applied at the site of injection is prohibited.

8.7 Compliance

Study drug will be administered to the subject in the study unit.

8.8 Study Drug Accountability

Study drug will be received, dispensed and returned to the Sponsor (unused study drug at the end of the study) by the USDD designated by the Principal Investigator and will be accounted for by the study drug dispenser on a study drug inventory/accountability log and will include:

- Subject ID and initials and randomization ID
- Date/time vials removed from storage
- Amount dispensed for injection
- Date/time dose prepared
- Amount remaining in inventory

Inventory records will not be reviewed by the study monitor during routine monitoring visits in order to maintain blinding.

8.9 Blinding

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

Active study drug and placebo are supplied as open labelled vials and the content of these vials may not be identical in appearance. Randomization, preparation of syringes and blinding will be done by an Investigator designated unblinded study drug dispenser (USDD) who is otherwise not involved in the assessment of study subjects. As an added precaution, in order to maintain the blind, study drug will be administered by a qualified caregiver who will not perform study assessments. This may also be the USDD.

Once the USDD has prepared the study drug to be administered using syringes, the barrel of the syringe will be wrapped in a clear yellow covering in order to maintain the blind to any staff member who may view the syringe.

For safety studies requiring decision on dose escalation, the blind will be broken after each dose cohort to evaluate safety, PK and PD, by the study statistician. Decisions regarding dose escalation by the Safety Review Committee (SRC) will be done on a blinded basis.

The study blind will be broken on completion of the clinical study and after the study database has been locked. After database lock, a request may be submitted to the Sponsor to receive study treatment assignment for a subject.

8.10 Breaking the Study Blind

During the study, the blind may be broken only in emergencies when knowledge of the subject's treatment group is necessary for further medical management. When possible, the Investigator should discuss the emergency with the Medical Monitor prior to unblinding.

In case of an emergency that requires unblinding of study drug assignment, the USDD will unblind the subject's treatment assignment to the Investigator (Principal or his/her designee) and the Medical Monitor using the Sponsor provided Protocol Inquiry Form (PIF), to document the reason for unblinding. A copy of the PIF will be maintained with the dispensing and inventory records until the completion of the study.

8.11 Replacement of Subjects

Subjects who withdraw from the study and who do not have adequate collection of safety and pharmacokinetic samples for evaluation of decisions regarding dose escalation may be replaced at the discretion of the Sponsor.

9 PROTOCOL VIOLATIONS

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

- Failure to meet inclusion/exclusion criteria
- Dosing error

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a subject or if data analysis will be censored.

When a protocol violation occurs, it will be discussed with the Investigator and a Protocol Inquiry Form (PIF) detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

10 ADVERSE EVENTS

10.1 Adverse Events

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

For all adverse events, the Investigator (Principal Investigator or Sub-Investigator) must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to PhaseBio Pharmaceuticals, Inc. For all adverse events, sufficient information should be obtained by the Investigator to determine the causality of the adverse event. The Investigator (Principal or physician Sub-Investigator) is required to assess causality. For adverse events with a causal relationship to the study drug, follow-up by the Investigator (Principal or physician Sub-Investigator) is required until the event or its sequelae resolve or stabilize at a level acceptable to the Investigator (Principal or physician Sub-Investigator) and PhaseBio's Medical Monitor concurs with that assessment.

10.2 Reporting Period

Serious adverse events require immediate notification to PhaseBio Pharmaceuticals, Inc. beginning from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving study drug (investigational product), through and including 28 calendar days after the last dose of study drug. Any serious adverse event occurring any time within the reporting period must be promptly reported if a causal relationship to investigational product is suspected.

- Adverse events (serious and non-serious) should be recorded on the eCRF from the time the subject has signed informed consent through last subject safety visit, unless otherwise specified.

- Any changes in the subject's baseline status between enrollment (signing informed consent) up to the time of study drug administration will be recorded as a pre-treatment adverse event and severity will be assessed.

10.3 Definition of an Adverse Event

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

- Clinically significant abnormal test findings;

- Clinically significant signs and symptoms;

- Clinically relevant changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of an underlying disease.

10.4 Assessment of Severity

- Mild – An event that is usually transient in nature and generally not interfering with normal activities.
- Moderate – An event that is sufficiently discomforting to interfere with normal activities.
- Severe – An event that is incapacitating with inability to work or do usual activity or inability to work or perform normal daily activity.

