CLINICAL STUDY PROTOCOL

Protocol title:	A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Hemodynamic Effects, Safety, Tolerability, and Pharmacokinetics of APD418 in Subjects with Heart Failure with Reduced Ejection Fraction
Protocol number:	APD418-201
Version:	Amendment 3.0, dated 26 April 2022
Compound name or number:	APD418
Study phase:	2
EudraCT number:	2020-006131-10
Indication:	Treatment of acute heart failure with reduced ejection fraction (HFrEF)
Sponsor name:	Arena Pharmaceuticals, Inc.
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Sponsor approval:	This protocol was approved by the Sponsor's Responsible Medical Officer or delegate. The electronic signature manifest is appended.

PROTOCOL HISTORY

Document	Amendment Type	Date
Amendment 3.0	Global	26 April 2022
Amendment 2.0	Global	19 October 2021
Amendment 1.3	Country-specific (Greece)	06 October 2021
Amendment 1.2	Country-specific (Serbia)	23 July 2021
Amendment 1.1	Country-specific (Germany)	14 July 2021
Amendment 1.0	Global	09 March 2021
Original Protocol	Not applicable	16 December 2020

PROTOCOL SYNOPSIS

Sponsor: Arena Pharmaceuticals, Inc.

Name of investigational study drug: APD418

Protocol title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Hemodynamic Effects, Safety, Tolerability, and Pharmacokinetics of APD418 in Subjects with Heart Failure with Reduced Ejection Fraction

Protocol number: APD418-201

Phase: 2

Country(ies)/region(s) (planned): United States and Europe

Objectives:

Primary Objective

- To assess the effect of intravenous (IV) infusion of APD418 on hemodynamic status based on cardiac index (CI) in subjects with heart failure with reduced ejection fraction (HFrEF)

Secondary Objectives

- To assess the effect of IV infusion of APD418 on additional hemodynamic, vital sign, and systolic function parameters in subjects with HFrEF
- To assess the pharmacokinetics (PK) of IV infusion of APD418 in subjects with HFrEF
- To assess the safety and tolerability of IV infusion of APD418 in subjects with HFrEF

Exploratory Objectives

- To assess select exposure-response (PK/pharmacodynamic [PD]) relationships in subjects with HFrEF
- To assess the relationships between select subject/disease characteristics and select PD measures in subjects with HFrEF
- To assess the effect of IV infusion of APD418 on markers of renal function in subjects with HFrEF
- To assess the effect of IV infusion of APD418 on cardiac biomarkers in subjects with HFrEF
- To assess the effect of IV infusion of APD418 on additional systolic and diastolic function parameters in subjects with HFrEF
- To assess the effect of IV infusion of APD418 on urine output in subjects with HFrEF
- To assess the effect of IV infusion of APD418 on body weight in subjects with HFrEF
- To assess the OATP genotype

Study Design:

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, single-dose study assessing the hemodynamic effects, safety, tolerability, and PK of APD418 in subjects with HFrEF to be conducted in 2 parts. Each part consists of a Screening Period (up to 21 days for Part A and up to

14 days for Part B), a single dose of randomized study treatment (APD418 or placebo) as a 6-hour IV infusion on Day 1 (Dosing Period) followed by an 18- to 24-hour in-clinic observation period (Postdose Period), and a Follow-Up phone call 7 days (± 2 days) after discharge. Subjects participating in Part A cannot participate in Part B.

On Day 1, potential eligible subjects (per initial Screening criteria) will undergo additional eligibility assessments during the Predose Period. Hemodynamic eligibility criteria based on right heart catheterization (RHC) will be assessed at Baseline for final confirmation of eligibility and randomization. Hemodynamic parameters based on RHC will be assessed at the end of Baseline (after at least a 2-hour stabilization period), during the Dosing Period throughout the study treatment administration (6-hour IV infusion), and for an additional 1 hour after cessation of study treatment administration. Subjects will continue to be observed during the Postdose Period for a minimum of 18 hours after the end of study treatment administration for PD, PK, and safety assessments prior to discharge on Day 2. Subjects will be contacted by phone call for follow-up 7 days (± 2 days) after discharge.

This study has an adaptive design, in which dose escalation in Part A will inform dose expansion in Part B. Part A is a single-ascending dose (SAD) study planned to consist of 5 cohorts. In each cohort, subjects will be randomized to APD418:placebo in a 5:2 ratio. Randomization will be stratified by Screening LVEF (> 25%, ≤ 25%). Following completion of all planned cohorts in Part A, 2 APD418 doses studied in Part A will be selected for expansion in Part B. Part B is a parallel-treatment group study planned to consist of a placebo group and 2 APD418 treatment groups by randomizing additional subjects in 1:1:1 ratio (15 subjects are planned in the placebo group and each APD418 treatment group). Randomization will be stratified by Screening LVEF (> 25%, ≤ 25%) and baseline carvedilol use (yes, no).

Each subject will receive a single dose of study treatment as an IV infusion over a duration of 6 hours. The initial APD418 dose to be studied in the first cohort of Part A will be 0.17 mg/kg/h (total dose 1 mg/kg). After 7 subjects have completed treatment in each cohort in Part A, an assessment of the safety/tolerability and PK data will be conducted by the dose escalation committee (blinded data review by the Sponsor and Investigator representatives) to determine whether dose escalation to the next dose level in Part A can occur. Doses for each subsequent cohort in Part A may be adjusted depending on the safety, tolerability, and PK results of previous cohort(s). The maximum dose in the study will not exceed 2 mg/kg/h (12 mg/kg) without a protocol amendment. At the conclusion of Part A, the dose selection committee will perform safety/tolerability and PD data assessment to identify 2 APD418 doses to be expanded in Part B (unblinded review of Part A data by the Sponsor representatives who are not directly involved in study conduct; site staff and sponsor representatives involved in study conduct will remain blinded throughout the study). Additional details about the dose escalation and the dose selection process are described in Sections 10.6.2 and 11.9. Additional subjects and/or cohorts may be enrolled in the study as described in Sections 6.4 and 11.9. The sample size will not increase by more than approximately 15% without a protocol amendment.

Number of subjects (planned):

Approximately 80 subjects (25 placebo; 55 APD418) are planned to be enrolled in the study. In Part A, 5 cohorts are planned and 7 subjects are planned to be enrolled in each cohort (5 APD418:2 placebo per cohort; total N = 35). In Part B, 2 APD418 doses assessed in Part A will be expanded by enrolling 45 additional subjects (15 subjects are planned in the placebo group and each APD418 treatment group; total N = 45).

Eligibility criteria:

Inclusion criteria:

Subjects must meet all of the following key inclusion criteria to be eligible for enrollment into the study:

- Advanced chronic HFrEF, defined as left ventricular ejection fraction (LVEF) ≤ 35% at Screening, including documented history of HFrEF (LVEF ≤ 35%) for at least 4 months prior to Screening
- New York Heart Association (NYHA) Class II-IV
- CI ≤ 2.5 L/min/m^2 and pulmonary capillary wedge pressure (PCWP) ≥ 15 mm Hg at Day 1
- Males and females 18 to 85 years of age inclusive, at time of informed consent
- Body mass index 18.0 to 37.0 kg/m^2, inclusive, and body weight < 150 kg at Screening and Day 1

Additional inclusion criteria are listed in Section 4.1.

Exclusion criteria:

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

- Hemodynamically unstable at Day 1 or in the opinion of the Investigator likely to progress to becoming hemodynamically unstable during the course of the study
- Treated with inotropes such as dobutamine, dopamine, or milrinone within 72 hours of Day 1 or with levosimendan within 21 days of Day 1, or expected to require therapy with these drugs any time from Day 1 through the end of study conduct
- Treated with IV vasoactive therapy other than inotropic agents listed in Exclusion Criterion 2 or IV diuretic therapy within 24 hours of Day 1, or expected to require IV therapy any time from Day 1 through the end of the in-clinic observation Postdose Period
- Treated with carvedilol at a dose higher than total of 25 mg per day any time within 72 hours of Day 1 through the end of the in-clinic observation Postdose Period
- Use of any other therapy directly acting on the beta-3 adrenergic receptor (β3-AdrR; eg, mirabegron) any time within 14 days of Day 1 through the end of the in-clinic observation Postdose Period
- Use of a phosphodiesterase-5 (PDE5) inhibitor any time within 4 days of Day 1 through the end of the in-clinic observation Postdose Period
- Receiving any mechanical (respiratory or circulatory) or renal support therapy at Screening or Day 1
- Systolic blood pressure (SBP) ≤ 90 mm Hg or ≥ 160 mm Hg at Screening or Day 1
- Heart rate (HR) < 50 beats per minute (bpm) or > 110 bpm at Screening or Day 1
- Patients suffering from current infection or patients that have recovered from recent Coronavirus disease 2019 (COVID-19) infection that in the opinion of the Investigator would prevent the individual from participating in the study due to risk to the scientific validity of study assessments or to the patient's personal well-being

Additional exclusion criteria are listed in Section 4.2.

Test product, dose, and mode of administration:

APD418, the investigational medicinal product, is an IV formulation containing active pharmaceutical ingredient (APD418) provided as 15 mg/mL (adjusted free-base concentration) strength. Diluted APD418 IV solution will be prepared for doses less than 1800 mg.

Subjects assigned to active treatment will receive a single dose as an IV infusion over a duration of 6 hours. The initial APD418 dose to be studied in the Cohort 1 of Part A will be 0.17 mg/kg/h (1 mg/kg). Planned doses for the remaining 4 cohorts in Part A are 0.50, 1.0, 1.5, and 2.0 mg/kg/h or 3, 6, 9, and 12 mg/kg, respectively. Doses for each subsequent cohort in Part A may be adjusted depending on the safety, tolerability, and PK results of previous cohort(s). The maximum dose in the

study will not exceed 2 mg/kg/h (12 mg/kg) without a protocol amendment. At the conclusion of Part A, 2 APD418 doses will be selected for expansion in Part B based on safety/tolerability and PD data. Additional details about the dose escalation and the dose selection process are described in Sections 10.6.2 and 11.9.

Duration of treatment:

This is a single-dose study. Study treatment will be administered only on Day 1 of the study.

Reference therapy, dose, and mode of administration

Placebo will be packaged to match APD418. Volume and mode of administration of placebo will match that of APD418 to maintain the blind.

Endpoints:

Primary endpoint:

Change in CI measured by RHC from Baseline to end of IV infusion at 6 hours

Secondary endpoints:

- Change in the following hemodynamic parameters measured by RHC from Baseline to end of IV infusion at 6 hours:
  - Cardiac output (CO)
  - Pulmonary capillary wedge pressure (PCWP)
  - Right atrial pressure (RAP)
  - Systolic/diastolic pulmonary arterial pressure (PAS/PAD)
  - Pulmonary artery pulsatility index (PAPi)
  - Systemic vascular resistance/systemic vascular resistance index (SVR/SVRI)
  - Pulmonary vascular resistance (PVR)
- Change in the following vital sign parameters from Baseline to end of IV infusion at 6 hours:
  - Systolic blood pressure (SBP)
  - Diastolic blood pressure (DBP)
  - Mean arterial pressure (MAP)
  - Heart rate (HR)
- Change in the following hemodynamic and systolic function parameters measured by echocardiogram (ECHO) from Baseline to end of IV infusion at 6 hours:
  - Stroke volume (SV)
  - SV index (SVI)
  - Left ventricular ejection fraction (LVEF)
  - Fractional shortening (FS)
  - Left ventricular end systolic/left ventricular end-diastolic volume (LVESV/LVEDV) and diameter
  - Left ventricular global longitudinal strain (LVGLS)
  - Left ventricular circumferential strain (LVGCS)
- Change in hemodynamic (measured by RHC) and vital sign parameters listed above at intermediate timepoints during 6-hour IV infusion (during Dosing Period)
- Plasma and urine PK parameters of APD418

- Safety and tolerability of APD418 by incidence of all treatment-emergent adverse events (TEAEs)

Exploratory endpoints:

- Change in hemodynamic parameters (measured by RHC) listed above at 1 hour after end of 6-hour IV infusion (during Postdose Period)
- Change in vital sign, hemodynamic (measured by ECHO), and cardiac systolic function (measured by ECHO) parameters listed above for 18 hours after end of 6-hour IV infusion (during Postdose Period)
- The relationships between select APD418 plasma exposure measures and change in select PD parameters
- The relationships between select subject/disease characteristics (eg, Baseline LVEF, Baseline CI, Baseline SBP, duration of HFrEF, renal function, concomitant medications) and change in select PD parameters
- Change in markers of renal function (estimated glomerular filtration rate [eGFR], blood urea nitrogren [BUN], cystatin C, urine protein/creatinine ratio, urinary sodium excretion)
- Change in cardiac biomarkers (N-terminal pro b-type natriuretic peptide [NT-pro-BNP, high-sensitivity cardiac troponin T [hs-cTnT])
- Change in the following additional systolic and diastolic function parameters measured by ECHO: E, A, E', S', early/late diastolic velocities [E/A] ratio, early mitral filling velocity/early diastolic mitral annular velocity [E/E'] ratio), tricuspid annular plane systolic excursion (TAPSE), tricuspid regurgitation (TR) velocity, and left atrial (LA) volume index
- Change in urine output
- Change in body weight
- The genotype of OATP

Safety Assessments:

Safety assessments will include adverse events (AEs), vital signs, clinical laboratory findings (including hs-cTnT), electrocardiograms (ECGs), physical examinations, and concomitant medications.

Pharmacodynamic Assessments:

Assessments of PD will include change in hemodynamic, vital sign, and cardiac function parameters obtained from RHC and ECHO, cardiac biomarkers (NT-pro-BNP and hs-cTnT), markers of renal function (eGFR, BUN, cystatin C, urine protein/creatinine ratio, and urinary sodium excretion), as well as urine output and body weight. Potential relationship between select subject/disease characteristics (eg, Baseline LVEF, Baseline CI, Baseline SBP, duration of HFrEF, renal function, concomitant medications), and select PD measures (eg, change in CI) may be explored.

Pharmacokinetic Assessments:

Blood samples for plasma PK analysis of APD418 will be collected at the following timepoints in relation to the start of the IV infusion: Baseline (within 2 hours prior to study treatment administration), during the Dosing Period at 0.5, 1, 2, 3, 4, 5, and 6 hours (within 10 minutes before the end of the IV infusion), and during the Postdose Period at 6.083, 6.167, 6.25, 6.5, 7, 8, 10, 18, and 24 hours.

Urine samples will be collected during the following intervals in relation to the start of the IV infusion: Baseline (within 2 hours prior to study treatment administration), 0 to 6 hours, 6 to 10 hours, and 10 to 24 hours.

Statistical methods:

Determination of sample size:

Approximately 80 subjects are planned to be enrolled in this study (35 in Part A, 45 in Part B).

It is assumed that baseline CI, as measured with RHC, is normally distributed with a mean of 2.0 and a standard deviation (SD) of 0.5. Sixty-five evaluable subjects (20 subjects in each of the 2 APD418 treatment groups and 25 in placebo) is sufficient to achieve at least 80% power to detect a treatment effect of 0.45 in favor of APD418 (a clinically significant improvement of 22.5% from placebo) between each of the APD418 treatment groups and placebo by a 2-sample t-test using a 2-sided significance level of 0.05.

The primary analysis will be based on pooled data from subjects in Part A and Part B. There will be 2 APD418 treatment groups of 20 subjects each (planned to consist of 5 subjects from Part A and 15 subjects from Part B) and 1 placebo treatment group of 25 subjects (planned to consist of 10 subjects from Part A and 15 subjects from Part B).

A blinded review of the data to evaluate the assumption regarding the SD of the change in CI may be conducted. The planned sample size will not be reduced as a result of the sample size re-estimation. Details will be specified in the Statistical Analysis Plan (SAP).

Stratification:

In Part A, randomization will be stratified by Screening LVEF (> 25%, ≤ 25%). In Part B, randomization will be stratified by Screening LVEF (> 25%, ≤ 25%) and baseline carvedilol use (yes, no).

