A Phase 1, Randomized, Double-blind, Placebo-Controlled, Safety, Tolerability, and Pharmacokinetic Study of a Multiple Ascending Dose (MAD) of AT 1-6(Ser-OGlc)-NH2, PNA5 in Healthy Participants

PNA5-102

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PNA5

Protocol Version:	2.0 (Amendment 1)
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Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the Sponsor.

Name of Authorized Signatory for Protocol	**Title**

Compliance Statement

This trial will be conducted in compliance with the protocol and in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Council for Harmonisation Harmonized Tripartite Guideline and all applicable regulatory requirements.

2. STUDY SUMMARY: PHASE 1 MAD SAFETY STUDY

Name of Sponsor/Company:	**Name of Investigational Product:**
Meredith Hay, PhD/University of Arizona	Glucose-Angiotensin I/II-(1-7) (PNA5)
Name of Active Ingredient: PNA5	Glucose-Angiotensin I/II-(1-7) (PNA5)
Study Number: PNA5-0001	**Phase: 1**

Title of Study: A Phase 1, Randomized, Double-blind, Placebo-Controlled, Safety, Tolerability and Pharmacokinetic Study of a Multiple Ascending Dose (MAD) of AT 1-6(Ser-OGlc)-NH2, PNA5 in Healthy Participants

Study center(s):

Phase 1 trial will be performed by our clinical trial corporate partner Syneos Health Clinical Research Services, LLC.

Principal Investigators (PIs): David J. Wyatt, MD

Studied period:	**Phase of development:**
14 days excluding screening period	Phase 1

Study Design:

This Phase 1, single-center, randomized, double-blind, placebo-controlled, MAD study is designed to assess the safety and tolerability of escalating doses of PNA5 in healthy adults. This study will occur only after review of all safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) data collected in the first-in-human Phase 1 single ascending dose (SAD) study in healthy adults. All doses used in the MAD cohorts will be administered only if there is acceptable safety, tolerability, PK, and PD data at the same or higher dose level after a single dose in the SAD healthy adult cohorts. The potential for accumulation and its impact on the likelihood of reaching the no-observed-adverse-effect level (NOAEL) exposure cap, will be considered when selecting doses for the MAD.

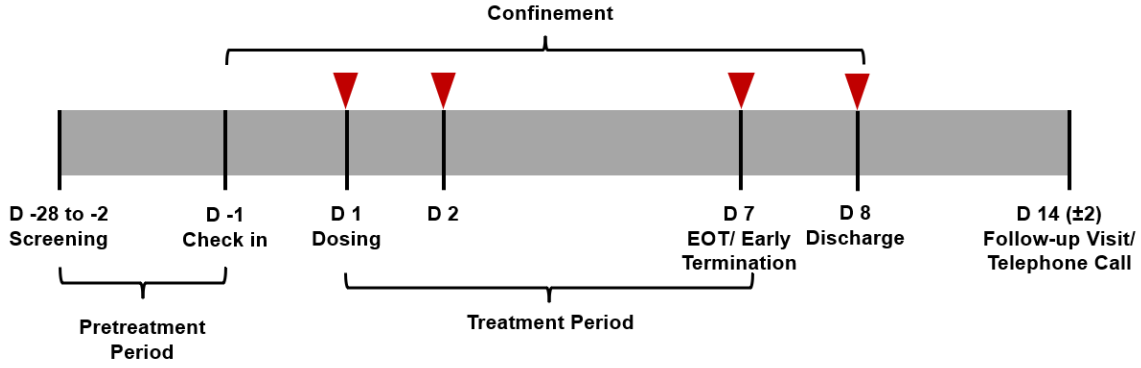
Approximately 24 participants will be enrolled and randomized to receive PNA5 or placebo in 1 of 3 sequential cohorts consisting of a low, medium and high dose. Each cohort will consist of 8 participants with 6 participants assigned to active drug and 2 participants assigned to placebo. Participants will be randomized to receive subcutaneous (SC) PNA5 at planned doses of 10 mg, 20 mg, 30 mg, or placebo daily for 7 days. Doses will be adjusted based on evidence from the SAD study.

Participants in Cohort 1 will receive 10 mg/day of PNA5 SC or placebo SC daily for 7 days. The doses selected for Cohorts 2 and 3 will be determined based on the results of Cohort 1 and preclinical studies, but will not be greater than twice the original starting dose of 10 mg/day. To ensure adequate safety and tolerability, recruitment of subsequent cohorts will be sequential and will only occur following review of safety, tolerability, PK, and PD data for the previous cohort.

The first 2 participants (1 active: 1 placebo) in each cohort will receive either PNA5 or placebo in parallel, followed by a minimum 24-hour gap to ensure adequate evaluation of safety and tolerability prior to administering the same dose of PNA5 or placebo to the remaining participants within the cohort (5 active: 1 placebo). Dosing of the remaining participants will proceed in a staggered fashion with no more than 3 participants being dosed at a time and having an approximate 24-hour gap before the next group of participants is dosed.

Participants will be followed for safety through Day 14, that is, 1 week after last dose.

The primary objective of this study is to assess safety and tolerability of escalating doses of PNA5 through evaluation of treatment-emergent adverse events(TEAEs). Secondary objectives include assessment of PK parameters and PD data for PNA5 and the potential immunogenicity of PNA5. Participants will be seen for safety visits during the confinement period and at Day 14.



Note: Red arrows represent sampling for pharmacokinetic assessment. Sampling for pharmacodynamic assessment will occur on Days 1 and 7.
Note: Safety will be assessed continuously during confinement and at the follow-up visit. Pre-treatment events will be collected during the pre-treatment period.
Note: The Follow-up Visit will occur by telephone unless abnormal, clinically significant findings are observed upon discharge. In these cases, participants may then be brought back to the clinic for re-evaluation per Investigator's discretion.
Note: Total confinement period will be 9 days

Participants will remain in the study unit for approximately 24 hours after their last dose for safety, PK, and PD assessments before discharge.

If the $t_{1/2}$ of PNA5 for any cohort differs significantly from what was predicted from toxicokinetic studies ($t_{1/2}$ longer than 20 minutes), the duration of confinement may be adjusted.

Objectives:

Primary Objectives:

- Determine the safety and tolerability profile of PNA5 when administered in multiple ascending doses SC in healthy volunteers

Secondary Objective:

- Obtain PK and PD data for PNA5
- Investigate potential immunogenicity of PNA5

Participant Population: Healthy male and female participants aged 18 to 55 years, inclusive, at the time of consent.

Number of Participants:	**Number of Sites:**
Per cohort: 8 (6 active: 2 placebo) Number of cohorts: 3 Estimated total: Up to 24 randomized healthy participants	Estimated total: 1 in the USA
Dose Levels: Cohort 1 dose 10 mg/day, subsequent dose levels to be determined by emerging safety, tolerability, PK and PD data in preceding cohorts.	**Route of Administration:** subcutaneous injection
Duration of Treatment: 7 days	**Period of Evaluation (First dose to Follow-up):** 14 days

Criteria for Inclusion:

Participant eligibility will be determined according to the following criteria prior to entry into the study; participants must meet all criteria listed below to be eligible to participate:

1. In the opinion of the Investigator, is capable of understanding and complying with protocol requirements.

2. Willing and able to provide written, informed consent and agree to any required privacy authorization prior to the initiation of any study procedures including requesting that a participant fast for any laboratory evaluations.

3. Is a healthy adult male or female.

4. Aged 18 to 55 years, inclusive at the time of consent.

5. Weighs at least 45 kg (99 lb) and has a body mass index (BMI) between 18.0 and 30.0 kg/m^2 inclusive at Screening.

6. A male participant who is non-sterilized* and sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 90 days after 5 half-lives have elapsed since last dose of study drug. This should be interpreted as 90 days from the Follow-up Call/Visit unless data indicates otherwise.

7. A female participant of childbearing potential* who is sexually active with a non-sterilized* male partner agrees to routinely use highly effective contraception with low user dependency* from signing of informed consent, throughout the duration of the study, and for 30 days after

5 half-lives have elapsed since the last dose of study drug. This should be interpreted as 30 days from the Follow-up Call/Visit unless data indicates otherwise.

*Definitions and acceptable methods of contraception are defined in Section 7.1.11 and reporting responsibilities are defined in Section 7.1.12.

Criteria for Exclusion:

Any participant who meets any of the following criteria will not qualify for entry into the study:

1. Received any investigational compound within 90 days prior to the first dose of study drug, including PNA5.

2. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

3. Has any clinically significant illness, such as cardiovascular, neurologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine, or psychiatric disease or disorder, or other abnormality, which may affect safety.

4. Has a known hypersensitivity to any excipients of PNA5.

5. Has a positive urine/blood result for drugs of abuse (defined as any illicit drug use) at Screening or Check-in (Day -1).

6. Has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to Screening or is unwilling to agree to abstain from alcohol and drugs throughout the study.

7. Has taken any prohibited medication, supplements, or food products during the time periods listed in the Prohibited Medications and Dietary Products table (Table 3).

8. If female, is pregnant, lactating, or intending to become pregnant before, during, or within 30 days after 5 half-lives have elapsed since the last dose of study drug (ie, 30 days from the Follow-up Call/Visit unless available data indicates otherwise); or intending to donate ova during such time period.

9. If male, intends to donate sperm during the study or within 90 days after 5 half-lives have elapsed since the last dose of study drug. This should be interpreted as 90 days from the Follow-up Call/Visit unless data indicates otherwise.

10. Has a condition that can potentially reduce drug clearance (eg, renal or hepatic insufficiency).

11. Has a history of cancer, except basal cell carcinoma which has been in remission for at least 5 years prior to Check-in (Day -1).

12. Has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis B core total antibody (Hbc total Ab), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV)-1, or HIV-2 at Screening. If HBc total AB of HCV antibody are positive, a viral load should be negative.

13. Has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum) within 28 days prior to Check-in Day -1. Cotinine test is positive at Screening or Check-in (Day -1).

14. Has poor peripheral venous access.

15. Has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis), or had a transfusion of any blood product within 90 days prior to first dose of study drug.

16. History of deep vein thrombosis, positive result on thrombophilia screen, or any predisposition to arterial or venous thrombosis.

17. Has a risk of suicide per the Columbia-suicide severity rating scale (C-SSRS; a score of 4 or 5 on ideation or any suicidal behavior) or according to the Investigator's clinical judgment, has made a suicide attempt in the previous 6 months, or has a history of deliberate self-harm in the past 6 months.

18. Laboratory values meeting the following criteria:

- Serum aspartate transaminase (AST) ≥ 2 × upper limit of normal (ULN).
- Serum alanine transaminase (ALT) ≥ 2 × ULN.
- Serum total, direct, or indirect bilirubin ≥ 2.0 mg/dL; except for participants with isolated elevation of indirect bilirubin relating to a confirmed diagnosis of Gilbert syndrome.
- Estimated glomerular filtration rate (GFR) by Cockroft-Gault formula < 80 mL/min/1.73 m^2.
- Total white blood cell count < 3000 cells/µL.
- Absolute neutrophil count < 1000 cells/µL.
- Platelet count < 100,000 cells/µL.
- Hemoglobin < 10 g/dL.