10.5 Assessment of Toxicity

If applicable, adverse events (also refer to Appendix A, Adverse Events of Special Interest for criteria and grading) should be graded according to the following grade scale:

Grade 1 – Mild

Grade 2 – Moderate

Grade 3 – Severe

Grade 4 – Life threatening or disabling

10.6 Causality Assessment

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

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

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

The following factors should also be considered:

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

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

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

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

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

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

10.6.1 Suspected Adverse Reaction

An adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of Investigational New Drug safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

10.7 Unexpected Adverse Events

An adverse event or suspected adverse reactions is considered "unexpected" if it is not listed in the investigator brochure (IB) or it is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. Unexpected, as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the IB as occurring with a class of drug or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

10.8 Serious Adverse Event Definition

An adverse event or suspected adverse event reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death;

- A life-threatening adverse event;

- NOTE: An adverse event or suspected adverse event is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at

immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.

- Requires hospitalization or prolongation of existing hospitalizations;

  NOTE: Any hospital admission will be considered an inpatient hospitalization, regardless of duration. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness.

  Admission to the hospital for a pre-planned procedure or social or situational reasons (i.e., no place to stay, lives too far away to come for hospital visits) will not be considered inpatient hospitalizations.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;

- A congenital anomaly/birth defect; or

- Other important medical event (event that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above).

  NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE 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 above. 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 hospitalizations, or the development of drug dependency.

10.9 Reporting

Each adverse event is to be assessed to determine if it meets the criteria for serious adverse event. If a serious adverse event occurs, expedited reporting will follow local and international regulations, as appropriate.

All adverse events will be reported on the adverse event page(s) of the CRF. It should be noted that the form for collection of serious adverse event information is not the same as the adverse event CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse event information.

10.9.1 Serious Adverse Event Reporting Requirements

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

Medical Monitor		**Sponsor Safety Coordinator**	
Poul Strange, MD, PhD		Lauren Richardson	
Office Tel	609-897-0505 Ext. 113	Office Tel	610-981-6507
SAE/Study Fax:	1-484-971-5974	SAE/Study Fax	1-484-971-5974
Cellular	609-897-0505 Ext. 113	SAE (24h/7d)	610-981-6507/ 610-608-8619

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

For all serious adverse events, the Investigator is obligated to pursue and provide information to PhaseBio Pharmaceuticals, Inc. in accordance with the timeframes for reporting specified above. In addition, an Investigator may be requested by PhaseBio Pharmaceuticals, Inc. to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to PhaseBio Pharmaceuticals, Inc. or its designated representative. The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment) or the subject dies. Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form and submit to PhaseBio.

10.9.2 Non-Serious Adverse Event Reporting Requirements and Ongoing Safety Review

Non-serious adverse events are to be reported in the CRF which will be reviewed by PhaseBio Pharmaceuticals, Inc. Medical Monitor on an ongoing basis.

10.10 Pregnancy Reporting

If the subject or partner of a subject participating in the study becomes pregnant during the study or within 28 days of discontinuing study medication, the Investigator should report the pregnancy to the Sponsor, or its representative, within 24 hours of being notified. The Exposure In Utero form must be completed by the site.

The subject or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify the Sponsor. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting an SAE. Otherwise, a follow up Exposure in Utero form should be completed.

11 DATA ANALYSIS AND STATISTICAL METHODS

11.1 Sample Size Determination

The sample size is not driven by inferential statistics. The sample size of four (4) (3 active and 1 placebo) for cohort 1 and eight (8) (6 active and 2 placebo) for subsequent cohorts for the 4 week multiple dose escalation study is set for qualitative investigation of toxicity as well as pharmacokinetics and to explore the potential of a pharmacodynamic response.

11.2 Analysis Populations

Three subject populations will be defined. The Safety and Intent-to-Treat (ITT) population will be the same and defined as all subjects who receive at least one dose of the study drug. The Per-Protocol (PP) population will be a subset of the ITT population excluding subjects who have any major violation of protocol. The pharmacokinetic analysis population will consist of all subjects that receive active study drug and have sufficient data for pharmacokinetic analysis.

11.3 Statistical Analysis

11.3.1 Safety

Safety will be evaluated by analyses of the incidence and severity of AEs and their relationship to study drug. Changes from baseline vital signs, 12 lead ECG, ECG telemetry (e.g., average heart rate, rhythm abnormalities), and safety laboratory parameters will be presented descriptively by dose and pooled placebo.

Additional analysis specific to 12 lead ECG, will include an analyses of central tendency (effect of PB1046 on the QT/QTc interval and analysis of changes occurring around the Cmax) and categorical analyses of QT/QTc interval (e.g., absolute QT/QTc intervals > 500 msec or changes from baseline; increases from baseline > 30 and > 60).