Testing strategy:

No formal testing strategy or adjustments of the Type I error will be employed for secondary or exploratory endpoints. Estimates and confidence intervals for treatment groups and from pairwise comparisons will be used in an exploratory manner.

Statistical analyses:

The primary and secondary endpoints will be analyzed using the Full Analysis Set (FAS) and safety endpoints will be performed using the Safety Set. Other important statistical considerations, such as handling missing data imputation strategies, will be described in the SAP.

The primary PD endpoint of the study is the change in CI measured by RHC from Baseline to end IV infusion at 6 hours. The primary PD analysis will be analyzed using a mixed effects model with repeated measures (MMRM) method. The MMRM model will include treatment group, timepoint, interaction of treatment-by-timepoint, and randomization stratification factors as factors, and Baseline CI as a covariate. An unstructured covariance matrix will be specified for the MMRM model. LS means at visit and LS mean differences between treatment group with p-values and corresponding 95% confidence intervals will be reported.

Continuous variables measured at scheduled timepoints will be analyzed using MMRM method. The MMRM model will include treatment group, timepoint, interaction of treatment-by-timepoint, and randomization stratification factor as factors, and Baseline measure as a covariate. An unstructured covariance matrix will be specified for the MMRM model. LS means at visit and LS mean differences between treatment group with p-values and corresponding 95% confidence intervals will be reported.

Unless otherwise specified, continuous endpoints will be analyzed using analysis of covariance (ANCOVA) with a model that includes treatment group and randomization stratification factors as factors and Baseline CI value and other Baseline values as covariates. LS means, Ses, and 95% confidence intervals for the treatments and their difference will be presented together with their p-values.

Where statistical assumptions (eg, normality, proportional odds) are not met, alternative approaches will be evaluated (eg, non-parametric analysis, log transformation).

Details regarding the statistical analyses will be provided in the SAP.

Pharmacokinetic analysis:

PK parameters will be calculated using noncompartmental modeling. Calculated plasma PK parameters will include, but will not necessarily be limited to, area under the plasma concentration-time curve from time 0 to 6 hours (AUC_{0-6}), area under the plasma concentration-time curve from time 0 to time of last quantifiable plasma concentration (AUC_{last}), area under the plasma concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$), maximum observed plasma concentration (C_{max}), terminal elimination half-life ($t_{1/2}$), distribution half-life ($t_{1/2\alpha}$), time to maximum observed plasma concentration (t_{max}), total clearance (CL), volume of distribution based on the terminal phase (Vd_z), volume of distribution at steady state (Vd_{SS}), mean residence time from time 0 to time of last quantifiable plasma concentration (MRT_{last}), average plasma concentration during the dosing interval (C_{ave}). Collected plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, or to assess other actions of APD418 with plasma constituents.

Urinary PK parameters will include, but not be limited to, the amount of unchanged drug excreted during each collection interval from t_1 to t_2 (Ae_{t1-t2}), total amount of unchanged excreted in urine over the collection period (amount excreted [Ae]), renal clearance (CL_r) and the fraction of drug excreted unchanged in the urine, expressed as a percentage of total dose (fraction excreted [F_e]).

Details regarding plasma and urine PK analysis will be provided in the SAP.

PK/PD and subject/disease characteristics/PD analysis:

Potential relationships may be explored between select plasma exposure measures of APD418 or subject/disease characteristics (eg, Baseline LVEF, Baseline CI, Baseline SBP, duration of HFrEF, renal function, concomitant medications) and select PD measures (eg, change in CI).

Safety analyses:

Aes will be listed and summarized by system organ class and preferred term, as well as according to severity and causality/relationship to study treatment. TEAEs will be summarized by cohort and treatment group. In addition, TEAEs will be pooled across treatment groups (ie, placebo, APD418). Observed values for clinical laboratory tests, vital signs, and safety 12-lead ECGs, will be summarized by cohort and treatment group. Individual data listings of clinical laboratory tests results will be presented for each subject. Observed values and changes from Baseline will be summarized descriptively. Safety 12-lead ECG data (observed values and change from Baseline) will be listed for each subject and timepoint. Observed values will be classified for normal, abnormality that is not clinically significant, and clinically significant abnormality by cohort, treatment, and timepoint of collection. Results of other safety assessments will be listed and summarized as appropriate.

Interim Analysis:

No formal interim analysis of efficacy is planned.

Dose Escalation and Dose Selection:

After treatment of each cohort in Part A, an assessment of the safety/tolerability and PK data will be performed by the dose escalation committee (blinded data review by the Sponsor and Investigator representatives) prior to dose escalation to the next dose level in Part A. Doses for each subsequent cohort in Part A may be adjusted depending on the safety, tolerability, and PK results of previous cohort(s).

At the conclusion of Part A, the dose selection committee will perform a safety/tolerability and PD data assessment to identify 2 doses to be expanded in Part B (unblinded review of Part A data by the Sponsor representatives who are not directly involved in study conduct; site staff and sponsor representatives involved in study conduct will remain blinded throughout the study).

Additional details about the dose escalation and the dose selection process are described in Sections 10.6.2 and 11.9.

Additional subjects and/or dose cohorts may be enrolled in the study as described in Sections 6.4 and 11.9.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
ACEI	angiotensin-converting enzyme inhibitor
ADR	adverse drug reaction
Ae	amount excreted
AE	adverse event
$Ae_{t1\text{-}t2}$	amount of unchanged drug excreted during each collection interval from t_1 to t_2
AHF	acute heart failure
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARB	angiotensin receptor blocker
Arena	Arena Pharmaceuticals, Inc.
ARNI	angiotensin receptor neprilysin inhibitor
AST	aspartate aminotransferase
$AUC_{0\text{-}\infty}$	area under the concentration-time curve from time 0 to infinity
$AUC_{0\text{-}6}$	area under the concentration-time curve from time 0 to 6 hours
$AUC_{0\text{-}24}$	area under the concentration-time curve from time 0 to 24 hours
AUC_{last}	area under the concentration-time curve from time 0 to time of the last quantifiable plasma concentration
β-AdrR	beta-adrenergic receptor
β1-AdrR	beta-1 adrenergic receptor
β2-AdrR	beta-2 adrenergic receptor
β3-AdrR	beta-3 adrenergic receptor
β-hCG	beta-human chorionic gonadotropin
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
cAMP	cyclic adenosine monophosphate
C_{ave}	average plasma concentration during dosing interval
CFR	Code of Federal Regulations
CI	cardiac index
CKD-Epi	Chronic Kidney Disease-Epidemiology Collaboration

Abbreviation	Explanation
CL	total clearance
CLr	renal clearance
C_{max}	maximum observed plasma concentration
CMP	Clinical Monitoring Plan
CMR	cardiac magnetic resonance
CNS	central nervous system
CO	cardiac output
COVID-19	Coronavirus disease 2019
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
cTnI	cardiac troponin I
cTnT	cardiac troponin T
CVA	cerebrovascular accident
CYP	cytochrome P450
D5W	5% dextrose in water
DBP	diastolic blood pressure
DDI	drug-drug interaction
DNA	deoxyribonucleic acid
E/A	early/late diastolic velocities
ECG	electrocardiogram
ECHO	echocardiogram
eCRF	electronic case report form
E/E'	early mitral filling velocity/early diastolic mitral annular velocity
eGFR	estimated glomerular filtration rate
FAS	Full Analysis Set
FDA	Food and Drug Administration
F_e	fraction excreted
FS	fractional shortening
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice

Abbreviation	Explanation
HF	heart failure
HFrEF	heart failure with reduced ejection fraction
HIV	human immunodeficiency virus
HOA	healthy older adult
HR	heart rate
hs-cTnI	high-sensitivity cardiac troponin I
hs-cTnT	high-sensitivity cardiac troponin T
HYA	healthy young adult
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICD	implantable cardioverter-defibrillator
ICF	informed consent form
ICH	International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LA	left atrial
LS	least square
LVAD	left ventricular assist device
LVEDV	left ventricular end-diastolic volume
LVEF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume
LVGCS	left ventricular global circumferential strain
LVGLS	left ventricular global longitudinal strain
MAP	mean arterial pressure
MATE	multidrug and toxin extrusion transporter
MedDRA	medical dictionary for regulatory activities
mFAS	modified Full Analysis Set

Abbreviation	Explanation
MMRM	mixed-effects model repeated measures
MRA	mineralocorticoid receptor antagonist
MRT	mean residence time
MRT_{last}	mean residence time from time 0 to time of last quantifiable plasma concentration
NOAEL	no-observed-adverse-effect level
NSTEMI	non-ST-segment elevation myocardial infarction
NT-pro-BNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
OAT3	organic anion transporter 3
OATP	organic-anion-transporting polypeptide
PAD	diastolic pulmonary arterial pressure
PAPi	pulmonary artery pulsatility index
PAS	systolic pulmonary arterial pressure
PCWP	pulmonary capillary wedge pressure
PD	pharmacodynamic(s)
PDE5	phosphodiesterase-5
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PVR	pulmonary vascular resistance
QTc	corrected QT interval
QTcB	corrected QT interval using Bazett's formula
QTcF	corrected QT interval using Fridericia's formula
RAP	right atrial pressure
RHC	right heart catheterization
RNA	ribonucleic acid
RSI	Reference Safety Information
SAD	single-ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SC	subcutaneous
SD	standard deviation

Abbreviation	Explanation
SE	standard error
SOPs	standard operating procedures
STEMI	ST-segment-elevation myocardial infarction
SV	stroke volume
SVI	stroke volume index
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
$t_{1/2}$	terminal elimination half-life
$t_{1/2\alpha}$	distribution half-life
TAPSE	tricuspid annular plane systolic excursion
TBIL	total bilirubin
TEAE	treatment-emergent adverse event
TIA	transient ischemic attack
TK	toxicokinetic
t_{max}	time to maximum observed plasma concentration
TMF	Trial Master File
TR	tricuspid regurgitation
UA	unstable angina
ULN	upper limit of normal
US	United States
UV	ultraviolet
Vd_{ss}	volume of distribution at steady state
Vd_z	volume of distribution based on the terminal phase
WHF	worsening of heart failure
w/v	weight per volume

1. INTRODUCTION

1.1. Disease and Unmet Medical Need

Heart failure (HF) is a clinical syndrome characterized by symptoms (eg, breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (eg, elevated jugular venous pressure, pulmonary crackles, and peripheral edema) caused by structural and/or functional cardiac abnormalities (Ponikowski 2016). HF can result from a number of underlying conditions that damage, weaken, or stiffen the heart leading to compromised cardiac function, including coronary artery disease, myocardial infarction, hypertension, defects in cardiac valves, cardiomyopathies, myocarditis, arrhythmias, or other congenital and chronic conditions (Metra 2017, Ponikowski 2016). Acute heart failure (AHF), a life-threatening clinical condition requiring hospitalization (Ponikowski 2016, Teerlink 2015) is of particular concern in HF patients. In the United States (US) alone, HF is responsible for approximately one million hospitalizations annually and it is the leading cause of hospitalization in the population above the age of 65 (Benjamin 2017, Gheorghiade 2013). Decompensation of chronic HF, characterized by (rapid or gradual) worsening of HF symptoms and signs, accounts for approximately 80% of HF hospitalizations, with a minority of remaining cases presenting as de novo (15%) or end stage (5%) HF (Gheorghiade 2013). Hospitalization for AHF can be caused by the onset or worsening of pathological cardiovascular processes such as myocardial infarction, abnormal heart rhythm or hypertension, or it can be triggered by low treatment adherence or intercurrent illness (Ponikowski 2016, Teerlink 2015). Although in-hospital mortality for patients hospitalized for AHF has improved, post-discharge risk of death continues to be significantly high; in addition, up to 30% of patients are re-hospitalized within 30 days and up to 70% within the first year (Abraham 2008, Chioncel 2017, Crespo-Leiro 2016, Dharmarajan 2015, Gheorghiade 2013, Levy 2002). With each event of decompensation leading to hospitalization, there is associated myocardial and/or renal damage leading to further progression of the disease and resulting in substantially increased risk of death (Gheorghiade 2005, Setoguchi 2007, Solomon 2007). Over 50% of patients hospitalized for AHF have reduced systolic function (ie, heart failure with reduced ejection fraction [HFrEF], defined as left ventricular ejection fraction [LVEF] < 40%) (Adams 2005, Chioncel 2017, Owan 2006, Packer 2017) and these patients exhibit mortality rates of up to 30% in the first year (Choi 2018, Owan 2006).

Patients hospitalized for AHF differ in clinical presentation, with clinical signs/symptoms of congestion (wet or dry) and peripheral hypoperfusion (cold or warm), as well as differences in systolic blood pressure (SBP), guiding the therapeutic approach (Ponikowski 2016). Current first-line management of patients hospitalized due to AHF is focused on identification and treatment of potential co-existing clinical conditions and precipitating factors, immediate stabilization, and symptom relief, as progressive cardiac decompensation can lead to respiratory and/or kidney failure, cardiogenic shock, or death (Metra 2017, Ponikowski 2016, Teerlink 2015). Patients hospitalized for AHF resulting from decompensation of HFrEF can present with decreased cardiac output (CO), causing hypoperfusion, and/or accumulation of fluids (congestion) in the lungs and/or peripheral tissues (Damman 2015, Mebazaa 2015, Ponikowski 2016, Teerlink 2015). Despite advancements in management of chronic HF, options for stabilization of acutely decompensated HFrEF patients are limited. Diuretics are used as first-line therapy to treat volume overload including congestion; vasodilators are also used as first-line therapy for symptom relief in hypertensive patients as well as in non-hypotensive patients who

fail to respond adequately to diuretics (Collins 2015, Mebazaa 2015, Ponikowski 2016). For patients presenting as hypotensive, who are at the highest risk of mortality, treatment options are particularly limited (Nohria 2003, Ponikowski 2016). Improvement of CO in patients with systolic dysfunction presenting with hypotension may require the use of inotropic agents, and currently available inotropic agents that alter intracellular calcium are associated with significant risk of unwanted hemodynamic effects, arrhythmias, and cardiotoxicity, leading to adverse outcomes and increased mortality (Francis 2014, Maack 2019, Mebazaa 2011, Nielsen 2014, Teerlink 2009). Despite their limitations, these agents are often the only available option for these patients (Metra 2017). Furthermore, a large proportion of hospitalized patients do not respond adequately to common therapies such as diuretics (ie, diuretic-resistant) (Felker 2012, Jardim 2019, Shah 2017), which may lead to in-hospital worsening of HF (WHF), requiring additional therapy to adequately recover from an AHF episode. Events of WHF are associated with longer length of hospitalization and significantly greater post-discharge mortality and readmission rates (Butler 2015, Cotter 2014, Cotter 2010, Davison 2015, Kelly 2015, Mentz 2015, Torre-Amione 2009, Weatherley 2009). Given the seriousness of this condition and the lack of targeted therapies with an acceptable safety profile that can be used to improve cardiac performance and provide hemodynamic stabilization, development of new treatment options is of high importance.

APD418 is a new chemical entity in development by Arena Pharmaceuticals, Inc. (Arena) for the treatment of AHF in patients with HFrEF. As a potential first-in-class beta-3 adrenergic receptor (β3-AdrR) antagonist and cardiac myotrope, APD418 is designed to prevent β3-AdrR-mediated repression of cardiac contractility and increase CO while avoiding known adverse events (AEs) associated with currently available inotropes (ie, hemodynamic instability, arrhythmias, and cardiotoxicity). Considering its cardioselective and disease specific mechanism of action, based on targeting the overexpressed β3-AdrR in the failing heart, APD418 represents a promising novel therapeutic approach to improve cardiac performance and provide hemodynamic stabilization in patients with AHF. Study APD418-201 is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study assessing the hemodynamic effects, safety, tolerability, and pharmacokinetics (PK) of APD418 in subjects with HFrEF. The study will be conducted in compliance with the International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements, the study protocol, and where applicable, sponsor and/or contract research organization (CRO) standard operating procedures (SOPs).