19. Clinically significant arrhythmia or evidence of predisposition to significant ventricular arrhythmia on electrocardiogram (ECG), or evidence of active and unstable coronary artery disease.

20. Male participant who has an ECG QT interval with Fridericia correction (QTcF) > 450 milliseconds or female participant who has an ECG QTcF > 470 milliseconds.

Main Criteria for Evaluation and Analyses:

Safety: The primary endpoints include adverse events (AEs), clinical laboratory test results, ECG, vital signs, and suicidality assessments.

Pharmacokinetics: The following PK parameters of PNA5 will be determined from plasma (where possible): maximum observed plasma concentration (C_{max}), maximum observed steady-state plasma concentration during a dosing interval ($C_{max,ss}$), time to reach C_{max} (t_{max}), area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last}),), area under the plasma concentration-time curve from time 0 to infinity ($AUC\infty$), area under the plasma concentration-time curve for the dosing interval

(AUC_{tau}), and accumulation ratios for C_{max} and AUC. Urine pharmacokinetic samples were assessed to characterize the elimination pathway for PNA5.

Pharmacodynamics and Immunogenicity: potential PNA5 immunogenicity, Ang-(1-7) levels, and CYP inhibition activation.

Statistical Considerations:

A detailed statistical analysis plan (SAP) will be developed for this study. All data collected will be provided in by-participant data listings, and data will be summarized by dose group, pooled placebo group, and overall.

Safety:

Treatment-emergent adverse events (AEs) will be summarized by coded system organ class and preferred term, and all AEs will be presented in data listings. Individual results of laboratory tests (hematology, chemistry, and urinalysis), vital signs, and ECGs will be provided in data listings and Baseline, post-dose, and change from Baseline values will be summarized. Physical examination findings and suicidality assessments (C-SSRS) will be presented in data listings.

Pharmacokinetic Measures:

The concentrations of PNA5 and Ang-(1-7) in plasma and urine will be summarized by study Day and dose level over each scheduled sampling time using descriptive statistics. Individual plasma concentration data vs time will be presented in a data listing. Descriptive statistics (N, arithmetic mean, standard deviation, median, minimum, maximum, geometric mean, and percent coefficient of variation [%CV]) will be used to summarize the plasma and urine PK parameters for PNA5 and metabolites by study Day, and dose level. Dose proportionality will be tested for PNA5 C_{max} and AUCs using a power model. Additional analyses will be included if appropriate.

Sample Size Justification: The sample size chosen, 8 participants in each cohort (6 active: 2 placebo), is considered to be sufficient for evaluation of safety, tolerability, PK, and PD data in each cohort. The sample size was not based on statistical power considerations.

Table 1 Study Procedures for Multiple Ascending Dose Study of PNA5

Study Day	Screening [a] D -28 to D-2	Check-in[b] D -1	D1	D2	End of Treatment D7/Early Termination	Discharge Day 8	Follow-up Visit/Telephone Call D14 (±2)
Written Informed Consent	x						
Demographics & Medical History	x						
Physical Exam, Triplicate 12-lead ECG[c]	x	x	x	x	x	x	
Vital Signs[d] Blood Pressure, Heart Rate, Respiratory Rate, Body Temperature	x	x	x	x	x	x	x
Clinical Laboratory[e] HIV, HCV, Hepatis B, Hematology, Blood Chemistry, Urinalysis, Urine Collection for Creatinine Clearance	x	x	x	x	x	x	
Thrombophilia Screen[f]	x						
Pregnancy Test[g]	x	x			x		x
Blood/Urine Drug Screen[h], Alcohol Breathalyzer	x	x					
Plasma PK Sampling for PNA5 Concentrations [i]			x	x	x	x	
Urine PK Sampling[j]			x		x		

Study Day	Screening [a] D -28 to D-2	Check-in[b] D -1	D1	D2	End of Treatment D7/Early Termination	Discharge Day 8	Follow-up Visit/Telephone Call D14 (±2)
Blood sampling for Angiotensin 1-7 Plasma Levels, ADA, and CYP characterization	x		x	x	x		
C-SSRS	x	x			x	x	x
Study Drug Injections[k]			x				
Recording of PTEs and AEs	x[l]						
Prior and Concomitant Medications	x[l]						

ADA = anti-drug antibody; AE = adverse event; C-SSRS = Columbia-suicide severity rating scale; CYP = cytochrome P450; D = day; ECG = electrocardiogram; FSH = follicle-stimulating hormone; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PK = pharmacokinetic; PTE = pre-treatment event.

a. Within 28 days before the first dose administration
b. Admission to Unit on Day -I and discharge on Day 3 after completion of procedures.
c. Triplicate ECG recorded in parallel with PK sampling via cardiac telemetry.
d. Measured at timepoints in Table 4. Heart rate and blood pressure will be measured after >5 minutes of rest in the supine position and again 1 to 3 minutes after sitting.
e. Hematology will include flow cytometry for measurement of white blood cell subsets. Tests for COVID-19, HIV, HCV, and Hepatis B will only occur at Screening and Check-in.
f. Includes antithrombin, protein C, protein S, lupus anticoagulant, factor V Leiden, prothrombin gene mutation, anti-β-2-glycoprotein-1 antibodies, and anti-cardiolipin antibodies
g. Serum hCG pregnancy test will be conducted at Screening and End of Treatment/Early termination, and at the Follow-up Visit if the participant is brought back to the clinic for re-evaluation. Urine hCG pregnancy test will be done at Check-in (Day -1). (b) FSH level will be obtained for female participants at Screening if they are postmenopausal (ie, no menses for 12 months without an alternative medical cause) and not surgically sterile.
h. Drug screen includes amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and cotinine.
i. Intensive PK samples will be collected on Days 1, and 7. Samples will be collected into tubes tube with peptidase inhibitors inhibitor and processed to maintain stability of PNA5. Assessments on Days 2 and 8 represent PK sampling 24 hours post dose on Days 1 and 7. See Table 6 for collection timepoints.
j. See Table 6 for collection timepoints.
k. Initial dose of study drug will occur on Day 1, followed by a 24-hour gap to assess safety. Daily dosing will then proceed on Days 2 to 7.

l. Collected continuously throughout the study. Collection of PTEs spans from signing of the informed consent form until the receipt of the first dose of study drug, while collection of AEs spans from administration of first dose of study drug until the follow-up visit on Day 14.

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List of Abbreviations

Abbreviation	Definition
Ab	Antibody
ACE	Angiotensin-converting enzyme
ADA	Anti-drug Antibody
ADRD	Alzheimer's disease related dementias
AE	Adverse events
AESI	Adverse event of special interest
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval
BMI	Body mass index
CBF	Cerebral blood flow
C_{max}	Maximum observed steady-state plasma concentration
$C_{max,ss}$	Maximum observed steady-state plasma concentration during a dosing interval
CNS	Central nervous system
CRO	Contract research organization
C-SSRS	Coumbia-suicide severity rating scale
CYP	Cytochrome P450
ECG	Electrocardiogram
eCRF	Electronic case report form
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
HBc	Hepatitis B core
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HED	Human equivalent doses
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IRB	Institutional Review Board

MAD	Multiple ascending dose
MasR	Mas receptor
NOAEL	No-observed-adverse-effect level
PTE	Pretreatment event
QTcF	QT interval with Fridericia correction method
ROS	Reactive oxygen species
SAD	Single ascending dose
SAE	Serious adverse events
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	System organ class
SPECT	Single-photon emission computed tomography
$t_{1/2}$	Plasma half-life
TEAE	Treatment-emergent adverse event
Tmax	Time to reach C_{max}
VCID	Vascular contributions to cognitive impairment and dementia

3. INTRODUCTION

3.1 Background

Vascular contributions to cognitive impairment and dementia (VCID) and Alzheimer's disease related dementias (ADRD) significantly contribute to the 47 million people world-wide who suffer with dementia. This number is estimated to increase to over 130 million people by 2050. A number of studies have shown that VCID and conversion to ADRD are strongly correlated with vascular disease, inflammation and decreased cerebral brain blood flow (Canobbio et al., 2015; Gorelick et al., 2017; Janota et al., 2016; Kapasi and Schneider, 2016; Santos et al., 2013; Toledo et al., 2012; van Oijen et al., 2007; Yarchoan et al., 2012). The relationship between vascular disease, cognitive function, and progression to dementia and possible AD have been recently reviewed (Sweeney et al., 2019). These authors successfully make the case for a close relationship between cardiovascular risk factors and risk for VCID and ADRD. Furthermore, conversion rates of VCI to dementia has been reported to be between 40% and 46% within 5 years of diagnosis of VCI (Hsiung et al., 2006; Wentzel et al., 2001). There is an urgent unmet medical need for therapeutics to prevent cognitive decline in individuals at risk for VCID.

A growing body of evidence indicates that increases in systemic and brain inflammatory mechanisms, increased reactive oxygen species (ROS), and decreased brain blood flow accelerate the progression of neurodegenerative diseases. In older adults, chronic systemic inflammatory related diseases, such as cardiac disease or heart failure that lead to increased brain and systemic inflammation and decreased brain perfusion, are known to increase the risk for dementia and the development of VCID (Cermakova et al., 2015; Love and Miners, 2016; Miners et al., 2017; Suzuki et al., 2016). The ideal therapeutic candidate to treat inflammation-related neurodegenerative disease in individuals who are at risk of developing VCID and ADRD would be designed to interrupt the inflammatory cascade by working at both sides of the blood-brain barrier, the brain vascular endothelium, and glia and neuronal cells to decrease ROS production in the brain and neuroinflammation and improve cerebral vascular blood flow.

It is estimated that 65% of people with heart failure at risk for VCID experience more cognitive impairment than healthy persons of similar age, with variation across studies related to differences in age and the severity of cardiac dysfunction (Dodson et al., 2013; Huijts et al., 2013; Riegel et al., 2012). Among older adults with heart failure, ages 60 or older, cognitive impairment is more prominent compared to age-matched controls, and these individuals experience faster age-related memory decline (Harkness et al., 2011; Vogels, Oosterman, van Harten, Scheltens, et al., 2007). While cognition can improve following heart transplant (Roman et al., 1997), significant cognitive impairment persists for many patients, as does the increased risk for VCID (Cermakova et al., 2015). Importantly, long-term studies have revealed that even cognitively normal heart failure patients have a significantly higher risk of VCID compared to age-matched controls (Qiu et al., 2006), suggesting that cardiovascular disease predisposes patients to dementia.

Mechanisms thought to contribute to cognitive impairment in heart failure patients at-risk for VCID include inflammation (Athilingam et al., 2013), changes in cerebral blood flow (CBF)(Alves et al., 2005; Vogels, Oosterman, van Harten, Gouw, et al., 2007), altered

cerebrovascular autoregulation (Zuccalà et al., 2005), and microembolism (Almeida et al., 2012). Inflammatory processes play an important role in heart failure-related brain dysfunction. Elevated levels of inflammatory markers are associated with cognitive impairment in heart failure (Athilingam et al., 2013). Several studies have reported reduced performance on episodic and working memory tasks in the presence of inflammation (Simpson et al., 2013; Yirmiya and Goshen, 2011). In studies by Gruhn et al. (2001), CBF measured with single-photon emission computed tomography (SPECT) was reduced by 30% in patients with severe heart failure. Decreased perfusion in heart failure has been attributed to low cardiac output, low blood pressure, and altered cerebrovascular reactivity (Alves et al., 2005; Zuccalà et al., 2001). Morphometric magnetic resonance imaging studies show decreases in gray and white matter volumes in heart failure patients compared to age-matched controls, particularly in areas critical for memory and executive function including the medial temporal lobe, cingulate gyrus, and frontal cortex (Vogels, Oosterman, van Harten, Gouw, et al., 2007; Almeida et al., 2012).