11.3.2 Pharmacokinetic and Pharmacokinetic Analyses

Actual blood sampling times will be used in all pharmacokinetic analyses. Per protocol times will be used to calculate mean serum concentrations for tabular and graphical displays. All non-compartmental pharmacokinetic calculations and generation of individual subject serum concentration vs. time graphs will be done using SAS® for Windows® Version 9.4 under Windows 8.1. Graphs of mean serum concentrations vs. time and other in-text figures will be prepared using SigmaPlot for Windows Version 12.5. Compartmental modeling will be done using Phoenix WinNonlin 6.4 or higher. Exploratory pharmacokinetic/pharmacodynamics analyses will be done using appropriate software.

11.3.2.1 Pharmacokinetic Parameters — Non-Compartmental Analysis

Pharmacokinetic parameters for PB1046 will be calculated using non-compartmental analysis. Only serum concentrations equal to or greater than the validated lower limit of the assay (LOQ)

will be used in the pharmacokinetic analysis. Serum concentrations <LOQ will be taken as 0 for the calculation of the descriptive statistics for serum concentrations at each sampling time. For the pharmacokinetic analysis, serum concentrations < LOQ that occur from pre-dose to the first concentration ≥ LOQ will be taken as 0 and those that occur thereafter will be taken as missing.

- First Dose

C_{max} and T_{max} will be taken directly from the data. The area under the curve over the 7-day dosing interval [AUC(0-τ)] will be calculated using the linear trapezoidal method.

- Fourth Dose

C_{max} and T_{max} will be taken directly from the data. The elimination rate constant, λz, will be calculated as the negative of the slope of the terminal log-linear segment of the serum concentration-time curve. The slope will be determined from a plot of the natural log of the terminal serum concentrations against time; at least 3 terminal serum concentration time points, beginning with the final concentration ≥ LOQ, will be selected for the determination of λz and the regression will have a coefficient of determination (r^2) ≥ 0.9000. The range of data to be used for each subject and treatment will be determined by visual inspection of a semi-logarithmic plot of concentration vs. time. Elimination half-life ($t_{½}$) will be calculated according to the following equation:

$$t_{½} = \frac{0.693}{\lambda z}$$

Area under the curve over the 7-day dosing interval [AUC(0-τ)] will be calculated using the linear trapezoidal.

Total serum clearance (CL) and volume of distribution (Vz), uncorrected for bioavailability (F), will be calculated according to

$$CL/F = \frac{Dose}{AUC\ (0-\tau)} \quad \text{and} \quad Vz/F = \frac{Dose}{\lambda z\ x\ AUC\ (0-\tau)}$$

respectively. For those subjects for whom λz cannot be estimated, λz, $t_{½}$, CL/F, and Vz/F will be assigned a value of missing.

The attainment of steady-state will be assessed from the pre-dose serum concentrations measured at Weeks 1 through 4 and the concentration 10 days after the last dose.

11.3.2.2 Pharmacokinetic Parameters — Compartmental Modeling

If the graphical presentations of the individual subject serum concentrations vs. time suggest that a compartmental model may be consistent with the data, then an appropriate model will be fit to each subject's complete set of data. The specific model will be determined after examination of the graphs and/or a statistical comparison of the fit of various models.

11.3.2.3 Pharmacokinetic/Pharmacodynamic Analysis

Relationships between pharmacodynamic and pharmacokinetic metrics may be explored graphically. If suggested by the graphs, appropriate models may be fit to the data.

11.3.3 Immunogenicity (Antibody) Analysis

Immunogenicity (antibody) samples will be screened for the presence of binding anti-drug antibodies (ADA). Samples testing positive and specific for antibodies against PB1046 will be further characterized to determine the domain specificity including whether the antibodies cross react with native VIP. Additional characterization of the antibody response may be performed as warranted. Samples testing positive and specific for anti-drug antibodies will be titered and further evaluated for their neutralizing potential using a cell based assay.

11.3.4 Exploratory

11.3.4.1 2-D Echocardiography

Change from baseline in select derived parameters such as Left ventricular (LV) Ejection Fraction, LV Stroke Volume and Index, LV Cardiac Output and Index, Ejection Time, Systemic Vascular Resistance, Mitral E and A velocities, LV and index, Myocardial tissue velocities S' and e', and myocardial strain (strain rate (SR)/strain rate image (SRI)), may be presented descriptively by dose and pooled placebo . If possible, inferential analyses (e.g., simple ANOVA) may be conducted to explorer the difference between treatment groups as measured by 2-D echocardiography with Doppler. Measurements may include:

- Blood pressure (BP) and heart rate (HR) (arterial peak, mean and diastolic blood pressure)
- Left ventricular internal diameter in diastole (cm)
- Left ventricular internal diameter in systole (cm)
- Left ventricular wall thickness in diastole (cm; both septum and posterior wall)
- Left ventricular outflow tract diameter in mid-systole (cm)
- Left ventricular volumes (end-diastole and end-systole, in mL; apical views)
- Left ventricular outflow tract flow-time velocity integral (by pulsed Doppler; in cm)
- Ascending aorta peak flow velocity (by Continuous Wave Doppler; in m/s)
- Transmitral flow velocity pattern (both by pulsed and Continuous Wave Doppler)
- Doppler tissue imaging of tricuspid, septal and mitral annulus (velocity; in cm/s)
- Left atrial volume (in mL/M2)

11.3.4.2 Biomarkers

Change from baseline in select biomarkers may be presented descriptively by dose and pooled placebo.

11.4 Interim (cohort) Safety Analysis for Dose Escalation

Analysis will be done after 75% of the subjects have received at least three doses (Day 14) of study drug and followed for a minimum of 7 days after the third dose. Summary tables (descriptive only) of safety, pharmacokinetic, immunogenicity, and other exploratory endpoints, as indicated, will be presented using the subjects of that dose group and summary data will be provided to the investigators and Study Review Committee in a blinded fashion.

12 DATA COLLECTION, RETENTION AND MONITORING

12.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug. Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a site number, subject number and initials. If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. Copies of final completed eCRFs will be provided on a compact disk (CD) or other similar media for archiving at the study site following database lock and at or prior to study closure.

12.2 Data Management Procedures

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

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

12.2.1 Data Quality Control and Reporting

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

12.2.2 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

Data should be entered onto the eCRF approximately no later than 72 hours after the visit has taken place.

12.2.3 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of the Medical Dictionary for Regulatory Activities for medical history and adverse events; and
- World Health Organization Drug Dictionary for prior and concomitant medications.

12.2.4 Data Validation

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

The CRFs must be reviewed and electronically signed by the Investigator who signed the protocol.

12.3 Archival of Data

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

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

12.4 Availability and Retention of Investigational Records

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

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

12.5 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor (or designee) according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

12.6 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs, blood samples, and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

12.7 Retained Blood Samples

Blood samples collected during the study for pharmacokinetic or immunogenicity analysis may be retained for future testing as necessary. Subject confidentiality will be maintained and only the site and subject number and initials will identify the sample. No other linked or identifying information is maintained by the Sponsor.

13 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Subjects (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312 Subpart D).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

13.1 Protocol Amendments

Any amendment to the protocol will be written by PhaseBio Pharmaceuticals Inc. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

13.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information

that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

13.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonization and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial and conducting any Screening visits. Information should be given in both oral and written form and subjects (or their legal representatives) must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject or legal representative of the subject and the original will be maintained with the subject's records.

13.4 Publications

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

14 SPONSOR DISCONTINUATION CRITERIA

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

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

15 REFERENCES

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APPENDIX A: ADVERSE EVENTS OF SPECIAL INTEREST

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.

APPENDIX B: IMMUNOGENICITY (ANTIBODY) AND PHARMACOKINETIC SAMPLE HANDLING, LABELING, AND SHIPMENT INSTRUCTIONS

Sample Identification and Specimen Collection

Specimen kits, requisition forms, and labels will be provided to appropriately identify specimens. At minimum, each label will contain the protocol number, subject number, and specimen collection date and time point. Refer to Laboratory Procedure Manual for additional instructions.

Labels should be placed on the tube such that all information is legible. Assure that labels adhere to the tubes and will not detach during storage.

Sample information must be accurately recorded on the PK and Immunogenicity Specimen Collection eCRF page and on the source documentation maintained by the site.

Collection and Processing of PK Samples

- Collect venous blood in 1 × 3.5 mL marble top serum separator tube (pre dose baseline) and 1 × 3.5 mL marble top serum separator tube for all subsequent sample collection time points. Each collection tube yields approximately 1.5 to 2 mL serum if filled completely.
- Gently invert each collection tube approximately 3 times.
- Allow the clot to form for approximately 30 minutes prior to centrifugation.
- Separate the serum centrifugation at 2500-3000 rpm (approximately1800 G or until there is complete separation of the serum and blood cells via the separator gel) for 15 minutes at room temperature.
- For each sampling time point, transfer an equal amount of serum (1.5-2.0 mL) into each of 2 pre-labeled 1.5 mL polypropylene tubes (label as set A and set B) and immediately store in a freezer at -70°C or lower until shipment is initiated.