1.2. Scientific Background

Beta-adrenergic receptors (β-AdrRs) play a pivotal role in regulating the function of the cardiovascular system, including both the myocardium and the vasculature where they regulate cardiac contractility and vascular tone, respectively (Dessy 2004, Emorine 1989, Gauthier 2000, Simard 1994). In the setting of HF, increased sympathetic activity and circulating levels of catecholamines stimulate beta-1/beta-2 adrenergic receptors (β1/β2-AdrRs) to mediate positive inotropic effects and preserve CO; however, long-term overstimulation of this pathway can negatively influence cardiac function and promote progression of HF (Anker 1998, Bristow 1990, Cohn 1984, Engelhardt 1999, Kaye 1995, Thomas 1978, Viquerat 1985). Unlike β1/β2-AdrRs, β3-AdrR activation exerts a repressive effect on cardiac contractility (Gauthier 1996). Furthermore, in contrast to β1/β2-AdrRs, β3-AdrR is expressed at much lower levels in

non-failing hearts but becomes upregulated in HF and is more resistant to desensitization (Gauthier 1996, Liggett 1993, Moniotte 2001). Owing to its differential expression pattern and resistance to desensitization, β3-AdrR potentially plays a crucial role in the regulation of cardiac function, especially in the setting of HF. In chronic HF, β3-AdrR upregulation and activation serves as a protective mechanism in response to excessive β1/β2-AdrR-mediated positive inotropy by acting as a physiological "brake" to compensate for the sustained sympathetic overstimulation of the adrenergic system caused by elevated levels of circulating catecholamines. However, during events of AHF, the β3-AdrR-mediated negative inotropic effect can be considered maladaptive and promotes unwanted contractile repression that impedes hemodynamic recovery and exacerbates systolic dysfunction (Balligand 2016, Moniotte 2001, Morimoto 2004, Napp 2009, Rozec 2006). In line with this, studies using a selective β3-AdrR antagonist, L-748,337, have demonstrated improved cardiac function in a dog model of ventricular pacing-induced HF (Masutani 2013, Morimoto 2004). Considering the growing evidence supporting the importance of β3-AdrR in modulating cardiac function in patients with HF, β3-AdrR antagonism has been proposed as a potential therapeutic approach in HF (Moniotte 2002). In particular, antagonism of β3-AdrR in the setting of AHF with systolic dysfunction may lead to improved contractility and restored CO, without the unwanted hemodynamic effects and cardiotoxic/arrhythmic potential of existing inotropic agents.

APD418 is a potential first-in-class, highly potent, and selective β3-AdrR antagonist and cardiac myotrope designed to improve myocardial contractility by regulating the activity of troponin I and remediating myofilament calcium sensitivity, without affecting intracellular cyclic adenosine monophosphate (cAMP) and calcium levels associated with stimulation of β1/β2-AdrR pathways, thereby avoiding unwanted effects on myocardial oxygen consumption, heart rate (HR) or blood pressure (Psotka 2019).

1.3. Nonclinical Summary

APD418 is a novel selective β3-AdrR antagonist with high affinity for the human β3-AdrR (over 400-fold greater affinity than for β1- and β2-AdrRs). Functional cAMP assays with recombinantly expressed dog and rat β3-AdrR have demonstrated similar potency and selectivity of APD418 to human β3-AdrR. Primary pharmacology studies indicate that acute intravenous (IV) infusion of APD418 improves cardiac contractile function and increases CO in a canine model of systolic heart failure (HFrEF) induced by sequential coronary microembolization, without any effects on myocardial oxygen consumption, and minimal effect on HR and mean aortic pressure (Sabbah 2019a, Sabbah 2019b). Moreover, APD418 showed improvement in additional measures of systolic functions, as well as diastolic function in the failing heart, and was well tolerated during and after infusion (Sabbah 2019a, Sabbah 2019b). APD418 was also tested on electrically paced human cardiac tissue from HF donors and enhanced the contractile response to catecholamine stimulation (Nguyen 2020).

CCI [redacted]

CCI [redacted]

Definitive Good Laboratory Practice (GLP)-compliant toxicity studies of APD418 administered as a 6-hour and 10-day continuous IV infusion were conducted in the Sprague Dawley rat and beagle dog to assess acute and delayed toxicity, reversibility, and toxicokinetics (TK) of APD418. CCI [redacted]

CCI [redacted] Exposure to APD418 at the no-observed-adverse-effect level (NOAEL; 255 mg/kg) corresponded to maximum observed plasma concentration (C_{max}) and area under the concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$) with respective values approximately 1.6- and 1.4-fold higher than those estimated at the highest clinical dose (25 mg/kg, 4.17 mg/kg/h) administered in Study APD418-101.

CCI [redacted] Exposure to APD418 at the NOAEL (60 mg/kg) corresponded to C_{max} and $AUC_{0-\infty}$ with respective values approximately 0.55- and 0.44-fold lower compared to those

estimated at the highest clinical dose (25 mg/kg, 4.17 mg/kg/h) administered in Study APD418-101.

CCI [redacted] The mean combined sex APD418 C_{max} was 13,000 ng/mL and area under the plasma concentration-time curve from time 0 to time of last quantifiable plasma concentration (AUC_{last}) was 270,000 ng·h/mL on Day 10 at 750 mg/kg/day, the dose at which was considered nonadverse from systemic toxicity findings.

CCI [redacted] the NOAEL was considered to be 30 mg/kg/day (corresponding to mean combined sex APD418 C_{max} of 620 ng/mL and AUC_{last} of 12,500 ng·h/mL on Day 10). The 60 mg/kg/day dose level, a dose level which did not result in adverse systemic toxicity liver or kidney findings, resulted in a corresponding mean combined sex APD418 C_{max} of 1260 ng/mL and AUC_{last} of 25,700 ng·h/mL on Day 10.

APD418 and its metabolites were not clastogenic or genotoxic. Local tolerance to APD418 and the vehicle was demonstrated after IV and perivenous injections to the rabbit ear. Some minor irritation of APD418 was observed after a subcutaneous (SC) injection. There was no erythema or edema observed after administration of APD418. Addition of APD418 (0.0938 to 1.50 mg/mL) to human whole blood had no effect on hemolysis or flocculation/turbidity parameters.

A complete summary of the nonclinical studies that are relevant to the investigational product and its study in human subjects is provided in the current edition of the Investigator's Brochure (IB).

1.4. Clinical Summary

The safety, tolerability, and PK, along with exploratory PD of single-ascending IV doses of APD418 have been evaluated in a Phase 1 study (Study APD418-101; Part A) in heathy young adults (HYA; age 18 to 40) and healthy older adults (HOA; age 50 to 65). The potential for drug-drug interactions (DDIs), based on PK of a single IV dose of APD418 when given with a

single oral dose or after multiple oral doses of rifampin, was also evaluated in healthy adult subjects (Study APD418-101; Part B).

In Part A of the Study APD418-101, study treatment was administered as an IV infusion over 6 hours in 5 cohorts of HYA (0.17, 0.50, 1.67, 2.83, or 4.17 mg/kg/h APD418 or placebo) and 2 cohorts of HOA (0.50 or 1.67 mg/kg/h APD418 or placebo). A total of 37/39 HYA and 15/15 HOA subjects completed treatment. Of those, 30 HYA and 11 HOA subjects received APD418. Safety data for Part A of Study APD418-101 demonstrated an acceptable safety profile for both the HYA and HOA subjects. Of the HYA subjects who received APD418, a total of 15 subjects (50%) reported at least 1 treatment-emergent adverse event (TEAE); TEAEs were reported in 1 (11%) placebo treated HYA subject. The most common TEAEs were related to infusion site events, primarily infusion site pain (8 [27%] APD418 subjects; 0% placebo) and infusion site erythema (4 [13%] APD418 subjects, 0%; placebo). Other common TEAEs included upper respiratory tract infection (2 [7%] APD418 subjects; 1 [11%] placebo), infusion site swelling, infusion site warmth, arthralgia, and dizziness (each event 2 [7%] APD418 subjects; 0% placebo). In general, infusion site TEAEs were more common at higher APD418 doses (46% of subjects across 2.83 and 4.17 mg/kg/h doses), while only 12% of subjects across the range of doses (ie, 0.17, 0.50, and 1.67 mg/kg/h) planned to be studied in Study APD418-201 experienced these events (planned doses for Study APD418-201 range from 0.17 to 2.0 mg/kg/h). Two HOA subjects, 1 subject in each HOA APD418 treatment group, experienced at least 1 TEAE (≤ 20%); no TEAEs were reported in HOA placebo subjects. Treatment was discontinued for 2 HYA subjects (1 subject each in 0.50 and 4.17 mg/kg/h cohorts), who experienced Grade 2 TEAEs at the infusion site, which were considered not related to study drug by the Investigator. No serious adverse events (SAEs) or deaths were reported. There were no clinically significant or concerning findings in vital signs, electrocardiogram (ECG), clinical laboratory (including high-sensitivity cardiac troponin T [hs-cTnT]), and echocardiogram (ECHO) data sets, and overall no clinically identified risks for APD418 in this study.

PK data from Study APD418-101 in healthy human volunteers showed that APD418 plasma concentrations generally increased rapidly during the IV infusion. Visual assessment of plasma concentrations suggested that plasma concentrations close to steady state occurred prior to end of infusion, at which point APD418 demonstrated a rapid decrease in plasma concentrations. Mean residence time (MRT) was ≤ 4 hours and reflects a relatively short residence time of APD418 in the body. Consistent with the short MRT, the area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24}) comprised > 95% of the $AUC_{0-\infty}$ and suggests clearance of most drug from the body by 24 hours postdose. Mean exposure to APD418 increased proportionately with dose. APD418 PK in HOA subjects was similar to HYA subjects at the 3 mg/kg dose level. The 10 mg/kg dose administered to HOA subjects resulted in a small increase (approximately 1.2-fold) in exposure to APD418 in HOA compared to the HYA subjects. APD418 exposures achieved in healthy human volunteers spanned and exceeded the range of pharmacologically active concentrations in the dog model of HF; no clinically identified risks were observed across this exposure range. Renal clearance comprised approximately 15% of total clearance in both HYA subjects and HOA subjects.

1.5. Benefit-Risk Considerations

Nonclinical findings suggest that in the setting of HFrEF, APD418 improves cardiac performance, which in the target population of patients with decompensated HFrEF may lead to faster hemodynamic stabilization. An improved clinical course of recovery is expected to be associated with reduced in-hospital WHF events, including in-hospital death and length of hospitalization, and potentially improvement in clinical outcomes.

In this Phase 2, proof-of-mechanism study, hemodynamic effects will be investigated in stable advanced chronic HFrEF patients (LVEF ≤ 35% for at least 4 months, New York Heart Association [NYHA] Class II-IV). It is anticipated that the population chosen for this study will exhibit elevated expression of β3-AdrR owing to their disease status and medical history (documented history of HFrEF; ie, LVEF ≤ 35% for at least 4 months) and as such could benefit from APD418-mediated improvement in CO. Thus, this population presents a suitable setting for the first-in-patient assessment of the safety, tolerability, and hemodynamic effects of APD418.

As of the date of this protocol, there are no clinically identified risks for APD418. Safety data for Part A of Study APD418-101, in which APD418 was administered as an IV infusion over 6 hours, demonstrated an acceptable safety profile for both the HYA and HOA subjects.

Extended single-dose, GLP-compliant, toxicity studies of APD418 administered as a 6-hour IV infusion were conducted in rats and dogs to assess acute and delayed toxicity, reversibility, and TK. These studies identified the following potential targets of APD418 toxicity: CNS, kidney, liver, and infusion site that demonstrated reversibility and are monitorable in the planned clinical study. Human safety data collected to date in Study APD418-101 have not identified any safety risks (including those observed in nonclinical studies) up to the highest dose administered. Corresponding exposures were approximately 1.8- (C_{max}) to 2.3-fold ($AUC_{0-\infty}$) higher than observed in the dog at the NOAEL.

The safety monitoring practices employed by this protocol (ie, physical examination, vital signs, safety 12-lead ECG, clinical laboratory tests including hs-cTnT, concomitant medications, and AE monitoring) are adequate to monitor and assess subject safety.

The risks of participation are primarily those associated with adverse reactions to the study treatment, although there may also be some discomfort from collection of blood samples and other study procedures.

Further description of identified risks, any potential risks, and the reference safety information for APD418 are provided in the current edition of the IB.

2. OBJECTIVES

Primary Objective

- To assess the effect of IV infusion of APD418 on hemodynamic status based on cardiac index (CI) in subjects with HrEF

Secondary Objectives

- To assess the effect of IV infusion of APD418 on additional hemodynamic, vital sign, and systolic function parameters in subjects with HFrEF
- To assess the PK of IV infusion of APD418 in subjects with HFrEF
- To assess the safety and tolerability of IV infusion of APD418 in subjects with HFrEF

Exploratory Objectives

- To assess select exposure-response (PK/pharmacodynamic [PD]) relationships in subjects with HFrEF
- To assess the relationships between select subject/disease characteristics and select PD measures in subjects with HFrEF
- To assess the effect of IV infusion of APD418 on markers of renal function in subjects with HFrEF
- To assess the effect of IV infusion of APD418 on cardiac biomarkers in subjects with HFrEF
- To assess the effect of IV infusion of APD418 on additional systolic and diastolic function parameters in subjects with HFrEF
- To assess the effect of IV infusion of APD418 on urine output in subjects with HFrEF
- To assess the effect of IV infusion of APD418 on body weight in subjects with HFrEF
- To assess the OATP genotype

3. STUDY DESIGN

3.1. Overall Design

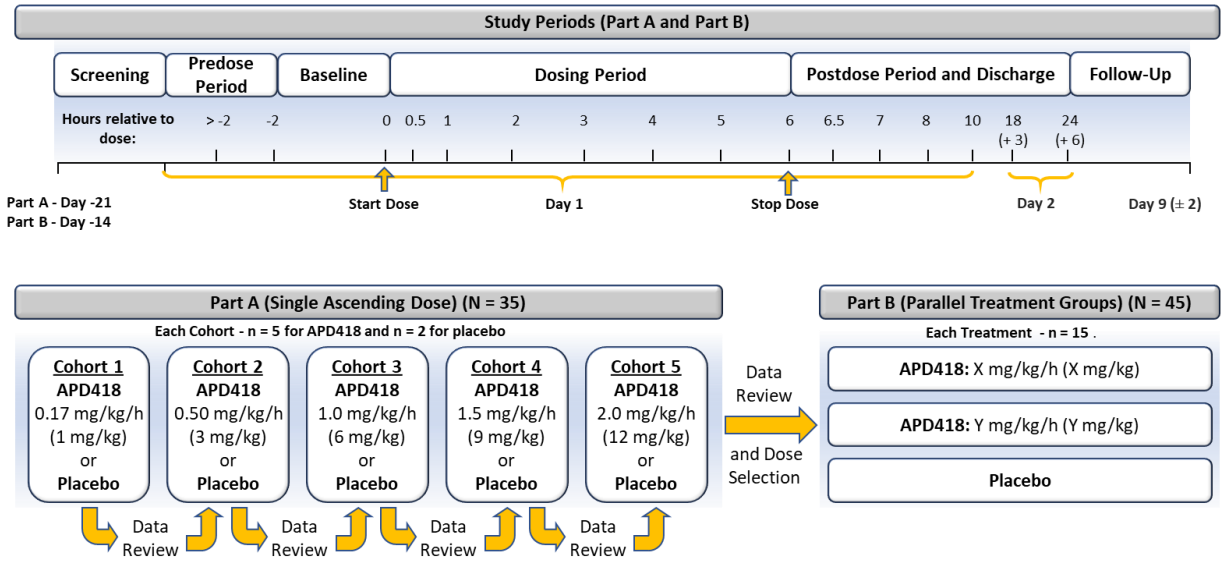
This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled, single-dose study assessing the hemodynamic effects, safety, tolerability, and PK of APD418 in subjects with HFrEF to be conducted in 2 parts (Part A and Part B). Each part consists of a Screening Period (up to 21 days in Part A and up to 14 days in Part B), a single dose of randomized study treatment (APD418 or placebo) as a 6-hour IV infusion on Day 1 (Dosing Period) followed by an 18- to 24-hour in-clinic observation period (Postdose Period), and a Follow-Up phone call 7 days (± 2 days) after discharge (Figure 1). Subjects participating in Part A cannot participate in Part B.