Angiotensin-(1-7) and the Brain

It has become recognized that the renin angiotensin system involves 2 separate enzymatic pathways that provide a physiological counterbalance of 2 related peptides acting at distinct receptors. The well described Angiotensin converting enzyme (ACE) -AngII-Angiotensin receptor, Type 1 (AT1R) system is thought to be physiologically opposed and balanced by the ACE2-Angiotensin-(1-7)-Mas receptor (MasR) system. In the brain and other tissues, Ang II activation of AT1 receptors increases ROS and inflammation while Ang-(1-7) and Mas receptor activation decreases brain ROS production and inflammation in pre-clinical models, increase CBF (Jiang et al., 2012; Jiang et al., 2013; Zimmerman, 2011) and is known to be safe in preliminary studies in humans (Petty et al., 2009).

The endogenous MasR for Ang-(1-7) are located on components of the neurovascular unit in brain regions involved in cognition and memory including cerebrovascular endothelial cells, microglia and neurons. Thus, Ang-(1–7) protects key regions of the brain important for learning and memory and provides protection against ischemia (Santos et al., 2013; Jiang et al., 2012; Jiang et al., 2013; Bunnemann et al., 1990; Santos et al., 2017). The hippocampus and perirhinal cortex, 2 areas important in memory, express high levels of the Ang-(1-7) MasR (Bunnemann et al., 1990; Doobay et al., 2007). Recently, the Ang-(1-7)/Mas pathway was found to be essential for normal object recognition memory (Lazaroni et al., 2012), suggesting that it is an important modulator of learning and memory. Our research team has shown in our preclinical model of VCID that cognitive impairment is reversed following 3 week treatment with subcutaneous PNA5 (Hay et al., 2019). Activation of MasR has been shown to decrease ROS and brain inflammation, increase cerebral circulation via increases in endothelial nitric oxide (NO) release, increase induction of neuroprotective cytokine, and inhibit hypoxia-inducing factor-1alpha (Chang et al., 2016; Ferrario, 2006; Sumners et al., 2013; Zheng et al., 2014). The relative importance of the vascular endothelium vs neuronal parenchyma with regards to inflammation and ROS-mediated changes in neuronal function and ultimately cognitive impairment has not been systematically investigated in models of VCID. What is well established and accepted is that the “neurovascular unit” which is composed of brain vasculature, neurons, glia, and astrocytes, is intimately integrated in healthy brains and in central nervous system (CNS) disease (Gorelick et al., 2017; Corriveau et al., 2016). Given that the inflammatory response in VCID is

known to involve increases in circulating and brain inflammatory factors, we believe that our glycosylated Ang-(1-7) derivatives will be better drugs than either the native Ang-(1-7) or related small molecules due to the ability of our glycosylated derivatives to access the brain MasR and inhibit inflammation and ROS formation within the blood-brain-barrier.

PNA5 is a synthetic glycopeptide derivative of Ang-(1-7) that has outstanding brain penetration and enhanced stability (Hay et al., 2019; Dhanasekaran and Polt, 2005; Jones and Polt, 2015; Malakoutikhah et al., 2008). PNA5 selectively activates the MasR and in preclinical studies of heart failure/VCID has been shown to be efficacious in the protection cognitive function. For the initial clinical efficacy studies, following successful safety Phase 1 trials, we plan on focusing our first trial in adult (40-85 years) heart failure patients with decreased ejection fraction and evidence of mild cognitive impairment or complaints of memory loss who have the most risk of developing VCID due to inflammation and decreased brain perfusion. These patients also have a high rate of hospital readmission due to poor medical compliance due to memory loss (Vogels, Scheltens, et al., 2007).

3.2 Rationale for the Proposed Study

The endogenous Mas receptors for Ang-(1-7) are located on components of the neurovascular unit in brain regions involved in cognition and memory including cerebrovascular endothelial cells, microglia and neurons. Thus, Ang-(1–7) protects key regions of the brain important for learning and memory and provides protection against ischemia (Santos et al., 2013; Jiang et al., 2012; Jiang et al., 2013; Bunnemann et al., 1990; Santos et al., 2017). PNA5 selectively activates the MasR and has been shown to be efficacious in the protection of cognitive function in preclinical studies of heart failure/VCID. The present study has, therefore, been designed to evaluate the safety, pharmacokinetic (PK), and pharmacodynamic (PD) effects of PNA5 in healthy volunteers before further clinical development.

3.3 Risk Benefit Profile

This Phase 1 study has been designed to mitigate the known risks associated with Ang-(1-7) agonists as a class and the potential risks based on the nonclinical toxicity data and preliminary clinical data for PNA5. As this is a study in healthy participants, there is no expected clinical benefit to the study participants.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1 Primary Objective

- Determine the safety and tolerability profile of PNA5 when administered in multiple ascending doses subcutaneously (SC) in healthy volunteers.

4.2 Secondary Objective

- Obtain pharmacokinetic and pharmacodynamic data for PNA5
- Investigate potential immunogenicity of PNA5.

4.3 Endpoints

4.3.1 Primary Endpoints

- Percentage of participants who experience at least 1 treatment-emergent adverse event (TEAE).
- Percentage of participants who discontinue due to an AE.
- Percentage of participants with reported suicidal ideation of any severity per the Columbia-Suicide Severity Rating Scale (C-SSRS).

4.3.2 Secondary Endpoints

- Plasma PK parameters of PNA5:
  - Maximum observed plasma concentration (C_{max})
  - Maximum observed steady-state plasma concentration during a dosing interval ($C_{max,ss}$)
  - Time to reach C_{max} (t_{max})
  - Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration (AUC_{last})
  - Area under the plasma concentration-time curve from time 0 to infinity (AUC_{∞})
  - Area under the plasma concentration-time curve during a dosing interval (AUC_{τ}).
  - Plasma half-life ($t_{1/2}$)
- Plasma PD parameters of PNA5:
  - Explore levels of renin-angiotensin system metabolites and components
  - Characterize of cytochrome P450 (CYP) inhibition and activation
- Investigate potential immunogenicity

5. STUDY DESIGN AND DESCRIPTION

5.1 Study Design

This Phase 1 single-center, randomized, double-blind, placebo-controlled, multiple ascending dose (MAD) study in healthy participants is designed to assess the safety and tolerability of PNA5. Approximately 24 healthy male and female volunteers will be enrolled and randomized to receive PNA5 or placebo in 1 of 3 cohorts. Each cohort will consist of 8 participants (6 active:2 placebo). Study drug will be injected subcutaneously.

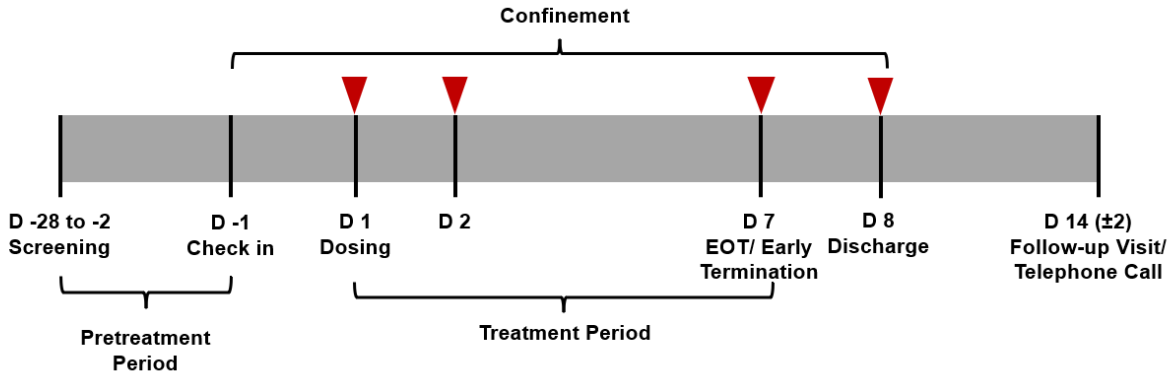
For each participant there will be a screening period, a 7-day treatment period, and a 1-week follow-up period or early withdrawal, as applicable. Participants will be confined to the study unit for approximately 24 hours after the last dose for safety, PK, and PD assessments before discharge. If the $t_{1/2}$ of PNA5 for any cohort differ significantly from what was predicted from toxicokinetic studies (a $t_{1/2}$ longer than 20 minutes), the duration of confinement may be increased.

Follow-up assessments will occur on Day 14, approximately 7 days after the final dose of study drug, to collect any ongoing AEs or serious adverse events (SAEs), worsening of AEs or SAEs, development of new AEs or SAEs, and concomitant medications taken since the final dose. Follow-up will occur by telephone unless abnormal, clinically significant findings are observed upon discharge or at the Investigator's discretion. In such cases, participants should return to the clinic for re-evaluation.

The dose of PNA5 for administration to the first MAD cohort will be chosen only after the first 3 single ascending dose (SAD) cohorts have been completed without safety concern in the first-in-human study, PNA5-101. The initial dose chosen for this MAD study will be equivalent to or lower than the highest dose administered and considered safe in the first 3 SAD cohorts. The first 2 participants (1 active: 1 placebo) in each MAD cohort will receive either PNA5 or placebo in parallel, followed by a minimum 24-hour gap to ensure adequate evaluation of safety and tolerability prior to administering the same dose of PNA5 or placebo to the remaining participants within the same cohort (5 active: 1 placebo). Dosing of the remaining participants will proceed in a staggered fashion with no more than 3 participants being dosed at a time and having an approximate 24-hour gap before the next group of participants is dosed. Each dose cohort will be examined sequentially to ensure adequate evaluation of safety, tolerability, and available PK and PD data prior to administering the next dose level.

A schematic of the study design for the MAD study is presented in Figure 1. A summary of study procedures is presented in Table 1.

Figure 1. MAD Study Design



D = Day; EOT = End of Treatment
Note: Red arrows represent sampling for pharmacokinetic assessment. Sampling for pharmacodynamic assessment will occur on Days 1 and 7.
Note: Safety will be assessed continuously during confinement and at the follow-up visit. Pre-treatment events will be collected during the pre-treatment period.
Note: The Follow-up Visit will occur by telephone unless abnormal, clinically significant findings are observed upon discharge. In these cases, participants may then be brought back to the clinic for re-evaluation per Investigator's discretion.
Note: Total confinement period will be 9 days

The planned first dose level to be studied is 10 mg/day for Cohort 1, to be confirmed upon evaluation of the first 3 cohorts in the SAD study (PNA5-101). The dose level in subsequent cohorts will be determined after review of all available safety, tolerability, PK, and PD data in the current and preceding cohorts, but will not exceed 30 mg/day. If necessary, the Sponsor team may unblind the data and perform additional analyses for an informed dose-escalation decision. The next dose level may be higher, lower, or remain the same as the current dose level. If the dose is not increased in the next cohort, staggered dosing is not necessary.