Collection and Processing of Immunogenicity Samples

- Collect venous blood in 2 × 3.5 mL marble top serum separator tube (pre dose baseline) and 1 x 3.5 mL for all subsequent sample collection time points. Each collection tube yields approximately 1.5 to 2 mL serum if filled completely.
- Gently invert each collection tube approximately 3 times.

- Allow the clot to form for approximately 30 minutes prior to centrifugation.

- Separate the serum centrifugation at 2500-3000 rpm (approximately1800 G or until there is complete separation of the serum and blood cells via the separator gel) for 15 minutes at room temperature.

- For each sampling time point, transfer an equal amount of serum into each of 4 pre-labeled 1.5 mL polypropylene tubes (label two vials as set A and two vials as set B) and immediately store in a freezer at -70°C or lower until shipment is initiated.

Shipment

The US Department of Transportation and the International Air Transport Association regulate shipments of blood and blood components because it is a biohazardous material. Federal rules require that anyone wishing to ship biohazardous material must have shipping training.

All samples will be shipped frozen to Medpace Reference Laboratory unless otherwise directed by the Sponsor or as further described in the laboratory manual. Additionally refer to the Laboratory Manual for specific specimen handling instructions.

APPENDIX C: RESPONSIBILITIES OF THE UNBLINDED STUDY DRUG DISPENSER (USDD)

General Responsibilities

The Investigator (Principal Investigator) will assign via the Delegation of Authority Log individual(s) who are qualified by training and experience to prepare study drug as the study designated Unblinded Study Drug Dispenser (USDD).

The USDD will sign a statement that assures PhaseBio Pharmaceuticals Inc. and regulatory authorities that he/she understands his/her obligations and responsibilities as specified in the protocol (i.e., correct dispensing of study drug and the manner in which it is to be administered). The original and/or copy of the signed statement will be forwarded to PhaseBio Pharmaceuticals Inc. and a copy will be retained in the Essential Document Regulatory File.

The USDD is responsible for all study drug inventory records will be responsible for maintaining the confidentiality and security of the treatment assignment/inventory records.

From time-to-time throughout the study, an unblinded Quality Assurance Representative from the Sponsor will evaluate (secured blinded document portal within the eCRF) the study drug inventory forms and request clarifications as needed.

Treatment Assignment and Preparation

The USDD will view the Randomization Module and Dosing and Treatment Allocation (active or placebo) for the subject via the eCRF page. The Dosing module will provide an auto-calculated dosing volume based on the assigned dose, subject weight (entered by the Study Coordinator or designee) and the study drug concentration (PB1046 at 40 mg/mL). Additional detailed instructions on access and the randomization procedure are provided in the pharmacy procedure manual. The USDD will prepare the study drug in accordance with Section 8.5.1.

Dispensing

The USDD will prepare study drug that is appropriately blinded and labeled with the Subject ID, Randomization Number, subject initials and date/time dose prepared. The USDD will deliver the prepared blinded study drug to the Investigator or designee.

The USDD will complete all dispensing information on the dispensing and inventory records provided by PhaseBio Pharmaceuticals Inc.

The USDD may be permitted to administer the study drug to the study subject but will not participate in the safety/efficacy evaluations for any study subject.

APPENDIX D SELF-MONITORED BLOOD PRESSURE DIARY

PB1046-PT-CL-0003
Blood Pressure Log
Subject ID/Initials: _____

IMPORTANT REMINDERS:

1. Check your blood pressure in the morning and evening **at least 30 minutes after** eating meals, exercising, bathing, smoking, or drinking alcohol or caffeine.
2. **MEASURE BLOOD PRESSURE WITH YOUR _____ ARM.**
3. Sit quietly for at least 5 minutes with feet flat on the floor and back supported.
4. Place cuff over arm (bare or no tight fitting clothing) and make sure blue strip is centered on the inside of your arm with the tubing pointing down toward your hand. Close cuff snugly. Put your arm on a table so that the cuff is level with your heart. Press START, the cuff will tighten and inflate automatically. You should see the "OK" if cuff is in proper place. If not, reposition and start again. You will need to sit for at least three minutes while the Blood Pressure Monitor automatically measures three consecutive blood pressures (1 minute apart). Record below.
5. Call the study nurse or doctor _____ at _____ if you have questions or are not feeling well. You may need to be seen.

DATE (Month/Day/ Year)	MORNING			EVENING			COMMENTS
	Time	Blood Pressure (systolic/ diastolic)	Heart Rate	Time	Blood Pressure (systolic/ diastolic)	Heart Rate	
		/			/		
		/			/		
		/			/		
		/			/		
		/			/		
		/			/		
		/			/		