On Day 1, potential eligible subjects (per initial Screening criteria) will undergo additional eligibility assessments during the Predose Period on Day 1. Hemodynamic eligibility criteria based on right heart catheterization (RHC) will be assessed at Baseline for final confirmation of eligibility and randomization. Hemodynamic parameters based on RHC will be assessed at the end of Baseline (after at least 2-hour stabilization period), during the Dosing Period throughout the study treatment administration (6-hour IV infusion), and for an additional 1 hour after cessation of study treatment administration. Subjects will continue to be observed during the Postdose Period for a minimum of 18 hours after the end of study treatment administration for PD, PK, and safety assessments prior to discharge on Day 2. Subjects will be contacted by phone call for follow-up 7 days (± 2 days) after discharge.

This study has an adaptive design, in which dose escalation in Part A will inform dose expansion in Part B. Part A is a single-ascending dose (SAD) study planned to consist of 5 cohorts. In each cohort, subjects will be randomized to APD418:placebo in a 5:2 ratio. Randomization will be stratified by Screening LVEF (> 25%, ≤ 25%). Following completion of all planned cohorts in Part A, 2 APD418 doses studied in Part A will be selected for expansion in Part B. Part B is a parallel-treatment group study planned to consist of a placebo group and 2 APD418 treatment groups by randomizing additional subjects in 1:1:1 ratio (15 subjects are planned in the placebo group and each APD418 treatment group; Figure 1). Randomization will be stratified by Screening LVEF (> 25%, ≤ 25%) and baseline carvedilol use (yes, no).

Each subject will receive a single dose of study treatment as an IV infusion over a duration of 6 hours. The initial APD418 dose to be studied in the first cohort of Part A will be 0.17 mg/kg/h (total dose 1 mg/kg). After 7 subjects have completed treatment in each cohort in Part A, an assessment of the safety/tolerability and PK data will be conducted by the dose escalation committee (blinded data review by the Sponsor and Investigator representatives) to determine whether dose escalation to the next dose level in Part A can occur. Doses for each subsequent cohort in Part A may be adjusted depending on the safety, tolerability, and PK results of previous cohort(s). The maximum dose in the study will not exceed 2 mg/kg/h (12 mg/kg) without a protocol amendment. At the conclusion of Part A, the dose selection committee will perform safety/tolerability and PD data assessment to identify 2 APD418 doses to be expanded in Part B (unblinded review of Part A data by the Sponsor representatives who are not directly involved in study conduct; site staff, and sponsor representatives involved in study conduct will remain blinded throughout the study). Additional details about the dose escalation and the dose selection process are described in Sections 10.6.2 and 11.9. Additional subjects and/or cohorts may be enrolled in the study as described in Sections 6.4 and 11.9. The sample size will not increase by more than approximately 15% without a protocol amendment.

Figure 1: Study Design Schematic



Note: After treatment of each cohort in Part A, an assessment of the safety/tolerability and PK data will be conducted by the dose escalation committee (blinded data review by the Sponsor and Investigator representatives) to determine whether dose escalation to the next dose level in Part A can occur. Doses for subsequent cohorts in Part A may be adjusted depending on the safety, tolerability, and PK results of previous cohort(s). At the conclusion of Part A, the dose selection committee will perform safety/tolerability and PD data assessment to identify 2 APD418 doses to be expanded in Part B (unblinded review of Part A data by the Sponsor representatives who are not directly involved in study conduct; site staff and sponsor representatives involved in study conduct will remain blinded throughout the study). Additional subjects and/or cohorts may be enrolled in the study.
PD, pharmacodynamic; PK, pharmacokinetic

3.2. Scientific Rationale for Study Design

This is a Phase 2, proof-of-mechanism study assessing the hemodynamic effects, safety, tolerability, and PK of APD418 in patients with stable advanced chronic HFrEF (LVEF ≤ 35%, NYHA Class II-IV). Study population will include subjects stabilized following recent hospitalization due to AHF, as well as subjects undergoing RHC for left ventricular assist device (LVAD) or transplant evaluation. These subjects represent the target patient population, with the exception that they are not experiencing an acute decompensation event and thus offer a suitable setting for the first in-patient assessments of hemodynamic effects and the safety/tolerability of APD418. It is anticipated that these subjects will exhibit elevated expression of β3-AdrR owing to their disease status and medical history (documented history of HFrEF, ie, LVEF ≤ 35% for at least 4 months) and as such could experience APD418-mediated improvement in CO. In support of this, APD418 improved cardiac performance in a canine model of pacing-induced heart failure, an HF model that has been shown to exhibit increased β3-AdR expression (Cheng 2001), while minimal effect of APD418 was observed prior to inducing HF (Cheng 2018). In addition, APD418 enhanced contractile response to catecholamine stimulation of human cardiac tissue from HF donors, but did not have any effect on cardiac tissue from healthy donors (Nguyen 2020). APD418 also did not induce any notable effects in non-invasive hemodynamic and ECHO assessments in healthy subjects studied in Study APD418-101. Thus, in order to describe the pharmacodynamic effects of APD418 in humans, it is necessary to evaluate patients who are expected to exhibit increased β3-AdrR expression.

This study has an adaptive design, in which dose escalation in Part A will inform dose expansion in Part B. This study has been designed as a randomized, double-blind, placebo-controlled study to reduce bias and account for placebo effect in the evaluation of hemodynamic effects and the safety/tolerability of APD418. The primary efficacy endpoint of the study will be the change in CI measured by RHC from Baseline to end of IV infusion at 6 hours. Additional PD assessments include: Other hemodynamic and cardiac function parameters assessed with RHC and ECHO, vital sign, cardiac biomarkers (eg, N-terminal pro b-type natriuretic peptide [NT-pro-BNP], hs-cTnT), markers of renal function (estimated glomerular filtration rate [eGFR], blood urea nitrogen [BUN], cystatin C, urine protein/creatinine ratio, and urinary sodium excretion), as well as urine output and body weight. The safety monitoring practices employed by this protocol (ie, physical examination, vital signs, safety 12-lead ECG, clinical laboratory tests including hs-cTnT, concomitant medications and AE monitoring) are adequate to monitor and assess subject safety. Based on available PK data, most (> 95%) of the administered study drug is expected to be eliminated by 24 hours after dosing and therefore subjects will be discharged the next day following all scheduled assessments.

It is expected that the described study design will provide relevant data on hemodynamic effects, safety, tolerability, and PK of APD418, and inform further clinical development of APD418 for treatment of AHF in patients with HFrEF, including the design and dose selection for future clinical studies with APD418 in the AHF setting.

3.3. Rationale for Dose Selection

The initial APD418 dose to be administered in Cohort 1 of Part A will be 0.17 mg/kg/h administered as an IV infusion over a duration of 6 hours (1 mg/kg). Planned doses for the remaining 4 cohorts in Part A are 0.50, 1.0, 1.5, and 2.0 mg/kg/h or 3, 6, 9, and 12 mg/kg, respectively. Doses for each subsequent cohort in Part A may be adjusted depending on the safety, tolerability, and PK results of previous cohort(s). The maximum dose in the study will not exceed 2 mg/kg/h (12 mg/kg) without a protocol amendment. At the conclusion of Part A, 2 APD418 doses will be selected for expansion in Part B based on safety/tolerability and PD data. Additional details about the dose escalation and the dose selection process are described in Sections 10.6.2 and 11.9.

The planned starting dose in this first-in-patient study is 0.17 mg/kg/h administered as an IV infusion over duration of 6 hours (total dose 1 mg/kg). This is 25-fold lower than the highest tested dose in HYA subjects in Study APD418-101, and 10-fold lower than the highest dose tested in HOA subjects. Based on dog pharmacology data, this dose level has potential to demonstrate a low but detectable increase in cardiac function, thus potentially providing some benefit for these subjects. The C_{max} attained with an infusion rate of 0.17 mg/kg/h over 6 hours (1 mg/kg) in healthy volunteers (Study APD418-101) was 407 ng/mL and approximated values observed during a 6-hour IV infusion in the dog model; notable improvement in CO was observed at APD418 at mean C_{max} concentration of approximately 717 ng/mL. Considering low expression of the β3-AdrR in cardiac tissue in healthy subjects, there were no APD418-related effects observed on cardiac function in Study APD418-101.

Estimated exposure to APD418 at the maximal planned dose of 2.0 mg/kg/h over 6 hours (total dose 12 mg/kg) in Study APD418-201 from PK values observed in HOA treated with 1.7 mg/kg/h in Study APD418-101 predicts a C_{max} and $AUC_{0-\infty}$ of approximately 5700 ng/mL

and 39,000 ng·h/mL, respectively. As such, subjects will not be exposed to higher APD418 exposures than previously observed in HYA subjects and only 1.2-fold higher than previously observed in HOA subjects in Study APD418-101. This dose level should provide exposure to APD418 that is about 8-fold higher than the C_{max} (ie, 717 ng/mL) resulting in improvement of cardiac function after 6-hour infusion in the dog pharmacology model and could provide a maximal therapeutic effect. There were no APD418-related safety concerns at doses up to 4.17 mg/kg/h over 6 hours (total dose 25 mg/kg) in Study APD418-101 and corresponding to APD418 exposure is approximately 1.8-fold higher than that expected at the maximal planned dose of 2.0 mg/kg/h (total dose 12 mg/kg) in Study APD418-201. Relative to nonclinical safety evaluations, the estimated APD418 plasma concentrations at the highest planned dose are 0.98-fold to 1.3-fold compared to that observed in the dog (NOAEL) during a 6-hour infusion.

4. STUDY POPULATION

4.1. Inclusion Criteria

Subjects must meet ALL of the following inclusion criteria to be eligible for enrollment into the study:

1. Advanced chronic HFrEF, defined as: LVEF ≤ 35% at Screening, including documented history of HFrEF (LVEF ≤ 35%) for at least 4 months prior to Screening
2. NYHA Class II-IV
3. CI ≤ 2.5 L/min/m^2 and pulmonary capillary wedge pressure (PCWP) ≥ 15 mm Hg at Day 1
4. Males or females 18 to 85 years of age inclusive, at the time of informed consent
5. Body mass index 18.0 to 37.0 kg/m^2, inclusive, and body weight < 150 kg at Screening and Day 1
6. Females must meet either a or b of the following criteria and males must meet criterion c to qualify for the study:

   a. A female who is <u>not</u> of childbearing potential must meet 1 of the following:
      i) Postmenopausal, defined as no menses for 12 months without an alternative medical cause
      ii) Permanent sterilization procedure, such as hysterectomy, bilateral salpingectomy, bilateral tubal ligation, or bilateral oophorectomy.
   b. A female who is of childbearing potential must agree to using a highly effective contraception method per drug/device labels during treatment and for 30 days following treatment that can achieve a failure rate of less than 1% per year when used consistently and correctly. The following methods are considered highly effective birth control methods:
      i) Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, which may be oral, intravaginal, or transdermal.
      ii) Progestogen-only hormonal contraception associated with inhibition of ovulation, which may be oral, injected, or implanted.

iii) Intrauterine device (IUD)
iv) Intrauterine hormone-releasing system (IUS)
v) Vasectomized partner provided that partner is the sole sexual partner of the women of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.
vi) Sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject. Periodic abstinence, such as calendar, symptothermal, and post-ovulation methods, are not acceptable.

c. A male must agree to using a condom with spermicide during treatment and for 90 days following treatment.

7. Willing to provide written informed consent and participate in the study

4.2. Exclusion Criteria

Subjects who meet ANY of the following exclusion criteria will not be eligible for enrollment into the study:

1. Hemodynamically unstable at Day 1 or in the opinion of the Investigator likely to progress to becoming hemodynamically unstable during the course of the study
2. Treated with inotropes such as dobutamine, dopamine, or milrinone within 72 hours of Day 1 or with levosimendan within 21 days of Day 1, or expected to require therapy with these drugs any time from Day 1 through the end of study conduct. Refer to Prohibited Medications List for details.
3. Treated with IV vasoactive therapy other than inotropic agents listed in Exclusion Criterion 2 or IV diuretic therapy within 24 hours of Day 1, or expected to require IV therapy any time from Day 1 through the end of the in-clinic observation Postdose Period. Refer to Prohibited Medications List for details.
4. Treated with carvedilol at a dose higher than total of 25 mg per day any time within 72 hours of Day 1 through the end of the in-clinic observation Postdose Period
5. Use of any other therapy directly acting on the β3-AdrR (eg, mirabegron) any time within 14 days of Day 1 through the end of the in-clinic observation Postdose Period
6. Use of a phosphodiesterase-5 (PDE5) inhibitor any time within 4 days of Day 1 through the end of the in-clinic observation Postdose Period. Refer to Prohibited Medications List for details.
7. Receiving any mechanical (respiratory or circulatory) or renal support therapy at Screening or Day 1

8. SBP ≤ 90 mm Hg or ≥ 160 mm Hg at Screening or Day 1
9. HR < 50 beats per minute (bpm) or > 110 bpm at Screening or Day 1
10. Cardiac troponin (hs-cTnT, high-sensitivity cardiac troponin I [hs-cTnI], cardiac troponin T [cTnT], or cardiac troponin I [cTnI]) > 5× upper limit of normal (ULN) at Day 1
11. Use of any medications or herbal products that are reported potent (moderate-to-strong) clinically relevant inhibitors of P-gp or OATP1B1/3 within 30 days or 5 half-lives (whichever is longer) of Day 1 through the end of the in-clinic observation Postdose Period. Amiodarone is permitted if administered at doses of 200 mg/day or less for the preceding 90 days. Refer to Prohibited Medications List for more details.

    Note: Topical formulations of the above clinically relevant inhibitors of P-gp or OATP1B1/3 are allowed.
12. The use of MATE1 substrates, with the exception of metformin, within 5 half-lives of Day 1 through the end of the in-clinic observation Postdose Period. Refer to Prohibited Medications List for details.
13. Hepatic dysfunction (history of cirrhosis, or abnormal ALT or AST 5-fold greater than the ULN) at Screening
14. Renal insufficiency (eGFR < 25 mL/min/1.73 m^2; calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-Epi] equation) at Screening
15. Any abnormal clinical laboratory (eg, chemistry, hematology), ECG, or physical finding at Screening that in the opinion of the Investigator is deemed clinically significant and that would prevent the individual from participating in the study due to risk to the scientific validity of study assessments or to the patient's personal well-being
16. Pacemaker or implantable cardioverter-defibrillator (ICD) implantation within 4 months of Screening
17. Hospitalization within 3 months of Screening for ST-segment-elevation myocardial infarction (STEMI) or pulmonary embolism, or within 4 weeks of Screening for non-ST-segment elevation myocardial infarction/unstable angina (NSTEMI/UA) or arrythmia
18. Cerebrovascular accident (CVA) or transient ischemic attack (TIA) within 3 months of Screening
19. Conditions that are thought in the opinion of the Investigator to:

a. Increase risk of infusion site reactions; eg, active connective tissue disorder or vasculitis, significant lymphedema affecting vascular access site extremity, history of hyperhomocysteinemia, nephrotic syndrome, or recent history of major trauma or major surgery within 3 months of Screening

b. Compromise subject assessment of the infusion site reactions; eg, extensive tattoos or areas of psoriasis or eczema that impact the selection of infusion site, severe diabetic neuropathy, barriers in communication

20. Any of the following diseases or conditions: Cardiogenic shock, uncorrected severe valvular disease; amyloid cardiomyopathy; hypertrophic obstructive cardiomyopathy; myocarditis; restrictive cardiomyopathy; constrictive pericardial disease; contraindications to pulmonary artery catheter placement (eg, bleeding diathesis, tricuspid or pulmonic valve replacements); endocarditis; intra-cardiac thrombus; or untreated severe ventricular arrhythmia
21. Any history or clinical manifestation of any pulmonary, endocrine, allergic, dermatological, hepatic, renal, hematological, gastrointestinal, neurological or psychiatric disorder, or malignancy (with the exception of treated basal cell carcinomas), as determined by the Investigator, that would prevent the individual from participating in the study due to risk to the scientific validity of study assessments or to personal well-being
22. Patients suffering from current infection or patients that have recovered from recent COVID-19 infection that in the opinion of the Investigator would prevent the individual from participating in the study due to risk to the scientific validity of study assessments or to the patient's personal well-being
23. Females who are pregnant or lactating
24. Known human immunodeficiency virus (HIV) or hepatitis infection
25. Known history of alcohol or substance use disorder within 6 months of Screening
26. Previous participation in a study with APD418
27. Subjects who have received any investigational device or investigational drug within 30 days, or 5 half-lives of the investigational drug (whichever is greater) prior to Day 1

5. SUBJECT RESTRICTIONS

5.1. Restricted Medications

Subjects are to follow the medication restrictions outlined in the Inclusion (Section 4.1) and Exclusion (Section 4.2) criteria from the time of consent through the end of study conduct (until the Follow-Up phone call), unless otherwise specified. A separate Prohibited Medications List with examples of medications that are not allowed in the study will be provided. If such medications are required, consider switching to another medication in the class that is not restricted. Investigators are also advised to refer to the local prescribing information. In addition to local prescribing information, refer to FDA guidance on drug development and drug interactions (FDA 2020).