The planned dose cohorts in the MAD study are listed in Table 2. In each cohort, a single dose will be administered on Day 1 followed by 24 hours of safety, tolerability, PK, and PD assessments. Daily dosing will proceed from Day 2 through Day 7.

Table 2. Summary of Multiple Ascending Dose Cohorts

Cohort[a]	Planned	Number of Participants
1	10 mg/day	6 PNA5, 2 placebo
2	20 mg/day	6 PNA5, 2 placebo
3	30 mg/day	6 PNA5, 2 placebo

MAD = multiple ascending dose; PD = pharmacodynamic; PK = pharmacokinetic; SAD = single ascending dose;
[a] Dosing for the first MAD cohort will not begin until there is acceptable safety, tolerability, and available PK and PD data at the same or higher dose level after a single dose in the first 3 SAD cohorts. Dose escalation to subsequent cohorts will be based on review of safety, tolerability, and available PK and PD data from previous cohorts. The subsequent dose level may be higher, lower, or the same as the preceding dose level.

5.2 Dose Escalation

All decisions concerning dose escalation will be made by the clinical science representative and pharmacovigilance physician, or appropriate delegates and the Principal Investigator. The Investigator and participants will remain blinded throughout the study, but at the completion of each cohort, study Sponsor personnel may be unblinded to analyze data considered necessary to determine subsequent doses.

The planned dose levels may be modified based on emerging safety, tolerability, and available PK and PD data. Dosing in all cohorts will be limited to an escalated dose which is predicted to give no greater than ~3-fold increase in either C_{max} or AUC. A smaller increment may be used at higher doses and a larger increment may be used at lower doses if exposures obtained are not sufficiently high, and if it is deemed safe to do so. In the event that the majority of plasma concentrations of PNA5 are below the limit of detection, the dose will be escalated to a higher dose level, if safety and tolerability are acceptable, and will ensure that no dose is ≤ 2-fold greater than the initial dose in Cohort 1.

After each cohort is completed (ie, all participants have completed the Treatment Period or discontinued prematurely, and are evaluated for safety at Day 14 or lost to follow-up), the Principal Investigator and Sponsor will review all safety, tolerability, PK, and PD data to determine whether the study should continue and subsequent cohort should be enrolled, the dose level of the subsequent cohort, and whether staggered dosing should be implemented in the subsequent cohorts. The blind may be broken for the Sponsor reviewers as needed to make these determinations.

All AEs reported from the date of the first dose up to the Follow-up Visit will be evaluated both within and across cohorts to assess the need for participant, cohort, and/or study termination in accordance with prespecified criteria (Section 6.5).

Dose escalation and study drug administration at the current level will be stopped if any of the stopping criteria are met (Section 5.5), and a safety review of all available data will be triggered.

5.3 Justification for Study Design, Dose and Endpoints

5.3.1 Study Design

This Phase 1 single-center, randomized, double-blind, placebo-controlled, MAD study is designed to assess the safety and tolerability of escalating doses of PNA5 in healthy adults. This study will be initiated only after review of all safety, tolerability, PK, and PD data is collected in the first-in-human Phase 1 SAD study in healthy adults (PNA5-101). All doses used in the MAD cohorts will be administered only if there is acceptable safety, tolerability, PK, and PD data at the same or higher dose level after a single dose in the SAD study. The potential for accumulation and its impact on the likelihood of reaching the no-observed-adverse-effect level (NOAEL) exposure cap will be considered when selecting doses for the MAD.

If the first 3 cohorts of the Phase 1 SAD study in healthy adults (PNA5-101) demonstrate acceptable tolerability, participants in the MAD Cohort 1 will receive 10 mg/day PNA5 or placebo SC daily for 7 days. The dose for Cohorts 2 and 3 will be determined based on the

results of Cohort 1 and ongoing preclinical studies but will not be greater than twice the original starting dose. To ensure adequate safety and tolerability, recruitment of subsequent cohorts will be sequential and will only occur following review of safety, tolerability, PK, and PD data for the previous cohort.

The first 2 participants (1 active:1 placebo) in each cohort will receive either PNA5 or placebo in parallel, followed by a minimum 24-hour gap to ensure adequate evaluation of safety and tolerability prior to administering the same dose of PNA5 or placebo to the remaining participants within the cohort (5 active: 1 placebo). Dosing of the remaining participants will proceed in a staggered fashion with no more than 3 participants being dosed at a time and having an approximate 24-hour gap before the next group of participants is dosed.

Participants will be followed for safety through Day 14, 1 week post last dose.

5.3.2 Dose

The nonclinical toxicity studies conducted to date with PNA5 provide adequate safety data to support a Phase 1 clinical study of up to 28 days in duration. The human equivalent doses (HEDs) were derived using the methodology described in the Food and Drug Administration (FDA) Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers. Based on the NOAEL results from the 28-day toxicity studies in rats and dogs, and the 6-month toxicity in rats, the maximum safe starting dose in humans was determined to be 33.6 mg/day. Emerging data from the single ascending dose Study PNA5-101 will be used to inform the dose levels in the present study (Study PNA5-102). The proposed dosing range in the single ascending dose Study PNA5-101 is 2.5 mg to 30 mg. Assuming no dose-limiting toxicities are observed in Study PNA5-101, the planned dose levels for Cohorts 1, 2, and 3 of Study PNA5-102 are 10, 20, and 30 mg/day, respectively, for 7 days.

5.3.3 Endpoints

The primary endpoints for this study are a composite of standard safety variables to determine tolerated doses and dose-limiting effects of PNA5. The C-SSRS is a widely used tool to assess suicidal ideation and behavior.

The secondary endpoints are standard PK variables to permit determination of PNA5 exposure at each dose and facilitate determination of dose escalations. Pharmacodynamic variables were chosen in alignment with what is understood of PNA5 mode of action and results from nonclinical studies.

5.4 Risk Mitigation

PNA5 is an analog of the native peptide Angiotensin-(1-7), which has been shown in previous clinical studies to be safe and non-toxic in human studies up to 400 µg/kg/day (Petty et al., 2009). Based on previous studies with Ang-(1-7) in humans, Ang-(1-7) is well tolerated. The key risk is moderate hypotension.

Because Study PNA5 represents the first time that PNA5 is being administered to humans, anticipated risks are based on the mode of action of PNA5, nonclinical findings, dose-limiting toxicities, and human experience with An-(1-7) agonists. These potential risks have been considered when designing this study by minimizing the number of participants exposed at any one time at each dose level, following strict escalation criteria between cohorts, and setting conservative stopping rules.

5.5 Premature Termination or Suspension of Study or Investigational Site

5.5.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria that require temporary suspension or early termination of the study are satisfied:

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a significant change in the known risk/benefit profile for the drug, such that the risk is no longer acceptable for participants participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises participant safety.
- Conditions for Cohort Stopping Criteria are met in more than 1 cohort.

The study may be terminated prior to full attainment of these criteria (eg, if just 1 participant experiences 1 of these events) if warranted by safety data from the other participants dosed in the study to that point.

5.5.2 Cohort Stopping Criteria

If any of the following criteria occur in any participants within a cohort, enrollment will be paused for review. After review, dosing may be resumed at the same or a lower dose.

- If ≥ 1 participant in a cohort have a:
  - Treatment emergent SAE
  - Severe (nonserious) AE
  - Grade 2 or higher laboratory AE
  - Grade 2 or higher non-laboratory AE
- Any participant develops QT prolongation on a postdose electrocardiogram (ECG), defined as a QT interval with Fridericia correction method (QTcF) > 500 msec or > 60 msec change from baseline.
- Any participant develops bradycardia (heart rate of ≤ 40 bpm) on scheduled assessments only (ie, not on telemetry) or a reduction in heart rate of 30 bpm from baseline.
- Any participant develops hypotension (i.e., systolic < 90 mmHg and/or diastolic < 60 mmHg) with symptoms or orthostatic hypotension (i.e., a decline of ≥20mm Hg in systolic or ≥10 mmHg in diastolic blood pressure after the sudden change in position from supine to sitting.

- Two or more participants in one cohort or 3 participants overall with positive suicidal ideation and/or behavior during study participation as determined by the C-SSRS assessments.

6. SELECTION AND DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS

All entry criteria, including test results, need to be confirmed at Screening and at Check-in (Day -1).

6.1 Inclusion Criteria

Participant eligibility will be determined according to the following criteria prior to entry into the study; participants must meet all criteria listed below to be eligible to participate:

1. In the opinion of the Investigator, is capable of understanding and complying with protocol requirements.
2. Willing and able to provide written, informed consent and agree to any required privacy authorization prior to the initiation of any study procedures including requesting that a participant fast for any laboratory evaluations.
3. Is a healthy adult male or female.
4. Aged 18 to 55 years, inclusive at the time of consent.
5. Weighs at least 45 kg (99 lb) and has a body mass index (BMI) between 18.0 and 30.0 kg/m^2 inclusive at Screening.
6. A male participant who is non-sterilized* and sexually active with a female partner of childbearing potential* agrees to use adequate contraception* from signing of informed consent throughout the duration of the study and for 90 days after 5 half-lives have elapsed since last dose of study drug. This should be interpreted as 90 days from the Follow-up Call/Visit unless data indicates otherwise.
7. A female participant of childbearing potential* who is sexually active with a non-sterilized* male partner agrees to routinely use highly effective contraception with low user dependency* from signing of informed consent, throughout the duration of the study, and for 30 days after 5 half-lives have elapsed since the last dose of study drug. This should be interpreted as 30 days from the Follow-up Call/Visit unless data indicates otherwise. *See Sections 7.1.11 and 7.1.12 for contraception definitions and reporting responsibilities, respectively.

6.2 Exclusion Criteria

Any participant who meets any of the following criteria will not qualify for entry into the study:

1. Received any investigational compound within 90 days prior to the first dose of study drug, including PNA5.
2. Is an immediate family member, study site employee, or is in a dependent relationship with a study site employee who is involved in the conduct of this study (eg, spouse, parent, child, sibling) or may consent under duress.

3. Has any clinically significant illness, such as cardiovascular, neurologic, pulmonary, hepatic, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine, or psychiatric disease or disorder, or other abnormality, which may affect safety.
4. Has a known hypersensitivity to any excipients of PNA5.
5. Has a positive urine/blood result for drugs of abuse (defined as any illicit drug use) at Screening or Check-in (Day -1).
6. Has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to Screening or is unwilling to agree to abstain from alcohol and drugs throughout the study.
7. Has taken any prohibited medication, supplements, or food products during the time periods listed in the Prohibited Medications and Dietary Products table (Table 3).
8. If female, is pregnant, lactating, or intending to become pregnant before, during, or within 30 days after 5 half-lives have elapsed since the last dose of study drug (ie, 30 days from the Follow-up Call/Visit unless available data indicates otherwise); or intending to donate ova during such time period.
9. If male, intends to donate sperm during the study or within 90 days after 5 half-lives have elapsed since the last dose of study drug. This should be interpreted as 90 days from the Follow-up Call/Visit unless data indicates otherwise.
10. Has a condition that can potentially reduce drug clearance (eg, renal or hepatic insufficiency).
11. Has a history of cancer, except basal cell carcinoma, which has been in remission for at least 5 years prior to Check-in (Day 1).
12. Has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis B core total antibody (HBc total Ab), hepatitis C virus (HCV) antibody, human immunodeficiency virus (HIV)-1, or HIV-2 at Screening. If HBc total Ab or HCV antibody are positive, a viral load should be negative.
13. Has used nicotine-containing products (including but not limited to cigarettes, pipes, cigars, chewing tobacco, nicotine patch, or nicotine gum) within 28 days prior to Check-in (Day -1). Cotinine test is positive at Screening or Check-in.
14. Has poor peripheral venous access.
15. Has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis), or had a transfusion of any blood product within 90 days prior to first dose of study drug.
16. History of deep vein thrombosis, positive result on thrombophilia screen, or any predisposition to arterial or venous thrombosis.
17. Has a risk of suicide per the C-SSRS (a score of 4 or 5 on ideation or any suicidal behavior) or, according to the Investigator's clinical judgment, has made a suicide attempt in the previous 6 months, or has a history of deliberate self-harm in the past 6 months.