5.2. Dietary Restrictions

Subjects should be advised to avoid alcohol and caffeine for 12 hours prior to RHC insertion as well as through the completion of the in-clinic observation Postdose Period.

Subjects will be allowed a light meal 2 hours prior to RHC insertion (at least 4 hours prior to Baseline hemodynamic parameters measurements). Another light meal will be provided after the 2-hour assessments are completed. After the end of the RHC assessments, the meals can be provided per the site's standard of care. Fluids will be restricted to no more than 250 mL every 2 hours from RHC insertion through the end of the RHC assessments. The type, amount, and time of consumption will be documented.

If deviations occur, the Investigator or designee in consultation with the Sponsor, if needed, will decide on a case-by-case basis whether the subject may continue participation in the study.

5.3. Other Restrictions

During the RHC assessments, subjects will remain supine, if possible, and awake. After the end of the RHC assessments and through the completion of the in-clinic observation Postdose Period, subjects should remain ambulatory, seated upright, or semi-reclined, except when a supine position is dictated by study procedures or during night rest; subjects may be allowed to rise for brief periods under supervision (eg, to use the toilet facilities).

6. STUDY TREATMENT

6.1. Study Treatment(s) Administered

Study treatments in this study include the pharmaceutical form of the active substance being tested (APD418), and the volume-matched placebo being used as a reference (reference therapy). Study treatment(s) are listed in Table 1.

The subject weight recorded during Predose Period on Day 1 will be used to calculate the study treatment dose.

Table 1: Proposed Study Treatment(s)

Study Treatment	Dose(s)[a]	Mode of Administration	Frequency	Formulation
APD418 (Part A: Cohort 1)	0.17 mg/kg/h (1 mg/kg)	IV infusion	Single 6-hour IV infusion	IV formulation
APD418 (Part A: Cohort 2)	0.50 mg/kg/h (3 mg/kg)	IV infusion	Single 6-hour IV infusion	IV formulation
APD418 (Part A: Cohort 3)	1.0 mg/kg/h (6 mg/kg)	IV infusion	Single 6-hour IV infusion	IV formulation
APD418 (Part A: Cohort 4)	1.5 mg/kg/h (9 mg/kg)	IV infusion	Single 6-hour IV infusion	IV formulation
APD418 (Part A: Cohort 5)	2.0 mg/kg/h (12 mg/kg)	IV infusion	Single 6-hour IV infusion	IV formulation
APD418 (Part B: Dose Group 1)	X mg/kg/h	IV infusion	Single 6-hour IV infusion	IV formulation
APD418 (Part B: Dose Group 2)	Y mg/kg/h	IV infusion	Single 6-hour IV infusion	IV formulation
Placebo (Part A and Part B)[b]	NA	IV infusion	Single 6-hour IV infusion	IV formulation

[a] After treatment of each cohort in Part A, a blinded safety/tolerability and PK data assessment will be conducted by the dose escalation committee to determine whether dose escalation to the next dose level in Part A can occur. Doses for each subsequent cohort in Part A may be adjusted depending on the safety, tolerability, and PK results of previous cohort(s). At the conclusion of Part A, the dose selection committee will perform an unblinded safety/tolerability and PD data assessment to identify 2 APD418 doses to be expanded in Part B. Additional cohorts (to study intermediate or higher doses) and/or additional subjects may be enrolled in the study based upon data reviews from the prior cohorts.

[b] Placebo will follow the same dilution instructions to match the volume of APD418 in the same cohort and mode of administration will match that of APD418.

IV, intravenous; NA, not applicable

6.2. Identity of Study Treatments

6.2.1. APD418

The active study treatment is an IV formulation containing the active pharmaceutical ingredient (APD418) provided as 15 mg/mL (adjusted free-base concentration) strength. Dilution with 5% dextrose in water (D5W) will be carried out for total doses less than 1800 mg. All subjects assigned to active treatment will receive a single 6-hour IV infusion.

6.2.2. Placebo

The placebo will be diluted with D5W to match the APD418 volume administered in the same cohort and mode of administration will match that of APD418.

6.3. Dosage and Administration

Each subject will receive a single dose as an IV infusion (APD418 or placebo) over a duration of 6 hours. The initial APD418 dose to be studied in Cohort 1 of Part A will be 0.17 mg/kg/h (1 mg/kg). Planned doses for the remaining 4 cohorts in Part A are 0.50, 1.0, 1.5, and 2.0 mg/kg/h or 3, 6, 9, and 12 mg/kg, respectively. Doses for each subsequent cohort may be adjusted depending on the safety, tolerability, and PK results of previous cohort(s). The maximum dose in the study will not exceed 2 mg/kg/h (12 mg/kg) without a protocol amendment. At the conclusion of Part A, 2 APD418 doses will be selected for expansion in Part B based on unblinded safety/tolerability and PD data. Additional details about the dose escalation and the dose selection process are described in Sections 10.6.2 and 11.9. Separate cohorts of subjects will be used for each dose level.

The study treatment will arrive at the site blinded and will be administered in a blinded fashion to the subjects. A delegated pharmacist or designee will be responsible for providing APD418 or placebo to the delegated qualified study personnel for administration as per the randomization scheme. Dilution instructions will be provided in a separate pharmacy manual. Placebo and APD418 treatments will be diluted based on the body mass of the subject and the assigned cohort dose level. Study treatment will be administered intravenously. Larger peripheral veins (ie, in the upper forearm) are advised for IV administration and (see Section 4.2). the infusion site will be noted as well as a change in the infusion site, if applicable. Selection of vascular access shall include assessment of the patient's condition of the vasculature at the insertion site and proximal to the intended insertion site, including condition of skin at intended insertion site and history of previous venipunctures and access devices. Areas of flexion or pain on palpation should be avoided as well as veins that are compromised (ie, sclerosed, corded, infiltrated). Additionally, it is advised to avoid extremities with impaired circulation, such as that caused by lymphedema. Hour 0 will correspond to the start of the IV infusion. The exact clock time of the start and end of the IV infusion will be recorded.

The location of IV infusion will be examined prior to start of infusion as well as anytime when a subject reports any relevant signs and symptoms such as swelling, redness, pain, tingling and/or burning sensation etc, which should be reported as AEs when appropriate.

6.3.1. Dose Interruptions

Dose interruptions should be avoided if possible. The IV infusion can be interrupted upon any sign of clinical concern or if a subject complains of pain, burning or stinging sensation at or around the insertion site or anywhere along the venous pathway. Prompt recognition and timely, appropriate action should be instituted to prevent any complication(s) and/or prolonging subject discomfort. If a mechanical issue (eg, occlusion or infiltration of IV lines) is identified or if the peripheral line is not well tolerated, the IV infusion site may be changed to another infusion site or a central line. The IV infusion may be interrupted to address these issues for up to 30 minutes. Following the interruption, the IV infusion should be resumed to complete the planned full

6 hours. However, in the event of an infusion site related AE, the subject may be discontinued from treatment at the discretion of the Investigator, as described in Section 10.6.1.

Subjects experiencing any type of infusion site AE should be closely observed for at least 24 hours after dosing or until symptom resolution, and should be clinically handled in accordance with the standard medical practice and relevant guidelines. At the conclusion of the Postdose in-clinic observation period, subjects who do not achieve complete symptom resolution but are improving and are stable for discharge should be instructed to monitor the affected area.

6.4. Method of Assigning Subjects to Treatment

Each subject will be assigned a unique identification number upon Screening. Eligible subjects will be centrally randomized into the study using an interactive response technology (IRT) system. In Part A, subjects who complete the study Screening assessments and meet all the eligibility criteria will be randomized to study treatment in a 5:2 ratio (APD418:placebo), stratified by Screening LVEF (> 25%, ≤ 25%). In Part B, subjects who complete the study Screening assessments and meet all the eligibility criteria will be randomized to study treatment in a 1:1:1 ratio (2 doses of APD418:placebo), stratified by Screening LVEF (> 25%, ≤ 25%) and baseline carvedilol use (yes, no).

Subject identification numbers will be 12 characters in length, including dashes, 201-CCSS-XXX. The first 3 digits represent the study number, the 4 digits following the first dash represent the combination of country code (CC) and the site number (SS), and the last 3 digits represent the subject number (XXX). Subject numbers will be assigned strictly sequentially at every site as subjects become eligible for enrollment, starting from 001. If a subject withdraws their participation in the study, then their unique subject number cannot be reused.

After the initial 7 subjects in each cohort in Part A have been randomized, subsequent subjects may be screened and, if possible, will not be randomized until the next dose level has been set; however, if it is not possible for the subject to wait for randomization into the subsequent dose cohort, the subject may be enrolled in the current dose cohort.

In Part A, in the event that a subject does not complete at least 4 hours of infusion and scheduled RHC assessments in that period, an additional subject may be allocated within the cohort to the same treatment as the discontinued subject at the discretion of the Sponsor. Additional subject(s) will only be enrolled in cases in which discontinuation was not the result of an AE considered probably related or related to study drug in the opinion of the Investigator, including the following:

- Technical issues resulting in incomplete study treatment administration
- Withdrawal based on subject or Investigator decision (not associated with an AE considered probably related or related to study drug in the opinion of the Investigator)

The sample size will not increase by more than approximately 15% without a protocol amendment.

6.5. Selection and Timing of Dose for Each Subject

This is a single-dose study. Study treatment administration will occur only on Day 1 of the study.

6.6. Blinding

The study treatment will arrive at the site blinded and will be administered in a blinded fashion to the subjects. The delegated pharmacist or designee will be blinded to active/placebo treatment and unblinded to the dose level in Part B of the study. The delegated pharmacist or designee will prepare APD418 or placebo and provide the appropriate study treatment to the blinded delegated qualified study personnel for administration. The Investigator and other clinical staff will be blinded to the treatment and will not be unblinded unless needed for safety reasons. Individuals who are part of the Sponsor's safety team (who are not otherwise involved with study conduct) may be unblinded to the treatment (eg, for the purpose of regulatory reporting). Representatives from the bioanalytical lab responsible for analyzing PK samples during the study will be unblinded to treatment assignments. These individuals will not be involved in the management of the study and will not access other subject data. The identity of specific treatments is not to be disclosed to subjects or to any other study personnel.

After treatment of each cohort in Part A, an assessment of the safety/tolerability and PK data will be conducted by the dose escalation committee (blinded data review by the Sponsor and Investigator representatives) to determine whether dose escalation to the next dose level in Part A can occur. Doses for each subsequent cohort in Part A may be adjusted depending on the safety, tolerability, and PK results of previous cohort(s). If warranted during blinded safety reviews, unblinded data may be reviewed by the dose selection committee, who are not involved in study conduct, to determine if dose escalation can continue. At the conclusion of Part A, the dose selection committee will perform safety/tolerability and PD data assessment to identify 2 APD418 doses to be expanded in Part B (unblinded review of Part A data by the Sponsor representatives who are not directly involved in study conduct; site staff and sponsor representatives involved in study conduct will remain blinded throughout the study).

6.6.1. Procedures for Breaking the Blind Prior to Study Completion

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the study treatment must be known to properly treat the subject.

Treatment assignments should remain blinded unless that knowledge is necessary to determine subject emergency medical care. In the event of a medical emergency, the Investigator has the sole responsibility for determining if unblinding of a subject's treatment assignment is warranted to provide appropriate medical care. Subject safety must always be the first consideration in making such a determination. The IRT is programmed with blind-breaking instructions to guide the Investigator on how to obtain treatment assignment in the event of an emergency unblinding. If a subject's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

6.7. Treatment Compliance

Treatment compliance will be assessed based on the administration of a single IV infusion (APD418 or placebo). The IV infusion will be performed by a delegated qualified personnel. Prior to and following IV infusion, the qualified designee will visually inspect the infusion site and the infusion bag to ensure that the subject has received the entire dose.

The date, time, and duration of the IV infusion will be documented. Comments will be recorded if there are any deviations from the planned IV infusion procedures. In the case of an incomplete dosing (ie, caused by an interruption of IV infusion for longer than 30 minutes) as assessed by the dose administration staff, the Investigator, and/or the Sponsor, the subject will be discontinued from study treatment (Section 8.1).

6.8. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or vaccine that a subject receives from 30 days prior to Screening through Follow-Up phone call must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant therapy.

6.8.1. Allowed Concomitant Therapy

Medications deemed by the Investigator to be appropriate and unlikely to interfere with the scientific validity of the study or personal well-being of the subject and which are not prohibited as indicated in inclusion and exclusion criteria and/or in Section 5.1 are permitted. Concomitant medications, including over-the-counter or prescription therapeutics, natural products, and vitamins, should not be changed during Screening or at any time during the duration of the study, unless medically necessary; such changes will be captured in the eCRF.

Subjects should be on guideline-directed medical therapies, unless documented intolerance or contradiction. Subjects should be maintained on their stable guideline-directed HF therapy, including beta blockers, angiotensin receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor neprilysin inhibitor (ARNI), and/or mineralocorticoid receptor antagonists (MRAs), and the type of medications or the dose should not change unless medically indicated from the time of consent through the end of study conduct (until the Follow-Up phone call). Subjects should have been stabilized on their HF medications for at least 2 weeks prior to Screening, if possible. On the morning of Day 1, subjects should take their morning medications no less than 2 hours prior to RHC insertion, but, if applicable, should withhold their morning diuretic dose.

7. STUDY TREATMENT MATERIALS MANAGEMENT

7.1. Packaging, Labeling, Storage, and Handling

APD418 injectable solution is a terminally sterilized concentrated solution composed of 15 mg/mL (adjusted free-base concentration) active pharmaceutical ingredient (APD418 mesylate hemihydrate) in a 10 mM acetate buffered aqueous solution (pH 4.5 ± 0.7) with glycerin (2.1% weight per volume [w/v]) as a tonicity adjuster. APD418 injectable solution will be provided in clear 20 mL vials with a stopper and flip-off cap seal and packaged in a single-vial carton. Each 20 mL vial contains excess volume to allow withdrawal of 20 mL. The supplied APD418 injection solution should be stored at room temperature (15 to 30°C) and protected from light until use.

The supplied APD418 injectable solution is to be used as is or appropriately diluted by the clinical pharmacy using D5W based on the dosage to be administered. The diluted product is to

be stored at room temperature (15 to 30°C), protected from light and used within 12 hours. If storage time of the diluted product is > 12 hours, this product should be stored refrigerated (2 to 8°C) and used within 24 hours. Hands should be washed with soap and water after handling drug product.

Placebo injection (sterile vehicle, 20 mL fill, 20 mL clear vial) will be supplied in a clear sterile vial, packaged in a single-vial carton, to be stored at room temperature (15 to 30°C), protected from light until use. The diluted placebo is to be stored at room temperature (15 to 30°C), protected from light and used within 12 hours. If storage time of the diluted placebo is > 12 hours, this product should be stored refrigerated (2 to 8°C) and used within 24 hours. Hands should be washed with soap and water after handling placebo.