18. Laboratory values meeting the following criteria:
    - Serum aspartate transaminase (AST) ≥ 2 × upper limit of normal (ULN).
    - Serum alanine transaminase (ALT) ≥ 2 ×ULN.
    - Serum total, direct, or indirect bilirubin ≥2.0 mg/dL; except for participants with isolated elevation of indirect bilirubin relating to a confirmed diagnosis of Gilbert syndrome.
    - Estimated glomerular filtration rate (GFR) by Cockroft-Gault formula <80 mL/min/1.73 m^2.
    - Total white blood cell count < 3000 cells/µL.
    - Absolute neutrophil count < 1000 cells/µL.
    - Platelet count < 100,000 cells/µL.
    - Hemoglobin < 10 g/dL.
19. Clinically significant arrhythmia or evidence of predisposition to significant ventricular arrhythmia on ECG, or evidence of active and unstable coronary artery disease.
20. Male participant who has an ECG QTcF > 450 milliseconds or female participant who has an ECG QTcF > 470 milliseconds.

6.3 Prohibited Medications, Dietary Products

Use of the agents in Table 3 (prescription or nonprescription) is prohibited from the time points specified until participant is discharged from the unit.

Table 3. Prohibited Medications and Dietary Products

Timepoint:	**28 days prior to Check-in (Day -1)**	**7 days prior to Check-in (Day -1)**	**72 hours prior to Check-in (Day -1)**
Medication/ product:	• Prescription medications • Nutraceuticals (eg, St. John's wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin) • Immunization/Vaccines[b] • Nicotine-containing products • Intake of known OTC inhibitors/inducers of	• OTC medications[a] • Vitamin supplements • Alcohol containing products	• Products containing caffeine or xanthine • Poppy seeds

Timepoint:	28 days prior to Check-in (Day -1)	7 days prior to Check-in (Day -1)	72 hours prior to Check-in (Day -1)
	CYPs 3A4/5, 2C9, 2C19, 2D6, 1A2, 2B6, 2E1, and 2A6(c) • Medications that prolong the QT interval		

CYP = cytochrome P450; OTC = over-the-counter.

[a] Occasional use of acetaminophen/paracetamol (≤1 g/day) or other medication as approved by study director on a case-by-case basis is allowed. Prohibition and approval on case-by-case basis may both be acceptable terms.

[b] Including, but not limited to, H1N1 and other flu vaccinations.

[c] Including, but not limited to, omeprazole, lansoprazole, cimetidine, ranitidine, and chlorpheniramine. Participants must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator.

6.4 Diet, Fluid, and Activity Control

Participants will remain in the study unit for a total duration of 9 days.

During this confinement period, participants will be given a menu that includes 3 meals and an evening snack, each containing approximately 30% fat (relative to the total calories). The meals served on the PK assessment days should be identical for each cohort in the study. The study menu should be recorded and submitted to the study file with a copy provided to the Sponsor prior to the start of the study. Consumption of the meal will be recorded including if the meal was fully consumed or, if not, the percentage consumed (0, 25%, 50%, or 75%).

If a blood draw or any study procedure coincides with a meal, the blood draw will take precedence followed by the study procedure and then the meal.

Participants will remain upright (seated, standing, or ambulatory) for 4 hours following dose administration, except as necessitated by the occurrence of an AE/or study procedures (eg, obtaining triplicate 12-lead ECG and assessing for orthostatic hypotension). Participants will refrain from strenuous and/or unaccustomed exercise throughout the duration of the study.

6.5 Criteria for Discontinuation or Withdrawal of a Participant

Participants may discontinue or be withdrawn from the study for any of the following reasons:

- Pretreatment event (PTE) or AE for which continued participation imposes an unacceptable risk to the participant's health or the participant is unwilling to continue because of the PTE or AE.
- Positive suicidal ideation and/or behavior during study participation as determined by the C-SSRS assessments.

- Hypotension (ie, systolic < 90 mmHg and/or diastolic < 60 mmHg) with symptoms or orthostatic hypotension (i.e., a decline of ≥ 20mm Hg in systolic or ≥ 10 mmHg in diastolic blood pressure after the sudden change in position from supine to sitting) with or without symptoms.
- Severe injection site reactions.
- Significant protocol deviation: if after randomization or after the first dose of study drug a participant is found to have failed to meet protocol entry criteria or did not adhere to protocol requirements and continued participation poses an unacceptable risk to the participant's health, they will be discontinued from the study.
- Lost to follow-up: a participant will be considered lost to follow-up if they do not return to the clinic and attempts to contact the participant were unsuccessful. Attempts to contact the participant must be documented.
- Voluntary withdrawal: a participant (or participant's legally acceptable representative) may withdraw from the study at any time. The reason for withdrawal, if provided, should be recorded in the electronic case report form (eCRF). Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded. Withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category.
- Study termination: the Sponsor, Institutional Review Board (IRB), or regulatory agency terminates the study based on the criteria in Section 5.5.1.
- Pregnancy: if a participant is found to be pregnant, the participant must be withdrawn immediately.
- Investigator's decision
- Other: the specific reason(s) should be recorded in the "specify" field of the eCRF

7. STUDY PLAN

7.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, participants are to be assessed by the same Investigator or site personnel whenever possible.

7.1.1 Informed Consent Procedure

Informed consent must be obtained prior to the participant entering the study and before any protocol-directed procedures are performed, including requesting that a participant fast for laboratory evaluations. A unique participant identification number (participant ID = site + participant number) will be assigned to each participant at the time that informed consent is obtained; this participant number will be used throughout the study.

7.1.2 Demographics, Medical History, and Medication History Procedure, Screening

Demographic information to be obtained will include age, sex, race as described by the participant, height, weight, caffeine consumption, and smoking status of the participant at Screening.

Medical history to be obtained will include determining whether the participant has any significant conditions or diseases relevant to the participant's safety that stopped at or prior to signing of informed consent.

Medication history information to be obtained includes any medication relevant to eligibility criteria and safety evaluation stopped at or within 28 days prior to signing of informed consent.

7.1.3 Physical Examination Procedure

A full physical examination will occur at the timepoints indicated in Table 1 and will consist of the following body systems: eyes; ears, nose, throat; cardiovascular; respiratory; gastrointestinal; dermatologic; extremities; musculoskeletal; lymph nodes; genitourinary, and neurological.

Any abnormal finding on a pretreatment physical examination assessment must be assessed as not clinically significant or clinically significant by the Investigator and recorded in the source document and eCRF. All clinically significant findings/changes will be recorded as a PTE or concurrent medical condition in the source document.

7.1.4 Weight, Height, and BMI

A participant should have weight and height measured while wearing indoor clothing and with shoes off. The study standard for collecting height is centimeters without decimal places and for weight is kilograms (kg) with 1 decimal place. BMI should be derived as:

Metric: BMI = weight (kg)/height $(m)^2$.

Note that although height is reported in centimeters, the formula uses meters for height; meters can be determined from centimeters by dividing by 100. Thus, for example, if height = 176 cm (1.76 meters) and weight = 79.2 kg, then BMI = 79.2/1.762 = 25.56818 kg/m^2.

The values should be reported to 1 decimal place by rounding. Thus, in the above example BMI would be reported as 25.6 kg/m^2. However, if BMI is used as entry criteria, then this determination must be made after rounding. Measurements will occur on study days indicated in Table 1

7.1.5 Vital Sign Procedure

Vital signs measurements will occur on study days indicated in Table 1 and a the timepoints detailed in Table 4; measurements will include body temperature (oral), supine blood pressure, respiration rate, and heart rate. Heart rate and blood pressure will be measured after 5 minutes supine and again at 1 and 3 minutes after sitting.

When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw. Vital signs may be repeated. All measurements will be recorded on the source documents and in the eCRF. Vital signs taken as safety measures (not protocol-specified) will be recorded as unscheduled.

Table 4. Schedule for Vital Signs Assessments

Vital Signs	Day	Schedule of Assessments
Oral temperature, respiration, HR[a], and BP	Screening, Check-in (Day -1), and Day 1	Predose (within 50 minutes prior to dosing), and at 2, 10, 15, 30, 60, 75, 90, 120, and 360 minutes post-dose.
	Day 2-6	On rising or early termination
	Day 7	Predose (within 50 minutes prior to dosing), and at 2, 10, 15, 30, 60, 75, 90, 120, and 360 minutes post-dose. At early termination
	Day 14 (±2)	As appropriate, if the participant must return to the site for a follow-up visit.

BP = blood pressure; HR = heart rate

[a] Heart rate and blood pressure will be measured after 5 minutes supine and again 1 and 3 minutes after sitting.

7.1.6 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the participant over the counter. All ongoing medications and any medications recently stopped (within 30 days prior to screening will be noted in the eCRF. At each study visit, participants will be asked whether they have taken any

medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF.

7.1.7 Documentation of Concurrent Medical Conditions

Concurrent medical conditions include ongoing conditions or diseases that are present at signing of informed consent and are not considered to affect safety. The condition (ie, diagnosis) should be described.

7.1.8 Electrocardiogram

Triplicate 12-lead ECGs will be recorded after the participant has been supine and at rest for at least 5 minutes and again 1 to 3 minutes after sitting at the times indicated in Table 1. On Days 1, 2, 7, and 8, triplicate 12-lead ECG recordings will occur concurrent to PK sampling timepoints (Table 6) via cardiac telemetry. The PR, RR, QT, and QTcF intervals; QRS duration; and heart rate will be collected. If any ECG abnormalities are identified, a second ECG will be performed to confirm the presence of the abnormality.

7.1.9 Procedures for Clinical Laboratory Samples

Blood samples for clinical laboratory assessments will be collected at timepoints indicated in Table 1. All samples will be collected in accordance with acceptable laboratory procedures. Table 5 lists the tests that will be obtained for each laboratory specimen.

Table 5. Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
Red blood cells White blood cells with differential (absolute counts) Hemoglobin Hematocrit Platelets PT/INR aPTT	ALT Albumin Alkaline phosphatase AST Total bilirubin Direct bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase γ-Glutamyl transferase Potassium Sodium Glucose	pH Specific gravity Protein Glucose Blood Nitrite Leukocyte esterase Ketones Bilirubin Urobilinogen

Hematology	Serum Chemistry	Urinalysis
	Chloride Bicarbonate Calcium	

Diagnostic Screening	
Serum	**Urine/Blood**
HIV Ab test Hepatitis panel, including HbsAg, HBc total Ab, anti-HCV Ab, and HB and or HC viral load, if HBc total Ab and/or HBC Ab are positive COVID-19 Thrombophilia screen, including antithrombin, protein C, protein S, lupus anticoagulant, factor V Leiden, prothrombin gene mutation, anti-β-2-glycoprotein-1 Abs, and anti-cardiolipin Abs Female participants: serum hCG[a] Female participants, if menopause is suspected and not surgically sterile: FSH[b]	Drug screen including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, opiates, and cotinine[c] Female participants: urine hCG[a]

Ab = antibody; ALT = alanine aminotransferase; AST = aspartate aminotransferase; aPTT = activated partial thromboplastin time,; COVID-19 = coronavirus disease 2019; FSH = follicle-stimulating hormone, HB = hepatitis B; HBc = hepatitis B core; HbsAg = hepatits B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; INR = international normalized ratio; PT = prothrombin time.

[a] Serum hCG pregnancy test will be done at Screening and End of Treatment/Early termination, and at the Follow-up Visit if the participant is brought back to the clinic for re-evaluation. Urine hCG pregnancy test will be done at Check-in (Day -1).

[b] FSH level will be obtained for female participants at Screening if they are postmenopausal (ie, no menses for 12 months without an alternative medical cause) and not surgically sterile. The result must be >40 IU/L for the participant to be enrolled.

[c] To be performed at Screening and Check-in Day -1.

The local laboratory will perform laboratory tests for hematology, serum chemistries, and urinalysis. The results of laboratory tests will be returned to the Investigator, who is responsible for reviewing and filing the results. The Investigator or designee is responsible for transcribing or attaching laboratory results to the eCRF. A copy of the laboratory accreditation and the reference ranges for the laboratory used will be maintained by the Investigator.

Laboratory reports must be signed and dated by the Principal Investigator or Subinvestigator indicating that the report has been reviewed and any abnormalities have been assessed for clinical significance. Any abnormalities identified prior to first dose will be clearly and completely documented, including the Investigator's assessment of not clinically significant, before proceeding with enrollment/randomization.

All clinically significant laboratory abnormalities must be recorded as a PTE/AE in the participant's source documents and on the appropriate eCRF. A clinically significant laboratory abnormality that has been verified by retesting will be followed until the abnormality returns to an acceptable level or a satisfactory explanation has been obtained. Participants with liver function test abnormalities after dosing should be followed until resolution or stabilization or the participant is lost to follow-up or withdraws consent.

7.1.10 Assessment of Injection Site Reactions

Injection site reaction (ISR) is defined as any AE that occurs at the study drug injection site. The injection site will be assessed by study personnel prior to and 30 minutes after each study treatment.

7.1.11 Contraception and Pregnancy Avoidance Procedure

From signing of informed consent, throughout the duration of the study, and for 90 days after 5 half-lives have elapsed since the last dose of study drug (ie, 90 days from the Follow-up Call/Visit unless data indicates otherwise), nonsterilized** male participants who are sexually active with a female partner of childbearing potential* must use barrier contraception (eg, condom with spermicidal cream or jelly). In addition, they must be advised not to donate sperm during this period. From signing of informed consent, throughout the duration of the study, and for 30 days after 5 half-lives have elapsed since the last dose of study drug (ie, 30 days from the Follow-up Call/Visit unless data indicates otherwise), female participants of childbearing potential* who are sexually active with a nonsterilized male partner** must use highly effective contraception (< 1% failure rate/year), which has low user dependency. In addition, they must be advised not to donate ova during this period.

Definitions:

*Females NOT of childbearing potential are defined as those who have been surgically sterilized (eg, hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (defined as at least 1 year since last regular menses with a follicle-stimulating hormone (FSH) > 40 IU/L or at least 5 years since last regular menses, confirmed before any study drug is implemented).

**Sterilized males should be at least 1-year post-vasectomy and have confirmed that they have obtained documentation of the absence of sperm in the ejaculate.

A highly effective method of contraception for women of child-bearing potential is defined as one that has no higher than a 1% failure rate per year. The acceptable methods of contraception are:

- Intrauterine device (IUD).
- Bilateral tubal occlusion.
- Vasectomized partner (provided that the partner is the sole sexual partner of the trial participant and that the absence of sperm in the ejaculate has been confirmed).
- Sexual abstinence, if it is the preferred and usual lifestyle of the participant. Participants practicing abstinence as a method of contraception must refrain from heterosexual

intercourse throughout the duration of the study and for 30 days (females) or 90 days (males) after 5 half-lives have elapsed since the last dose of the study drug. This should be interpreted as 30 days (females) or 90 days (males) from the Follow-up Call/Visit unless available data indicates otherwise.

The use of hormonal contraceptives is not recommended for PNA5 studies as there is currently no data on possible drug-drug interactions between PNA5 and hormonal contraceptives.

Participants will be provided with information on acceptable methods of contraception as part of the participant informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova, and sperm donation during the study.

Serum hCG pregnancy tests must be conducted for all female participants at Screening and End of Treatment/Early Termination. In addition to a negative serum hCG pregnancy test at Screening, participants also must have a negative urine hCG pregnancy test prior to receiving any dose of study drug (eg, at Check-in Day -1).

During the course of the study, participants will receive continued guidance with respect to the avoidance of pregnancy and sperm donation as part of the study procedures.

7.1.12 **Pregnancy**

If any participant is found to be pregnant during the study, any Sponsor-supplied drug should be immediately discontinued.

If the pregnancy occurs during administration of active study drug, eg, within 12 weeks of the last dose of active study drug, the pregnancy should be reported immediately, using a pregnancy notification form, to the study contact.

Should the pregnancy occur during or after administration of blinded drug, the Investigator must inform the participant of their right to receive treatment information. If the participant chooses to receive unblinded treatment information, the individual blind should be broken by the Investigator. Participants randomized to placebo need not be followed.

If the female participant or female partner of a male participant agrees to the primary care physician being informed, the Investigator should notify the primary care physician that the participant/male partner of the participant was participating in a clinical study at the time the woman became pregnant and provide details of treatment the participant received (blinded or unblinded, as applicable).

All reported pregnancies will be followed up to 6 weeks after pregnancy termination to include the puerperium (and the neonatal period in the newborn, if applicable) using the pregnancy form. The outcome, including any premature termination, must be reported to the Sponsor. An evaluation after the birth of the child will also be conducted.

7.1.13 Pharmacokinetic Sample Collection

Blood and urine samples will be collected for the determination of concentrations of PNA5 and its metabolites based on the schedule in Table 6. Intensive PK samples will be collected on Days 1 and 7.

Table 6. Collection of Blood and Urine Samples for Pharmacokinetic Analysis

Sample Type	Dosing Day	Time Postdose (minutes)
Plasma	1, 7	Predose (within 15 minutes prior to dosing) and at 5, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 360, 480, and 600 minutes post dose (Days 1 and 7), and 24 hours post dose (Days 2 and 8).
Urine [a]	1, 7	24-hour urine collection (intervals: 0-2, 2-4, 4-6, 6-8, 8-12, 12-24 hours) Bioanalysis samples predose (within 1 hour prior to dosing) and at 60 and 360 minutes post dose.

PK = pharmacokinetic

[a] During 24-hour urine collection intervals during total urine is to be collected, excreted volumes recorded, and a sample taken for bioanalysis.
Note: Depending on the PK profile of PNA5, PK sampling may be expanded with samples 48, 72, and 96h after the last dose; sampling timepoints may be skipped; or their scheduled timing adjusted to optimize PK sample collection.

Blood samples (one 4-mL sample per scheduled time) for PK analysis will be collected into chilled Vacutainers containing anticoagulant (K_2EDTA) and peptidase inhibitors.

Plasma and urine samples for PNA5 will be assessed by high-performance liquid chromatography coupled with tandem mass spectrometry.

7.1.14 Pharmacokinetic Parameters

The PK parameters presented in Table 7 will be calculated for plasma concentration values of PNA5.

Table 7. Pharmacokinetic Parameter Definitions

Symbol/Term	Definition
AUC_{24}	Area under the plasma concentration-time curve from time 0 to 24 hours postdose.
AUC_{τ}	Area under the plasma concentration-time curve during a dosing interval, where tau (τ) is the length of the dosing interval

Symbol/Term	Definition
AUC_{last}	Area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration
AUC_{∞}	Area under the plasma concentration-time curve from time 0 to infinity, calculated as $AUC_{\infty} = AUC_{last}+C_{last/\lambda z}$
$C_{av,ss}$	Average plasma concentration at steady state, calculated as $AUC\tau/\tau$
C_{max}	Maximum observed plasma concentration
$C_{max,ss}$	Maximum observed steady-state plasma concentration during a dosing interval
t_{max}	Time of first occurrence of C_{max}
$t_{1/2}$	Plasma half-life, is the time required for plasma concentration to diminish by 50%

7.1.15 Pharmacodynamic and Immunogenicity Parameters

The following parameters will also be measured in plasma samples:

1. Renin-angiotensin-system metabolites and components: Ang-(1-7)
2. CYP-inhibition, activation assay
3. PNA5 potential immunogenicity including Anti-Drug Antibody (ADA) analysis, Neutralizing Antibody (NAb) assay development and validation.

7.1.16 Documentation of Screen Failure

Investigators must account for all participants who sign informed consent. If the participant is found to be not eligible at this visit, the Investigator should complete the eCRF screen failure form.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Does not meet inclusion criteria or does meet exclusion criteria (specify reason).
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal (specify reason).
- Study termination.
- Other (specify reason).

7.1.17 Documentation of Randomization

Only participants who meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into the treatment phase.

If the participant is found to be not eligible for randomization, the Investigator should record the primary reason for failure on the applicable eCRF.

7.1.18 Assessment of Suicidal Ideation and Behavior

The C-SSRS was developed by researchers at Columbia University as a tool to help systematically assess suicidal ideation and behavior in participants during participation in a clinical trial of centrally-acting drugs (The Columbia Lighthouse Project, 2016). The C-SSRS is composed of 3 questions addressing suicidal behavior and 5 questions addressing suicidal ideation, with sub-questions assessing the severity. The tool is administered via interview with the participant.

The Screening/Baseline C-SSRS will be performed at Screening and Check-in (Day -1) and will assess suicidal ideation and behavior during a participant's lifetime and within the 6 months before Screening. The Since Last Visit C-SSRS will be performed on Day 7 at End of Treatment or Early Termination and at the Follow-up Visit to provide an assessment of suicidal ideation and behavior during treatment.

7.2 Monitoring Participant Treatment Compliance

Study drug will be administered while participants are under observation in the clinical research unit. The date and time of each dose will be recorded in the source documents and on the eCRFs. An inventory of the study drug supplies dispensed will be performed by the site pharmacist or authorized study designee and recorded onto the Drug Accountability Log in the participant's source document records or equivalent. The exact dose time of consecutive participants may be staggered to facilitate logistics at the site.

7.3 Schedule of Observations and Procedures

The schedule for all study-related procedures for all evaluations is shown in Table 1. Assessments should be completed at the designated visit/time point(s). Additional assessments may be conducted or timing of existing assessments may be amended based on emerging safety, PK, or PD data.