7.2. Preparation

A separate pharmacy manual will detail the study treatment preparation procedures to be followed for this study.

7.3. Accountability, Retention, and Disposal

The lot numbers and expiration dates (where available) of the study treatment materials supplied will be recorded in the final Clinical Study Report.

The Investigator or qualified designee will maintain accurate records of the receipt of all study treatment materials. In addition, accurate records will be kept regarding when and how much study treatment is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. Study treatment will be reconciled by the Sponsor monitor or contracted designee. The Investigator or qualified designee agrees to provide access to study treatment and study treatment records as required for the reconciliation process to be completed in a timely fashion.

At the conclusion of the study, any unused study treatments will be retained by the study site, returned to the Sponsor or designee, or destroyed, as per Sponsor instructions. If no supplies remain, this fact will be documented in the pharmacy product accountability records. Any remaining supplies that were purchased by study site, such as D5W, will be destroyed. If no supplies remain, this fact will be documented in the pharmacy product accountability records.

8. REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

8.1. Discontinuation of Study Treatment

A subject's study treatment may be discontinued from study treatment for any of the following reasons:

- AE (details described in Section 10.6.1)
- Death
- Investigator decision
- Protocol deviation
- Dose interruption (refer to Section 6.7)
- Withdrawal by subject
- Other

8.2. Discontinuation from the Study

Subjects may discontinue/be discontinued from the study at any time for any of the following reasons:

- AE (details described in Section 10.6.1)
- Death
- Lost to follow-up
- Investigator decision
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject
- Other

A subject may elect to discontinue study participation at any time for any reason without prejudice to their future medical care by the physician or at the institution. When possible, all follow-up procedures specified in protocol Section 9.3 (Follow-Up) and Section 9.4 (Early Termination) should be performed.

If a subject withdraws consent, no further evaluation should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent. The Investigator should make a reasonable attempt to document the specific reason why consent was withdrawn.

8.3. Lost to Follow-Up

A subject will be considered lost to follow-up if all reasonable attempts made by the Investigator and delegated study staff fail to complete the scheduled Follow-Up phone call with the subject. A minimum of 3 attempts must be made to contact the subject. Each attempt must be documented in the subject's records (ie, method of communication, times and dates). If all 3 attempts fail, site must have receipt of a registered letter sent to the subject as the last attempt before considering the subject lost-to-follow-up in the eCRF.

8.4. Premature Termination of the Study or a Study Site

The Sponsor has the right to terminate this study at any time.

The Sponsor must terminate the study for the following reasons:

- At the conclusion of Part A, if none of the evaluated doses demonstrate a favorable safety profile and/or meaningful PD effects, the study will be terminated prior to the conduct of Part B (details described in Section 11.9)
- Upon request of Health Authorities

Reasons for terminating the study may also include, but are not limited to, the following:

- The incidence or severity of AEs in this or other APD418 studies indicates a health hazard to subjects (specific examples of AEs that may indicate a health hazard to subjects and will be evaluated as part of study treatment and dose escalation stopping criteria in this study are described in Sections 10.6.1 and 10.6.2)
- Subject enrollment is unsatisfactory

The Sponsor will notify the Investigator if the study is placed on hold or if the Sponsor decides to discontinue the study. Health authorities and (Independent Ethics Committee[s]/Institutional Review Board[s] [IECs/IRBs]) will be informed about the termination of the study in accordance with applicable regulations.

The Sponsor has the right to replace a study site at any time. Reasons for replacing a study site may include, but are not limited to:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the ICH guidelines for GCP

9. STUDY PERIODS

9.1. Screening

The Screening Period is to occur up to 21 days prior to and including Day 1 (Days –21 to 1) for Part A and 14 days prior to and including Day 1 (Days –14 to 1) for Part B. Screening assessments will be performed as described in the Schedule of Assessments (Table 4). Subjects must sign the informed consent before any study-specific procedure can be performed. Eligible subjects meeting all inclusion/exclusion criteria requirements may be enrolled.

9.2. Treatment Period

On Day 1 during Predose Period (prior to RHC insertion), potential eligible subjects (per initial Screening criteria) will undergo additional assessments for confirmation of eligibility. Following RHC insertion, subjects will enter Baseline stabilization period of at least 2 hours prior to study drug administration, which will occur if the patient is deemed eligible for the study based on observed hemodynamic parameters, as described in Section 10.3.1. Hemodynamic parameters based on RHC will be assessed at the end of Baseline, during Dosing Period throughout the study treatment administration (6-hour IV infusion), and for an additional 1 hour after cessation of study treatment administration. Subjects will continue to be observed during the Postdose Period for a minimum of 18 hours after the end of study treatment administration for PD, PK, and safety assessments prior to discharge on Day 2. Subjects are discharged at the Investigator's discretion based upon clinical presentation (if the patient's clinical state allows) and after all scheduled assessments at Hour 24 (+ 6 hours) have been completed.

Treatment Period (Day 1 and Day 2) assessments are presented in the Schedule of Assessments (Table 4).

9.3. Follow-Up/End of Study

Subjects will be contacted by phone call for follow-up 7 days (± 2 days) after discharge to assess for AEs and changes in concomitant medications. For each subject, study participation is completed once the Follow-Up phone call has been conducted. End of Study is defined as completion of the final Follow-Up phone call for the last subject.

9.4. Early Termination

9.4.1. Early Termination of Study Treatment

Subjects who discontinue study treatment (Section 8.1) prior to the end of the full 6-hour IV infusion should immediately, if possible, complete the Early End of Infusion assessments followed by all Postdose Period/Follow-Up assessments as indicated in the Schedule of Assessments (Table 4).

9.4.2. Early Termination from Study Participation

Subjects who discontinue from participating in the study (Section 8.2; individual missing data points do not count as early discontinuation) should receive the Follow-Up phone call. Site staff should work with subjects who withdraw early to obtain as much follow-up data as possible.

10. STUDY ASSESSMENTS AND PROCEDURES

10.1. Subject Informed Consent

The Investigator, or a person delegated by the Investigator, will obtain written informed consent from each subject before any study-specific activity is performed (refer to Section 12.3).

10.2. Screening and Eligibility

Subject eligibility will be assessed based on protocol inclusion and exclusion criteria. All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria.

Certain Screening and eligibility assessments must be performed on Day 1 prior to randomization, as described in the Schedule of Assessments (Table 4). All other Screening and eligibility assessments must be completed any time within the Screening Period prior to randomization on Day 1, unless otherwise specified (Table 4).

Individuals may qualify for study enrollment following a clinically significant abnormal laboratory test, vital signs, or ECG finding by having that test repeated once with acceptable results as judged by the Investigator (or designee). The Investigator may consult with the Medical Monitor as needed. If additional retests are considered, the Clinical Lead should be consulted, and the outcome of the conversation should be documented.

10.2.1. Rescreening

Subjects who have not been randomized and/or do not meet the remaining inclusion and exclusion criteria may be re-consented and re-screened with a new screening number if the Investigator assesses that the subject is an appropriate candidate for re-screening. The Investigator may consult with the Medical Monitor if there are any questions related to rescreening a subject. Subjects may not be rescreened more than once.

10.2.2. Demography and Other Subject Characteristics

Demographics including year of birth, sex at birth, reproductive status for female subjects, ethnicity, and race as described by the subject will be collected at Screening. Other subject characteristic information such as height and weight will also be collected.

10.2.3. Social History

At Screening, a social history including the amount and duration of tobacco, alcohol, and caffeine use will be collected.

10.2.4. Prior and Ongoing Therapies

All medications and procedures conducted within 30 days prior to the first dose will be recorded at Screening. Updates to medications or procedures prior to dosing should be made as needed.

10.2.5. Medical History/Cardiovascular History

A complete medical history of each subject will be collected and documented at Screening to determine subject eligibility. The history should include baseline disease characteristics relevant to the study, ie, the cardiovascular history including date and details of diagnosis, associated interventional procedures, and/or hospitalizations; blood donations (within 30 days), illnesses, participation in other investigational drug studies, and participation in any medical device clinical investigations will also be documented.

10.2.6. Drugs of Abuse

A standard urine drug screen will be performed on Day 1; however, it is not required to result the urine drug screen prior to randomization. If urine samples for urine drug screen cannot be obtained prior to study treatment administration due to the timing of events as required by subject safety considerations, then it can be obtained after study treatment administration and prior to discharge.

10.2.7. Pregnancy Testing

A serum pregnancy test for beta-human chorionic gonadotropin (β-hCG) will be performed at Screening on women of childbearing potential to determine eligibility. Urine pregnancy test (β-hCG) will be performed, and a negative result is required to be documented, for female subjects of childbearing potential on Day 1 prior to randomization to confirm eligibility as indicated in the Schedule of Assessments (Table 4). In the case of a positive urine β-hCG test, a serum β-hCG test will be performed to confirm pregnancy; only in cases where the serum pregnancy test is negative, can the subject be enrolled in the study.

Women who are surgically sterile or who are postmenopausal are not considered to be of childbearing potential. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

10.2.8. Clinical Laboratory Assessments

Clinical chemistry, hematology, and coagulation parameters assessed at Screening to determine eligibility are identified in Table 2 and in the Schedule of Assessments (Table 4). These assessments will be performed at the central laboratory; however, if it is not possible to obtain central laboratory results for Screening assessments prior to Day 1 (eg, for a subject who is stabilizing during hospitalization for an AHF event), local laboratory assessments may be used instead for determining eligibility at Screening as long as they can be used to confirm all relevant exclusion criteria and the local laboratory panels are comparable to those outlined in Table 2. Central labs should not be collected when using local labs to confirm eligibility.

10.2.9. Urinalysis

Urinalysis parameters assessed at Screening to determine eligibility are identified in Table 2 and in the Schedule of Assessments (Table 4). These assessments will be performed at the central laboratory; however, if it is not possible to obtain central laboratory results for Screening assessments prior to Day 1 (eg, for a subject who is stabilizing during hospitalization for an AHF event), local laboratory assessments may be used instead for determining eligibility at Screening as long as they can be used to confirm all relevant exclusion criteria and the local laboratory

panels are comparable to those outlined in Table 2. Central labs should not be collected when using local labs to confirm eligibility.

10.3. Pharmacodynamic/Hemodynamic Assessments

10.3.1. Right Heart Catheterization Hemodynamic Assessments

During the RHC assessments, an experienced cardiologist or designee will measure the following hemodynamic parameters: CO/CI, PCWP, right atrial pressure (RAP), systolic/diastolic pulmonary arterial pressure (PAS/PAD), systemic vascular resistance/systemic vascular resistance index (SVR/SVRI), pulmonary vascular resistance (PVR), and pulmonary artery pulsatility index (PAPi). Additional hemodynamic parameters may be assessed, if deemed necessary.

RHC measurements of hemodynamic eligibility criteria will be performed at Baseline on Day 1 to determine subject eligibility, no less than 1 hour following RHC insertion. PCWP will be assessed by 2 successive measurements at least 10 minutes apart. CI measurements will be based on the average of 3 individual thermodilution recordings, with no delay between recordings. PCWP and CI measurements are required to be within 10% and 15%, respectively, of each other (Note: The lower value must be within 10% or 15% of the higher value, respectively).

Baseline hemodynamic parameters measurements will be performed after at least 2 hours following RHC insertion and stabilization (and preferably within 1 hour of assessment of hemodynamic eligibility criteria), and immediately before the start of study treatment administration. The Baseline CI measurement will be based on the average of 3 individual thermodilution recordings, with no delay between recordings. Additional recordings may be taken as needed until the final 3 recordings are within 15% of each other (Note: The lower value must be within 15% of the higher value). During Dosing and Postdose Periods, CI measurements will also be based on triplicate thermodilution recordings performed the same way as the Baseline CI measurement.

Additional details regarding the procedures for collection, transfer, and analysis of RHC data will be provided in a separate operation manual by the RHC core lab. Planned timepoints for RHC assessments are provided in the Schedule of Assessments (Table 4).

10.3.2. Vital Signs (Blood Pressure and Heart Rate) Assessments

The following vital sign parameters will be measured as a component of the following PD assessments: SBP, diastolic blood pressure (DBP), mean arterial pressure (MAP), and HR.

Vital signs (SBP, DBP, HR) will be measured and MAP will be calculated. The same equipment should be used whenever possible through the study; however, during the RHC assessment period, the same equipment must be used. During RHC assessments, vital signs should be collected within ± 5 minutes of hemodynamic parameter measurements. For subjects with atrial fibrillation, HR should be assessed by pulse measurement over at least 30 seconds.

Planned timepoints for SBP, DBP, and HR assessments are provided in the Schedule of Assessments (Table 4).

10.3.3. Echocardiography Assessments

During the ECHO assessments, an experienced sonographer will measure cardiac structure and function, including the following hemodynamic and cardiac function parameters: Stroke volume (SV), SV index (SVI), LVEF, fractional shortening (FS), left ventricular global longitudinal strain (LVGLS), left ventricular circumferential strain (LVGCS), left ventricular end-systolic/left ventricular/end-diastolic volume (LVESV/LVEDV), E, A, E', S', early/late diastolic velocities (E/A) ratio, early mitral filling velocity/early diastolic mitral annular velocity (E/E') ratio, tricuspid annular plane systolic excursion (TAPSE), tricuspid regurgitation (TR) velocity, and left atrial (LA) volume index.

LVEF at Screening will be assessed by ECHO to determine subject eligibility; however, historical LVEF can be assessed by other modalities (eg, cardiac magnetic resonance imaging (CMR), computed tomography (CT), nuclear imaging, catheterization).

Additional details regarding the procedures for collection, transfer, and analysis of ECHO data will be provided in a separate operation manual by the ECHO core lab. Planned timepoints for ECHO assessments are provided in the Schedule of Assessments (Table 4).

10.3.4. Markers of Renal Function, Urine Output, and Body Weight

The following markers of renal function will be measured: eGFR (calculated using the CKD-Epi equation), BUN, cystatin C, urine protein/creatinine ratio, and urinary sodium excretion (Table 2). These assessments will be based on blood and spot urine sampling.

Blood samples for eGFR to determine subject eligibility will be assessed centrally during the Screening Period; however, if it is not possible to obtain central laboratory results for Screening assessments prior to Day 1, local laboratory assessments may be used instead for determining eligibility (Section 10.2.8). At all other timepoints eGFR analysis will be performed by the central laboratory. Detailed instructions regarding blood and urine sample collection, processing, shipping, and analysis for markers of renal function will be provided in a separate laboratory manual. The planned timepoints for blood/urine collection are provided in the Schedule of Assessments (Table 4).

Urine output will be assessed during prespecified intervals by having the subject empty his/her bladder and capturing the urine volume at timepoints indicated in the Schedule of Assessments (Table 4), beginning with Baseline (subjects will be asked to void prior to RHC insertion) followed by 2-hour intervals during the IV infusion (Dosing Period). During the Postdose Period, urine output will be measured during the following intervals in relation to the start of the IV infusion: 6 to 10 hours and 10 to 24 hours. Any urine collected during the spot urine sampling should be accounted for in the total volume of the appropriate interval. During these intervals, the urine samples will be pooled for assessment of both urine volume and PK assessments (Section 10.4).

Body weight will be evaluated as indicated in the Schedule of Assessments (Table 4).

10.3.5. Cardiac Biomarkers

The following cardiac biomarkers will be measured: NT-pro-BNP and hs-cTnT (Table 2).

Blood samples for cardiac troponin (hs-cTnT, hs-cTnI, cTnT, or cTnI) to determine subject eligibility will be assessed locally during the Predose Period, and in certain circumstances during the Screening Period (Section 10.2.8). At all other timepoints hs-cTnT analysis will be performed by the central laboratory. Detailed instructions regarding blood sample collection, processing, shipping, and analysis for cardiac biomarkers will be provided in a separate laboratory manual. Planned timepoints for blood collection are provided in the Schedule of Assessments (Table 4).