7.3.1 Screening

Participants will be screened within 28 days prior to randomization. Procedures to be completed at Screening (all cohorts) include the following:

- Informed consent
- Inclusion/exclusion criteria
- Demographics, medical history, and medication history
- Physical examination, including complete neurological examination

- Vital signs, including temperature and orthostatic changes in blood pressure
- Weight, height, and BMI
- Concurrent medical conditions
- Screening clinical laboratory tests
- HIV and HCV antibodies, hepatitis B surface antigen, hepatitis B and HCV viral load, COVID-19 PCR test
- Thrombophilia screen
- Liver function tests
- FSH (postmenopausal women)
- Serum pregnancy test (hCG) (all female participants)
- Pregnancy avoidance counseling
- Urine drug screen and alcohol breathalyzer
- Triplicate 12-lead ECG
- C-SSRS (Baseline/Screening version)
- Blood sampling for Angiotensin-(1-7), ADA, and CYP characterization
- Pretreatment event assessment

7.3.2 Check-in

Participants will be checked into the study unit 1 day prior to randomization. Procedures to be completed at check-in include the following:

- Physical examination
- Triplicate 12-lead ECG
- Vital signs
- Screening clinical laboratory tests
- HIV and HCV antibodies, hepatitis B surface antigen, COVID-19 PCR test
- Serum and urine pregnancy test (hCG) (all female participants)
- Urine drug screen and alcohol breathalyzer
- Medication history
- C-SSRS
- Pre-treatment event assessment

7.3.3 Treatment Period

The following procedures are to be completed by all cohorts at each study visit:

- Physical examination
- Vital signs, including temperature and orthostatic changes in blood pressure
- Weight, height, and BMI
- Concomitant medications
- Adverse event assessment
- Assessment of injection site at least 30 minutes after study drug administration
- Clinical laboratory tests
- Triplicate 12-lead ECG

- Pharmakokinetic blood and urine sampling
- Blood sampling for Ang-(1-7), ADA, and CYP characterization

7.3.4 End of Treatment

The following procedures are to be completed by all cohorts at End of Treatment (Day 7):

- Physical examination, including complete neurological examination
- Vital signs
- Height, weight, and BMI
- Concomitant medications
- Clinical laboratory tests
- Serum pregnancy test (hCG)
- Pregnancy avoidance counseling
- Triplicate 12-lead ECG
- C-SSRS (Since Last Visit version)
- Pharmacokinetic blood and urine collections
- Adverse event assessment
- Blood sampling for Ang-(1-7), ADA, and CYP characterization

The Investigator must complete the End of Study eCRF page for all participants receiving study drug.

7.3.5 Discharge/Early Termination

In the event of early termination, procedures identified in Table 1 should be conducted. The reason for discontinuation must be documented in the source document and eCRF.

7.3.6 Follow-up Call/Visit

Follow-up assessments are scheduled to occur on Day 14 (±2 days) for all participants to inquire for any ongoing AEs or SAEs, worsening of AEs or SAEs, or development of new AEs or SAEs, and for concomitant medications taken since final dose.

Participants with unresolved SAEs; clinically significant laboratory abnormalities, ECG, or physical examination findings; or at the Investigator's discretion should return to the clinic for appropriate repeat procedure(s).). If a participant returns to clinic, vital signs assessment, C-SSRS assessment, and a pregnancy serum test (if female) will be performed. A follow-up phone call will be made to all other participants on Day 14 (±2) for an assessment of AEs and concomitant medications.

7.4 Blood Volume

Total blood sampling volume for individual participants is shown in Table 8.

Table 8. Approximate Blood Volume

Sample Type	Sample Volume (mL)	Number of Samples per Participant						Total Volume (mL)
		Screening	Study Day					
			-1	1	2	7	8	
Safety Laboratory	10	1	1	1	1	1	1	60
PK	4	--	--	15	1	15	1	128
PD	4	1	--	1		1	--	12
Total Blood Sample Volume (mL)								200

-- = no samples collected; PD = pharmacodynamics; PK = pharmacokinetic

8. PRETREATMENT EVENTS AND ADVERSE EVENTS

8.1 Definitions

8.1.1 Pretreatment events

A PTE is defined as any untoward medical occurrence in a clinical investigation participant who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

8.1.2 Treatment-emergent Adverse Events

A TEAE is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A TEAE can, therefore, be any unfavorable and unintended sign (eg, a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

8.1.3 Additional Points to Consider for Adverse Events

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition.
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the Investigator for any reason.

Pretreatment events/AEs caused by a study procedure (eg, a bruise after blood draw) should be recorded as an AE.

Diagnoses versus signs and symptoms:

Each event recorded should represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as an AE(s).

Laboratory values and ECG findings:

Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory re-test and/or continued monitoring of an abnormal value are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.

If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased creatinine in renal failure), only the diagnosis should be reported as a PTE or as an AE.

Pre-existing conditions:

Participants with pre-existing conditions are not eligible for enrollment into the study.

Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (eg, laboratory tests, ECG, X-rays, etc) should NOT be recorded as PTEs unless related to study procedures. However, if the participant experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (eg, "worsening of…").

If a participant has a degenerative concurrent condition (eg, cataracts, rheumatoid arthritis), worsening of the condition should only be captured as a PTE/AE if it occurs to a greater extent than would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Worsening of PTEs or AEs:

If a participant experiences a worsening or complication of a PTE after starting administration of the study drug, the worsening or complication should be recorded appropriately as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

If the participant experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

8.1.4 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death.
- Is life threatening. The term "life threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event that satisfies any of the following:
  - May require intervention to prevent items 1 through 5 above.

- May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

8.1.5 Severity of Pretreatment Events and Adverse Events

The different categories of intensity (severity) are characterized as follows:

- Mild: The event is transient and easily tolerated by the participant.
- Moderate: The event causes the participant discomfort and interrupts the participant's usual activities.
- Severe: The event causes considerable interference with the participant's usual activities.

8.1.6 Adverse Events of Special Interest

An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for Investigators as to how and when they should be reported to the Sponsor.

Based on Angiotensin-(1-7) agonist class effects, deep vein thrombosis and hypotension (moderate or severe as defined by Common Terminology Criteria for Adverse Events [CTCAE] v5.0) are considered AESIs for this study.

8.1.7 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

- **Related:** An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant drugs and concurrent treatments, may also be responsible.
- **Not Related:** An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant drugs and concurrent treatments.

8.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the Investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

8.1.9 **Start Date**

The start date of an AE/PTE is the date that the first signs/symptoms were noted by the participant and/or physician.

8.1.10 **Stop Date**

The stop date of an AE/PTE is the date at which the participant recovered, the event resolved but with sequelae, or the participant died.

8.1.11 **Action Concerning Study Drug**

The action taken with study drug as a result of an AE include the following categories:

- Drug withdrawn: a study drug is stopped due the AE.
- Dose reduced: study drug dose is reduced due to the AE.
- Dose interrupted: study drug dose is interrupted due to the AE
- Dose not changed: the AE does not require stopping a study drug.
- Unknown – only to be used if it was not possible to determine what action has been taken.
- Not applicable – a study drug is stopped for a reason other than the particular AE eg, the study has been terminated, the participant died, dosing with study drug was already stopped before the onset of the AE.

8.1.12 **Outcome**

The outcome of an AE/PTE includes the following categories:

- Recovered/Resolved: Participant returns to first assessment status with respect to the AE/PTE.
- Recovering/Resolving: the intensity of the AE/PTE is lowered by 1 or more stages; the diagnosis or signs/symptoms have almost disappeared; the abnormal laboratory value improves, but has not returned to the normal range or to baseline; the participant died from a cause other than the particular AE/PTE with the condition remaining “recovering/resolving”.
- Not recovered/not resolved: there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/ symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the participant dies from another cause with the particular AE/PTE state remaining “Not recovered/not resolved.”
- Resolved with sequelae: the participant recovers from an acute AE/PTE but was left with permanent and/or significant impairment (eg, recovered from a cardiovascular accident but with some persisting paresis).

- Fatal: the AE/PTE is considered the cause of death.
- Unknown: the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the participant's participation in the study

8.2 Procedures

8.2.1 Collection and Reporting of AEs

8.2.1.1 PTE and AE Collection Period

Collection of PTEs will commence from the time the participant signs the informed consent to participate in the study and will continue until the participant receives the first dose of study drug or until screen failure. For participants who discontinue prior to study drug administration, PTEs will be collected until the participant discontinues study participation.

Collection of AEs will commence from the time that the participant is first administered study drug and will continue until the follow up visit on Day 14.

8.2.1.2 PTE and AE Reporting

At each study visit, the Investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Participants may report AEs occurring at any other time during the study. Participants experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed-up for the purposes of the protocol.

All participants experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the Investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

- Event term
- Start and stop date and time
- Severity
- Investigator's opinion of the causal relationship between the event and administration of study drug(s) (related or not related) (not completed for PTEs)
- Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure
- Action concerning study drug (not applicable for PTEs)
- Outcome of event

- Seriousness

8.2.1.3 AESI Reporting

If an AESI that occurs during the treatment period or the follow-up period is considered clinically significant at the Investigator's discretion and based on the criteria below, it should be recorded as an AESI on the AE eCRF. The form should be completed and reported to the clinical contract research organization (CRO)/Pharmacovigilance (PV) department within 24 hours. Clinically significant AESIs included:

- Any AESI leading to premature termination
- Deep-vein thrombosis
- Moderate or severe hypotension

8.2.2 Collection and Reporting of SAEs

When an SAE occurs during the AE collection period it should be reported to the Sponsor with as much detail as possible but should contain, at a minimum:

- An event term with a short description of the event and the reason why the event is categorized as serious
- Participant identification number
- Investigator's name
- Name of the study drug(s)
- Causality assessment

The SAE form should be transmitted within 24 hours to the attention of the study contact. Any SAE spontaneously reported to the Investigator following the AE collection period should be reported to the Sponsor if considered related to study participation. Reporting of Serious PTEs will follow the procedure described for SAEs.

8.3 Follow-up of SAEs

If information is not available at the time the first report becomes available, the Investigator should complete a follow-up SAE form at a later date or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (eg, ECGs, laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested

8.3.1 Safety Reporting to Investigators, IRB, and Regulatory Authorities

The Sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, including the US Food and Drug Administration (FDA). Relative to the first awareness of the event by/or further provision to the Sponsor or Sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 calendar days for fatal and life-threatening events and within

15 calendar days for other serious events, as required by the US FDA. The Sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational medicinal product or that would be sufficient to consider changes in the investigational medicinal products administration or in the overall conduct of the trial. The investigational site also will forward a copy of all expedited reports to the IRB in accordance with national regulations.

9. STUDY-SPECIFIC COMMITTEES

No steering committee, data safety monitoring committee, or clinical endpoint committee will be used in this study.

The Sponsor (at a minimum, the clinical science representative, clinical pharmacologist, and pharmacovigilance physician) and the Principal Investigator will review the safety and tolerability data and available PK data for each cohort prior to dosing an additional cohort. The decision for the subsequent dose must be agreed upon by all representatives of the Sponsor and the Principal Investigator. If any one person has concerns regarding subsequent dosing, then this acts as veto and the decision not to proceed with an additional cohort will be escalated to management.

10. DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling and versions of the dictionaries to be used will be documented in the Data Management Plan. Adverse events, PTEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities. Previous and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

10.1 CRFs (Electronic)

Completed eCRFs are required for each participant who signs an informed consent.

The Sponsor or its designee will supply investigative sites with access to eCRFs. The Sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the Sponsor and regulatory authorities. eCRFs must be completed in English. Data is transcribed directly onto the eCRFs.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values. Queries may be issued by the CRO personnel (or designees) and will be answered by the site.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should be included.

The Principal Investigator must review the eCRFs for completeness and accuracy and must sign and date the appropriate eCRFs as indicated. Furthermore, the Investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs.

After the lock of the clinical study database, any change, modification, or addition to the data on the eCRFs should be made by the Investigator with use of change and modification records of the eCRFs. The Principal Investigator must review the data change for completeness and accuracy, and must sign and date. Electronic CRFs will be reviewed for completeness and acceptability at the study site during periodic visits by study monitors.

The Sponsor or its designee will be permitted to review the participant’s medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the Sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the Sponsor.

10.2 Record Retention

The Investigator agrees to keep all records and documents including, but not limited to, study-specific documents, identification log of all participating participants, medical records, temporary media (eg, thermal sensitive paper), source worksheets, all original signed and dated informed consent forms (ICFs), participant authorization forms regarding the use of personal health information (if separate from the ICFs), electronic copy of eCRFs (including the audit

trail), and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the Sponsor or its designees. Any source documentation printed on degradable thermal sensitive paper should be photocopied by the site and filed with the original in the participant's chart to ensure long-term legibility. Furthermore, International Council for Harmonisation (ICH) E6 R2 Section 4.9.5 requires the Investigator to retain essential documents specified in ICH E6 R2 until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 R2 Section 4.9.5 states that the study records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the Investigator and Sponsor.

11. STATISTICAL METHODS

11.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

11.1.1 Analysis Sets

The following analysis sets will be used for presentation of data:

- **Safety Set**: The safety analysis set will consist of all participants who are enrolled and received at least 1 dose of study drug. Participants in this analysis set will be used for demographics, baseline characteristics, and safety summaries.
- **PK Set**: The PK set will consist of all participants who receive at least 1 dose of study drug and have at least 1 measurable plasma concentration or amount of drug in the urine.
- **PD Set**: The PD set will consist of all participants who receive at least 1 dose of study drug and have at least 1 postdose PD measurement.

All data will be presented in the participant listings.

11.1.2 Analysis of Demographics and Other Baseline Characteristics

Data will be presented for each dose level and overall; the participants that received placebo will be pooled across cohorts and summarized in a single placebo group. Descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) will be presented for continuous variables and count and percent will be presented for categorical variables.

Demographic and baseline characteristics include age, height, weight, BMI, sex, ethnicity, and race. Demographic variables of screen failure participants and reasons for screen failures will be summarized overall for participants who are screened, but not enrolled in the study.

Individual demographic characteristics, date of informed consent, and reason for screen failure will be listed.

11.1.3 Pharmacokinetic Analysis

11.1.3.1 Concentrations in Plasma and Urine

The concentration of PNA5 in plasma and amounts excreted in urine will be summarized by day and dose level over each scheduled sampling time (or urine collection interval) using descriptive statistics. Individual plasma concentration data vs time will be presented in a data listing.

11.1.3.2 Pharmacokinetic Parameters

Descriptive statistics (N, arithmetic mean, SD, median, minimum, maximum, geometric mean, and percent coefficient of variation [%CV]) will be used to summarize the plasma and urine PK parameters for PNA5 and Ang(1-7) by Day and dose level.

Dose proportionality will be tested for PNA5 C_{max} and AUCs using a power model. The power fit will be assumed as described by the following equation:

$\ln(\text{PK parameter}) = \beta_0 + \beta_1 \ln(\text{Dose}) + e$

where β_0 is the intercept and β_1 is the slope. Dose proportionality would be declared if the 90% confidence interval (CI) for β_1 lies entirely within the critical region, where r is the ratio of the highest and the lowest dose in this study. This criterion implies that the 90% CI for the ratio of the central values of PK parameter of interest from the highest dose to the lowest dose is contained completely within the bioequivalence range of (0.80, 1.25). Plots of ln(AUC) or $\ln(C_{max})$ vs ln(Dose) may also be used to illustrate dose proportionality or lack of it.

11.1.4 Safety Analysis

All safety data will be presented in listings. Where applicable, safety data will be summarized by placebo, each PNA5 dose level, PNA5 overall, and overall total. Placebo data will be pooled across cohorts.

11.1.5 Adverse Events

All AEs will be coded by system organ class (SOC) and preferred term using Medical Dictionary for Regulatory Activities. TEAEs with onset occurring within 14 days (onset date – last date of dose + 1≤14) after study drug administration will be listed and included in the summary tables. TEAEs will be summarized by SOC and preferred term. The following summary tables will be included in the report: TEAEs, drug-related AEs, AEs by relationship to study drug (related vs not-related), and AEs and related AEs by severity. Data listings will be provided for all AEs including PTE, TEAEs, AEs leading to study drug discontinuation, and SAEs.

Individual results of laboratory tests (hematology, chemistry, and urinalysis), vital signs, and ECGs will be listed and Baseline, post-dose, and changes from Baseline to post-dose laboratory, vital signs, and ECG data will be summarized. Physical examination findings and suicidality assessments (C-SSRS) will be presented in data listings.

11.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

11.3 Determination of Sample Size

The sample size of 8 participants in each cohort (6 active: 2 placebo) is considered to be sufficient for evaluation of safety, tolerability, and PK of each cohort. The sample size was not based on statistical power considerations.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The Investigator and institution will guarantee access to source documents by the Sponsor or its designee (CRO) and by the IRB.

All aspects of the study and its documentation will be subject to review by the Sponsor or designee (as long as blinding is not jeopardized), including, but not limited to, the Investigator's Binder, study drug, participant medical records, informed consent documentation, documentation of participant authorization to use personal health information (if separate from the ICFs), and review of eCRFs and associated source documents. It is important that the Investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

12.2 Protocol Deviations

The Investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study participants. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the Investigator should consult with the Sponsor or designee (and IRB, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the inclusion or exclusion criteria.

The site should document all protocol deviations in the participant's source documents. In the event of a significant deviation, the site should notify the Sponsor or its designee (and IRB, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the participant, or confound interpretation of primary study assessment. A Protocol Deviation Form should be completed by the site and signed by the Sponsor or designee for any significant deviation from the protocol.

Every attempt will be made to collect each PK and/or PD blood sample at the designated time point, and the actual time of each blood sample will be recorded on the source document and eCRF.

13. ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual participants and according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonized Tripartite Guideline for GCP. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and Investigator responsibilities.

13.1 IRB Approval

The IRB must be constituted according to the applicable requirements of the participating region.

The Sponsor or designee will supply relevant documents for submission to the IRB for review and approval of the protocol. This protocol, the Investigator's Brochure, a copy of the ICF, and, if applicable, participant recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to the IRB for approval. The IRB's written approval of the protocol and participant informed consent must be obtained and submitted to the Sponsor or designee before commencement of the study (ie, before shipment of the Sponsor-supplied drug or study specific screening activity). The Sponsor will notify the site and ship drug once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from competent authority to begin the trial. Until the site receives drug, no protocol activities, including screening may occur.

the site must adhere to all requirements stipulated by the IRB. This may include notification to the IRB regarding protocol amendments, updates to the ICF, recruitment materials intended for viewing by participants, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the IRB, and submission of the Investigator's final status report to the IRB. All IRB approvals and relevant documentation for these items must be provided to the Sponsor or its designee. Participant incentives should not exert undue influence on participation. Payments to participants must be approved by the IRB and Sponsor.

13.2 Participant Information, Informed Consent, and Participant Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The ICF describes the planned and permitted uses, transfers, and disclosures of the participant's personal and personal health information for purposes of conducting the study. The ICF further explains the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given.

The ICF will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The Investigator is responsible for the preparation, content, and IRB approval of the ICF. The ICF must be approved by the IRB and the Sponsor prior to use.

The ICF must be written in a language fully comprehensible to the prospective participant. It is the responsibility of the Investigator to explain the detailed elements of the ICF to the participant. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB. In the event the participant is not capable of rendering adequate written informed consent, then the participant's legally acceptable representative may provide such consent for the participant in accordance with applicable laws and regulations.

The participant, or the participant's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the participant, or the participant's legally acceptable representative, determines he or she will participate in the study, then the ICF must be signed and dated by the participant, or the participant's legally acceptable representative, at the time of consent and prior to the participant entering into the study.

The participant or the participant's legally acceptable representative should be instructed to sign using their legal name, not nicknames, using blue or black ballpoint ink. The Investigator must also sign and date the ICF at the time of consent and prior to participant entering into the study; however, the Sponsor may allow a designee of the Investigator to sign to the extent permitted by applicable law.

Once signed, the original ICF will be stored in the Investigator's site file. The Investigator must document the date the participant signs the informed consent in the participant's medical record. Copies of the signed ICF shall be given to the participant.

All revised ICFs must be reviewed and signed by relevant participants or the relevant participant's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the participant's medical record, and the participant should receive a copy of the revised ICF.

13.3 Participant Confidentiality

The Sponsor and designees affirm and uphold the principle of the participant's right to protection against invasion of privacy. Throughout this study, a participant's source data will only be linked to the Sponsor's clinical study database or documentation via a unique identification number. As permitted by all applicable laws and regulations, limited participant attributes, such as sex, age or date of birth, and participant initials may be used to verify the participant and accuracy of the participant's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, FDA, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), and the Sponsor's designated auditors to review the participant's original medical records (source data or documents) including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a participant's study participation, and autopsy reports. Access to a participant's original medical records requires the specific authorization of the participant as part of the informed consent process. Copies of any participant source documents that are provided to

the Sponsor must have certain personally identifiable information removed (ie, participant name, address, and other identifier fields not collected on the participant's eCRF).

13.4 Publication, Disclosure, and Clinical Trial Registration Policy

13.4.1 Publication and Disclosure

The Investigator is obliged to provide the Sponsor with complete test results and all data derived by the Investigator from the study. During and after the study, only the Sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor. The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator.

Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the clinical study site agreement. In the event of any discrepancy between the protocol and the clinical study site agreement, the clinical study site agreement will prevail. The Sponsor may publish any data and information from the study (including data and information generated by the Investigator) without the consent of the Investigator.

13.4.2 Clinical Trial Registration

To ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations, and guidance, the Sponsor will, at a minimum, register interventional clinical trials that it sponsors anywhere in the world on ClinicalTrials.gov.

13.5 Insurance and Compensation for Injury

Each participant in the study must be insured in accordance with the regulations applicable to the site where the participant is participating. If a local underwriter is required, then the Sponsor or Sponsor's designee will obtain clinical study insurance against the risk of injury to clinical study participants. Refer to the clinical study site agreement regarding the Sponsor's policy on participant compensation and treatment for injury. If the Investigator has questions regarding this policy, he or she should contact the Sponsor or Sponsor's designee

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