10.4. Pharmacokinetic Assessments

Blood samples for plasma PK analysis of APD418 will be collected at the following timepoints in relation to the start of the IV infusion: At Baseline (within 2 hours prior to the start of study treatment administration), during the Dosing Period at 0.5, 1, 2, 3, 4, 5, and 6 hours (within 10 minutes before the end of the IV infusion), and during the Postdose Period at 6.083, 6.167, 6.25, 6.5, 7, 8, 10, 18, and 24 hours, as indicated by PK blood sample footnote in the Schedule of Assessments (Table 4). Detailed instructions regarding sample collection, processing, and shipping will be provided in a separate laboratory manual.

Pooled urine samples for PK analysis of APD418 will be collected during the following intervals in relation to the start of the IV infusion: Baseline (within 2 hours prior to the start of study treatment administration), during Dosing Period (0 to 6 hours), and during Postdose Period at the same intervals as for urine output (6 to 10 hours and 10 to 24 hours), as indicated in Section 10.3.4 and the Schedule of Assessments (Table 4). Any extra urine collected during the spot urine sampling (Section 10.3.4) should be included in the above pools. Detailed instructions regarding sample collection, processing, and shipping will be provided in a separate laboratory manual.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

10.5. Safety Assessments

Safety assessments include assessment of AEs, vital signs, clinical laboratory tests (including hs-cTnT), ECGs, physical examinations, and concomitant medications.

Planned timepoints for all safety assessments are provided in the Schedule of Assessments (Table 4).

10.5.1. Vital Signs

Resting vital signs measurements will be performed with the subject in the supine or seated position (rest time at least 5 minutes prior to collection of vital signs) and include HR, blood pressure (BP), body temperature, and respiratory rate. Vital signs will be measured prior to any blood draws that occur at the same study visit or overlapping timepoint. For subjects with atrial fibrillation, HR should be assessed by pulse measurement over at least 30 seconds.

Planned timepoints for vital signs assessments are provided in the Schedule of Assessments (Table 4).

10.5.2. Physical Examinations

A physical examination will be performed by a licensed physician or designee per the site's standard of care (including examination of general appearance, skin/dermatologic, lymph nodes, head, eyes, ears, nose and throat, neck, chest, thorax/lungs, and the following systems: Cardiovascular, gastrointestinal, neurologic, hematologic, and musculoskeletal). Abbreviated physical examination includes examination of general appearance, thorax/lungs, cardiovascular system, and abdomen, as well as assessments of any changes in the subject's health since the last examination.

Planned timepoints for physical examinations are provided in the Schedule of Assessments (Table 4). A symptom-based physical exam may also be performed at the Investigator's discretion at any time during the study.

10.5.3. Electrocardiography

All ECGs will be recorded from a 12-lead ECG machine. Every attempt should be made to ensure the subject ECG readings are obtained using the same machine throughout the study. Intervals to be provided on the confirmed read for each safety ECG are RR, PR, QRS, QT, QTc, corrected QT interval using Bazett's formula (QTcB), and corrected QT interval using Fridericia's formula (QTcF). All ECGs will be recorded with subjects in supine position (rest time at least 5 minutes prior to collection). If applicable, it is recommended to collect ECGs at least 30 minutes after the end of the subject's most recent meal.

The Investigator will be responsible for review and interpretation of ECGs on site for eligibility purposes and for determining if the ECG is normal, abnormal clinically insignificant, or abnormal clinically significant and recording any clinically relevant worsening from Baseline occurring during the study in the AE section of the eCRF. ECGs will also be analyzed by the core lab. Both local and central reports must be filed with the source documents.

Planned timepoints for ECGs are provided in the Schedule of Assessments (Table 4).

10.5.4. Clinical Laboratory Assessments

All clinical laboratory assessments will be analyzed by a central laboratory unless otherwise stated. Details regarding clinical laboratory sample collection, preparation, and shipment of central lab samples will be provided in the laboratory manual by the central laboratory. Refer to Table 2 for the list of clinical laboratory tests to be performed and the Schedule of Assessments (Table 4) for timing and frequency for each test.

Lab results that are invalid, or appear to be invalid, should be repeated when possible. If lab tests used to determine subject eligibility are invalid, the tests may be repeated to determine subject eligibility as judged by the Investigator (or designee) (ie, it is not required to screen-fail a subject prior to repeating the lab test).

Central laboratory reports and, when applicable, local laboratory reports used for Screening and eligibility purposes must be filed with the source documents. The Investigator must review all the laboratory reports from the local and central laboratory, document the review, and record any clinically relevant changes on the AE section of the eCRF. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition. All laboratory

tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or Baseline, or are no longer considered clinically significant by the investigator or Medical Monitor.

In cases when laboratory values from non-protocol-specified assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the Investigator (eg, AE or dose modification), then the details must be documented on the AE section of the eCRF.

Table 2: Clinical Laboratory Tests

Pregnancy Testing	**Coagulation**
Serum and urine pregnancy test beta-human chorionic gonadotropin (β-hCG, female subjects only)	Prothrombin time (PT) Activated partial thromboplastin time (aPTT) International Normalized Ratio (INR) Thrombin time Fibrinogen/Fibrin Fibrin degradation products (FDP) Functional plasminogen
Urinalysis	**Hematology**
Appearance Bilirubin Color Glucose Ketones Microscopic examination of sediment Nitrite Occult blood pH Protein Specific gravity Urobilinogen Leukocyte esterase	Hematocrit Hemoglobin Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean corpuscular volume (MCV) Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential
Serum Chemistry	
Albumin Alkaline phosphatase (ALP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Bicarbonate Blood urea nitrogen (BUN) Calcium Chloride Creatinine Creatine kinase Glucose	Lactate dehydrogenase (LDH) Phosphorus Potassium Sodium Thyroid-stimulating hormone (TSH) Total bilirubin Direct bilirubin Total cholesterol Total protein Triglycerides Uric acid
Cardiac Biomarkers	**Renal Function Biomarkers**
High-sensitivity cardiac troponin T (hs-cTnT) N-terminal pro b-type natriuretic peptide (NT-pro-BNP)	Estimated glomerular filtration rate (eGFR) Cystatin C Blood urea nitrogen (BUN) Urine protein/creatinine ratio Urinary sodium excretion

Exploratory Inflammatory and Endothelial Biomarkers	
Pro-inflammatory cytokines (tumor necrosis factor-alpha [TNF-α], interleukin [IL]-1β, IL-6) high-sensitivity C-reactive protein (hs-CRP) Vascular adhesion molecule 1 (VCAM-1)	Vascular endothelial growth factor (VEGF) Von Willebrand factor (VWF)
Drugs of Abuse	
Opiates Amphetamines Barbiturates	Benzodiazepines Cocaine metabolites Cannabinoids
Additional Tests	
Optional organic anion transporting polypeptide (OATP) genotypic analysis	

10.5.4.1. Clinical Chemistry, Hematology, and Coagulation

Clinical chemistry, hematology, and coagulation parameters to be assessed during the study are identified in Table 2. Planned timepoints for collection of samples is provided in the Schedule of Assessments (Table 4).

10.5.4.2. Exploratory Inflammatory and Endothelial Biomarkers

Exploratory inflammatory and endothelial biomarkers to be assessed during the study are identified in Table 2. Planned timepoints for collection of samples is provided in the Schedule of Assessments (Table 4).

10.5.4.3. Urinalysis

Urinalysis parameters to be assessed during the study are identified in Table 2. Planned timepoints for collection of samples is provided in the Schedule of Assessments (Table 4).

10.5.5. Adverse Events

10.5.5.1. Definitions

10.5.5.1.1. Adverse Event

An AE is any untoward medical occurrence that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs can include, but are not limited to, any of the following:

- Unfavorable changes in general condition
- Subjective or objective signs/symptoms
- Concomitant disease or accidents
- Clinically relevant adverse changes in laboratory parameters over the course of the study

- Pre-existing conditions that worsen in severity, increase in frequency, or have new signs/symptoms

10.5.5.1.2. Serious Adverse Event

An AE should be classified as an SAE if it meets one of the following criteria:

Fatal:	The AE resulted in death.
Life-threatening:	The AE placed the subject at immediate risk of death. This classification does not apply to an adverse event that hypothetically might cause death if it were more severe.
Hospitalization:	The AE required or prolonged an existing inpatient hospitalization. Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this definition.
Disabling/ incapacitating:	The AE resulted in a persistent or significant incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	An adverse outcome in a child or fetus of a subject exposed to the study treatment before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

10.5.5.1.3. Adverse Drug Reaction

An adverse drug reaction (ADR) in the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established, is any noxious and unintended response to a medicinal product related to any dose. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (ie, the relationship cannot be ruled out).

10.5.5.1.4. Severity

The severity of each AE will be assessed at the onset by a nurse/or physician. When recording the outcome of the adverse event the maximum severity of the AE experienced will also be recorded. The severity of each AE will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE):

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care activities of daily living (eg, preparing meals, shopping for groceries or clothes, using the telephone, managing money).
Grade 4:	Life-threatening consequences, urgent intervention indicated.
Grade 5:	Death related to adverse event.

10.5.5.1.5. Relationship

The Investigator is obligated to assess the relationship (causal relationship) between the study treatment and each occurrence of each AE. The AE relationship (causal relationship) to study treatment must be characterized as one of the following categories:

Not Related:	The AE does not follow a reasonable temporal sequence from administration of the drug, does not abate upon discontinuation of the drug, does not follow a known or hypothesized cause-effect relationship, and (if applicable) does not reappear when the drug is reintroduced, furthermore, there may exist a clear alternative medical explanation (eg, underlying disease state) or association with study procedure or study conduct.
Unlikely Related:	The temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
Probably Related:	The AE follows a reasonable temporal sequence from administration of the drug and cannot be reasonably explained by the known characteristics of the subject's clinical state, environmental, or toxic factors, or other modes of therapy administered to the subject.
Related:	The AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to the study treatment administration should be considered and investigated. The Investigator should consult the IB and the Product Information of marketed products within the drug class, when applicable. For each AE, the Investigator must document in the medical notes that he/she has reviewed the adverse event and has provided an assessment of causality. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor; however, the Investigator should always make an initial assessment of causality for every event before the initial transmission of the SAE to the Sponsor. The Investigator may change his/her opinion of causality based on subsequent receipt of information and send an SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.5.5.2. Eliciting, Recording, and Reporting Adverse Events

10.5.5.2.1. Eliciting Adverse Events

Subjects will be instructed that they may report AEs at any time. An open-ended or nondirected method of questioning should be used at each study visit to elicit the reporting of AEs.

10.5.5.2.2. Recording Adverse Events

The AE reporting period for safety surveillance begins when the subject is initially included in the study (date of first signature of informed consent) and continues up to 30 days after the last study treatment administration. If an AE is not resolved or stabilized by this time, the Sponsor in consultation with the Investigator will decide whether to continue to monitor the AE or closeout the event in the database if no further follow-up is necessary.

Investigator and study personnel will record all AEs and SAEs whether received through an unsolicited report by a subject, elicited during subject questioning, discovered during physical examination, laboratory testing, and/or other means by recording them on the eCRF and SAE Report Form, as appropriate. The following information should be recorded on the AE eCRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment or other causality
- Outcome

Any SAE suspected to be related to the study treatment must be reported whenever it occurs, irrespective of the time elapsed since the last study treatment administration.

For SAEs, events occurring secondary to the primary event should be described on the SAE Report Form in the narrative description of the case.

The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on both the SAE Report Form and eCRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

10.5.5.2.3. Diagnosis Versus Signs or Symptoms

In general, the use of a unifying diagnosis is preferred to the listing out of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical textbooks. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate adverse event.

10.5.5.3. Reporting Serious Adverse Events

All SAEs are subject to reporting requirements.

10.5.5.3.1. Serious Adverse Events

All SAEs, whether or not considered related to study treatment, must be reported to the Sponsor Contact **immediately, without undue delay, and under no circumstances later than 24 hours of becoming aware of the event**. In addition, a completed report using the Sponsor's SAE Report Form must be submitted within 24 hours of notification to the designated Sponsor Contact.

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Phone: +1-866-599-1341

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If additional follow-up information is required or becomes available for a previously reported SAE, the new information should be reported to the designated Sponsor Contact **within 24 hours of awareness.**

Elective hospitalization and/or surgery for clearly preexisting conditions (eg, a surgery that has been scheduled prior to the subject's entry into the study) will not be reported as an SAE. All other hospitalizations, including elective hospitalizations for any condition that was not preexisting, will be reported as an SAE.

Any SAE that is ongoing when the subject completes the study or discontinues the study will be followed by the Investigator until the event resolves, stabilizes or returns to baseline status.

10.5.5.3.2. Serious, Unexpected Adverse Drug Reactions

All ADRs that are both serious and unexpected are subject to expedited reporting to regulatory agencies and will be reported in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries. An unexpected ADR is one for which the nature or severity is not consistent with information in the relevant source documents.

The following documents or circumstances will be used (*by the Sponsor*) to determine whether an adverse event/ADR is expected:

1. For a medicinal product not yet approved for marketing in a country, the Reference Safety Information (RSI) section of a company's IB will serve as the source document in that country.
2. Reports that add significant information on specificity or severity of a known, already documented serious ADR constitute unexpected events. For example, an event more specific or more severe than described in the RSI in the IB would be considered "unexpected".

10.5.6. Pregnancy

Details of all pregnancies in female subjects and female partners of male subjects will be collected after the start of study treatment and until 90 days after the end of study treatment.

Pregnancy (during maternal or paternal exposure to study treatment) does not meet the definition of an adverse event; however, to fulfill regulatory requirements, any pregnancy and/or pregnancy

outcome should be reported via the **Pregnancy Report Form** to the designated Sponsor Contact **within 24 hours of awareness.**

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and should be reported as such even if outside the SAE reporting period.

10.6. Safety-Related Stopping Criteria

10.6.1. Study Treatment Stopping Criteria

Study treatment will be discontinued per subject and the subject will follow procedures described in Section 9.4.1 if the following safety-related criteria occur:

- A subject experiences an AE of arrythmia or hemodynamic instability, which is not tolerated and is considered probably related or related to study drug in the opinion of the Investigator
- A subject experiences a complication related to an infusion site reaction and/or the RHC procedure, which in the opinion of the Investigator puts subject safety at risk

10.6.2. Dose Escalation Stopping Criteria

Safety data will be monitored in a blinded manner on an ongoing basis throughout the duration of the study. After treatment of each cohort in Part A, an assessment of the safety/tolerability and PK data will be conducted by the dose escalation committee (blinded data review by the Sponsor and Investigator representatives) to determine whether dose escalation to the next dose level in Part A can occur. Doses for each subsequent cohort in Part A may be adjusted depending on the safety, tolerability, and PK results of previous cohort(s).

The dose escalation committee will use the following safety-related criteria per cohort to preclude escalation to the next planned dose level in Part A:

- Two or more subjects experience an SAE considered probably related or related to study drug in the opinion of the Investigator and the dose selection committee
- Two or more subjects experience an AE Grade 3 or higher related to clinical instability associated with hemodynamic/arrhythmia events requiring intervention (pharmacologic or mechanical) considered probably related or related to study drug in the opinion of the Investigator
- Two or more subjects experience a CNS-associated AE Grade 3 or higher considered probably related or related to study drug in the opinion of the Investigator
- Three or more subjects experience an infusion site related AE Grade 3 or higher considered probably related or related to study drug in the opinion of the Investigator
- Two or more subjects experience a clinically significant increase in ALT or AST, and TBIL, indicative of drug-induced liver injury. For subjects with values < 2× ULN prior to dosing, this criterion is met with ALT or AST ≥ 3 × ULN, and TBIL ≥ 2 × ULN, following study treatment administration. For subjects with values ≥ 2 × ULN prior to dosing, a 100% increase from baseline values meets the criterion

- Two or more subjects experience clinical worsening of renal function requiring intervention (pharmacologic or mechanical; eg, intensification of diuretic treatment due to renal function deterioration or the need for dialysis)
- Mean cohort C_{max} exceeds 5700 ng/mL and/or $AUC_{0-\infty}$ with the 6-hour infusion exceeds 39,000 ng·h/mL

In addition to the safety-related dose escalation stopping criteria listed above, the dose escalation safety committee will review overall safety (including AEs, clinical laboratory, and vital sign/ECG data) and PK data of each cohort when deciding whether to escalate to the next planned dose level in Part A.

If warranted during blinded safety reviews, unblinded data may also be reviewed by the dose selection committee, who are not involved in study conduct, to adjudicate relatedness of SAEs or assess overall subject safety and determine if dose escalation can continue.

In the event that dose escalation cannot occur as planned, alternative (lower) dose(s) may be explored in the subsequent cohort(s) in Part A (details described in Section 11.9).

10.7. Maximum Blood Volume

Blood sample collection during RHC assessments must be performed via indwelling catheter. Standard venipuncture may be used for blood collection during other study periods.

The maximum amount of blood collected from each subject over the duration of the study, including planned PK and planned clinical laboratory samples will not exceed 260 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

10.8. Procedures for Overdose

The current version of the IB should be referenced for overdose procedures.

10.9. Pharmacogenomic and Future Analyses

10.9.1. Pharmacogenomic Samples

Participation in the genetic testing portion of the study is optional. Subjects who do not wish to participate in the genetic research may still participate in the study. A blood sample will be collected at Baseline only from the subjects who give consent to participate in the genetic research. The sample will be utilized to determine OATP genotype.

The biological material will be stored at a secure laboratory designated by the Sponsor for up to 10 years after the study is completed. In addition to analyses performed during the study, samples will be saved for potential future exploratory research aimed at identifying/exploring genetic variations and response to APD418 that may affect its PK, pharmacodynamics, safety, or tolerability, if warranted. The Sponsor and CRO involved in the clinical conduct, bioanalytical analyses, PK and/or statistical analyses of the data will have access to the samples and the data that result from the analysis, if performed. Samples will not be submitted to a public database. By signing the informed consent form (ICF), subjects agree to the possible future analysis of these samples. At any time, the subjects can contact the clinical staff to request destruction of their residual samples after the required assessments are completed.

Details on processes for collection, labeling, shipment, and destruction of pharmacogenomic samples are provided in a separate laboratory manual.

10.9.2. Future PK and Biomarker Research

Any residual plasma and/or urine from PK sample collection will be stored by the Sponsor or bioanalytical facility for up to 3 years (or according to local regulations) after the closing of the study and may be used for future drug related research such as profiling of drug binding proteins, bioanalytical method development and validation purposes, stability assessments, metabolite assessments, or to assess other actions of the drug with plasma constituents. The analyses will only focus on analytes and/or additional biomarkers to further study the disposition and efficacy of APD418 and/or its mechanism of action. No disease/conditions, deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) will be the focus of these analyses. Samples will not be submitted to a public database. The Sponsor and CROs involved in the clinical conduct and analyses of the samples/data will have access to the samples and/or the data that result from the analyses, if performed. At any time, the subjects can contact the clinical staff to request destruction of their residual samples after the required assessments are completed.

11. PLANNED STATISTICAL METHODS

11.1. General Considerations

Details regarding the statistical analyses will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to database lock and unblinding.

Continuous variables will be summarized using the number of observations, mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Continuous variables measured at scheduled timepoints will be analyzed using a mixed-effects model with repeated measures (MMRM) method. The MMRM model will include treatment group, timepoint, interaction of treatment-by-timepoint, and randomization stratification factors as factors, and Baseline measure as a covariate. An unstructured covariance matrix will be specified for the MMRM model. Least square (LS) means at visit and LS mean differences between treatment group with p-values and corresponding 95% confidence intervals will be reported.

Unless otherwise specified, continuous endpoints will be analyzed using analysis of covariance (ANCOVA) with a model that includes treatment group and randomization stratification factors as factors, and Baseline CI value and other Baseline value as covariates. The LS means, standard errors (SE), and 95% confidence intervals for the treatments and their difference will be presented together with their p-values.

Categorical endpoints will be analyzed by either the Cochran-Mantel-Haenszel method, Fisher's exact test, or by logistic regression with a model that includes treatment group and randomization stratification factors as factors, and Baseline CI value and other and Baseline value as covariates. The odds ratio relative to placebo and percentage of difference from placebo will be presented together with corresponding 95% confidence intervals and the p-value.

Where statistical assumptions (eg, normality, proportional odds) are not met, alternative approaches will be evaluated (eg, non-parametric analysis, log transformation).

Efficacy data will be analyzed by randomized treatment, while safety data will be analyzed by actual treatment.

11.2. Determination of Sample Size

Approximately 80 subjects are planned to be enrolled in this study (35 in Part A and 45 in Part B). It is assumed that CI, as measured with RHC, from Baseline to end of infusion is normally distributed with a mean of 2.0 and SD of 0.5. Sixty-five evaluable subjects (20 subjects in each of the 2 APD418 treatment groups and 25 in placebo) is sufficient to achieve at least 80% power to detect a treatment effect of 0.45 in favor of APD418 (a clinically significant improvement of 22.5% from placebo) between each of the APD418 treatment groups and placebo by a 2-sample t-test using a 2-sided significance level of 0.05.

The primary endpoint analysis will be based on pooled data from subjects in Part A and Part B. There will be 2 APD418 treatment groups of 20 subjects each (planned to consist of 5 subjects from Part A and 15 subjects from Part B) and one placebo treatment group of 25 subjects (planned to consist of 10 subjects from Part A and 15 subjects from Part B).

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11.3. Stratification

In Part A, randomization will be stratified by Screening LVEF (> 25%, ≤ 25%). In Part B, randomization will be stratified by Screening LVEF (> 25%, ≤ 25%) and baseline carvedilol use (yes, no).

11.4. Analysis Sets

The primary and secondary endpoints will be analyzed using the Full Analysis Set (FAS) and safety endpoints will be performed using the Safety Set. For purposes of analysis, the following populations are defined (Table 3).

Table 3: Analysis Sets

Analysis Set	Description
Full Analysis Set (FAS)	The FAS will include all randomized subjects, irrespective of whether they received any study treatment.
Modified Full Analysis Set (mFAS)	The mFAS will include all randomized subjects who receive any study treatment and have a baseline measurement and at least 1 post-baseline measurement. The mFAS is endpoint specific, therefore subjects included in the analysis set for one endpoint may differ from another endpoint, based on the baseline and post-baseline data.
Per Protocol Set	The Per Protocol Set will include all subjects from the FAS without major protocol violations that might affect the evaluation of the effect of study treatment on the primary endpoint.
Pharmacokinetic (PK) Set	The Pharmacokinetic Set will include all subjects in the Safety Set with at least 1 postdose PK measurement.
Safety Set	The Safety Set will include all randomized subjects who received at least one dose of study treatment.

11.5. Missing Data

Imputation strategies for the handling of missing data is described in detail in the SAP.

11.6. Study Endpoints

11.6.1. Primary Endpoint

Change in CI measured by RHC from Baseline to end of IV infusion at 6 hours

11.6.2. Secondary Endpoints

Secondary endpoints are:

- Change in the following hemodynamic parameters measured by RHC from Baseline to end of IV infusion at 6 hours:
  - CO
  - PCWP
  - RAP
  - PAS/PAD
  - PAPi
  - SVR/SVRI
  - PVR
- Change in the following vital sign parameters from Baseline to end of IV infusion at 6 hours:
  - SBP
  - DBP
  - MAP
  - HR

- Change in the following hemodynamic and systolic function parameters measured by ECHO from Baseline to end of IV infusion at 6 hours:
  - SV
  - SVI
  - LVEF
  - FS
  - LVESV/LVEDV and diameter
  - LVGLS
  - LVGCS
- Change in hemodynamic (measured by RHC) and vital sign parameters listed above at intermediate timepoints during 6-hour IV infusion (during Dosing Period)
- Plasma and urine PK parameters of APD418
- Safety and tolerability of APD418 by incidence of all TEAEs

11.6.3. Pharmacokinetic Endpoints

PK endpoints are PK profiles of APD418, including, but not limited to, the following measures:

- Area under the concentration-time curve from time 0 to 6 hours (AUC_{0-6})
- Area under the concentration-time curve from time 0 to time of the last quantifiable plasma concentration (AUC_{last})
- $AUC_{0-\infty}$
- C_{max}
- Terminal elimination half-life ($t_{1/2}$)
- Distribution half-life ($t_{1/2\alpha}$)
- Time to maximum observed plasma concentration (t_{max})
- CL
- Volume of distribution based on the terminal phase (Vd_z)
- Volume of distribution at steady state (Vd_{ss})
- Mean residence time from time 0 to time of last quantifiable plasma concentration (MRT_{last})
- Average plasma concentration during dosing interval (C_{ave})
- Renal clearance (CLr)

11.6.4. Exploratory Endpoints

Exploratory endpoints are:

- Change in hemodynamic parameters (measured by RHC) listed above at 1 hour after the end of 6-hour IV infusion (during Postdose Period)
- Change in vital sign, hemodynamic (measured by ECHO), and cardiac systolic function (measured by ECHO) parameters listed above for 18 hours after end of 6-hour IV infusion (during Postdose Period)
- The relationships between select APD418 plasma exposure measures and change in select PD parameters
- The relationships between select subject/disease characteristics (eg, Baseline LVEF, Baseline CI, Baseline SBP, duration of HFrEF, renal function, concomitant medications) and change in select PD parameters
- Change in markers of renal function (eGFR, BUN, cystatin C, urine protein/creatinine ratio, urinary sodium excretion)
- Change in cardiac biomarkers (NT-pro-BNP, hs-cTnT)
- Change in the following additional systolic and diastolic function parameters measured by ECHO: E, A, E′, S′, E/A E/E′ ratio), TAPSE, tricuspid regurgitation (TR) velocity, and LA volume index
- Change in urine output
- Change in body weight
- The OATP genotype

11.6.5. Safety Endpoints

- Safety and tolerability of APD418 by incidence of all TEAEs

11.7. Testing Strategy

No formal testing strategy or adjustments of the Type I error will be employed for secondary or exploratory endpoints. Estimates and confidence intervals for treatment groups and from pairwise comparisons will be used in an exploratory manner.

11.8. Interim Analysis

No formal interim analysis of efficacy is planned..

11.9. Dose Escalation and Dose Selection

After treatment of each cohort in Part A, an assessment of the safety/tolerability and PK data will be performed by the dose escalation committee (blinded data review by the Sponsor and Investigator representatives) prior to dose escalation to the next dose level in Part A. The decision to escalate to the next planned dose level in Part A will be made with consideration of

the safety-related dose escalation stopping criteria and overall safety (including AEs, clinical laboratory, and vital sign/ECG data) and PK data of each cohort, as described in Section 10.6.2.

Doses for each subsequent cohort in Part A may be adjusted depending on the safety, tolerability, and PK results of previous cohort(s). The maximum dose in the study will not exceed 2 mg/kg/h (12 mg/kg) and will not produce exposures to APD418 higher than that predicted for a 12 mg/kg dose (ie, C_{max} of 5700 ng/mL or $AUC_{0-\infty}$ of 39,000 ng·h/mL) without a protocol amendment.

The dose escalation committee may decide to evaluate an alternative dose(s) in the subsequent cohort(s) in Part A in the following scenarios:

- Based on the safety profile observed, lower or higher than planned dose(s) may be chosen to be evaluated in the subsequent cohort(s) (not to exceed 12 mg/kg without a protocol amendment)
- If large deviations from the expected PK profile are observed, adjustment to the planned dose escalations may occur to ensure evaluation of dose levels that will elicit appropriate exposure
- If warranted based on the emerging safety and PK data, up to 1 additional or 1 fewer cohort may be studied than originally planned

At the conclusion of Part A, the dose selection committee will perform a safety/tolerability and PD data assessment to identify 2 doses to be expanded in Part B (unblinded review of Part A data by the Sponsor representatives who are not directly involved in study conduct; site staff, and sponsor representatives involved in study conduct will remain blinded throughout the study). Selection of doses will be based on the criteria including, but not limited to:

- Doses selected for expansion in Part B have shown a favorable safety profile in Part A as determined by the criteria described in Section 10.6.2
- Doses selected for expansion in Part B have shown clinically relevant PD effects indicating a clinically meaningful benefit in cardiac function (eg, SV, CO, LVEF)

Sample size for Part B may also be adjusted based on data review of Part A. The sample size will not increase by more than approximately 15% of the sample size without a protocol amendment.

11.10. Pharmacodynamic Analysis

The primary PD endpoint of the study is the change in CI measured by RHC from Baseline to end of infusion at 6 hours. The primary PD analysis will be analyzed be MMRM method. The MMRM model will include treatment group, timepoint, interaction of treatment-by-timepoint, and randomization stratification factor as factors, and Baseline CI as a covariate. An unstructured covariance matrix will be specified for the MMRM model. LS means at visit and LS mean differences between treatment group with p-values and corresponding 95% confidence intervals will be reported.

Potential relationships may be explored between select subject/disease characteristics (eg, Baseline LVEF, Baseline CI, Baseline SBP, duration of HFrEF, renal function, concomitant medications) and select PD measures (eg, change in CI).

Details regarding the statistical analyses will be provided in the SAP.

11.11. Pharmacokinetic Analyses

PK parameters will be calculated using noncompartmental modeling.

Calculated plasma PK parameters will include, but will not necessarily be limited to AUC_{0-6}, AUC_{last}, $AUC_{0-\infty}$, C_{max}, $t_{1/2}$, $t_{1/2\alpha}$, t_{max}, CL, Vd_z, Vd_{SS}, MRT_{last}, and C_{ave}. Urinary PK parameters will include, but not be limited to, the amount of unchanged drug excreted during each collection interval from t_1 to t_2 (Ae_{t1-t2}), total amount of unchanged excreted in urine over the collection period (amount excreted [Ae]), renal clearance (CL_r) and the fraction of drug excreted unchanged in the urine, expressed as a percentage of total dose (fraction excreted [F_e]).

Collected plasma and urine PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, or to assess other actions of APD418 with plasma constituents.

A detailed description of all PK analyses will be provided in the SAP.

Potential relationships may be explored between select plasma APD418 exposure parameters and select PD measures (eg, change in CI).

OATP genotyping will be analyzed and presented in the listing to allow any potential future analysis.

11.12. Safety Analyses

AEs will be listed and summarized by system organ class and preferred term, as well as according to severity and causality/relationship to study treatment. TEAEs will be summarized by cohort and treatment group. In addition, TEAEs will be pooled across treatment groups (ie, placebo, APD418). Observed values for clinical laboratory tests, vital signs, and safety 12-lead and ECGs will be summarized by cohort and treatment group. Individual data listings of clinical laboratory tests results will be presented for each subject. Observed values and changes from Baseline will be summarized descriptively. Safety 12-lead ECG data (observed values and change from Baseline) will be listed for each subject and timepoint. Observed values will be classified for normal, abnormality that is not clinically significant, and clinically significant abnormality by cohort, treatment, and timepoint of collection. Results of other safety assessments will be listed and summarized as appropriate.

A detailed description of all safety analyses will be provided in the SAP.

11.12.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

For each treatment group, the proportion of subjects with TEAEs will be summarized overall, by severity, and by relationship to study treatment. SAEs will also be summarized by treatment group. A TEAE is defined as:

- An AE that occurs after initiation of study treatment that was not present at the time of treatment start.
- An AE that increases in severity after the initiation of medication, if the event was present at the time of treatment start.

AEs occurring before the first dose of study treatment will be summarized separately.

11.12.2. Extent of Exposure

The duration of time on study and time on study treatment will be summarized for each treatment group using descriptive statistics.

11.12.3. Clinical Laboratory Parameters

Laboratory parameters will be summarized by treatment group at each scheduled assessment timepoint using descriptive statistics.

11.12.4. Electrocardiograms

Individual ECG values will be listed by cohort, treatment, and timepoint, and summarized using descriptive statistics. Intervals to be provided for each ECG are RR, PR, QRS, QT, QTc, QTcB, and QTcF. Post-Baseline ECGs for each subject will be compared with the Baseline ECG. Any clinically significant change from Baseline may be recorded as an AE if deemed appropriate by the Investigator, or Investigator in consultation with the Clinical Lead. Outlier analysis will be performed on all subjects with QTcF values greater than 500 ms or change from Baseline > 60 ms in the absence of Baseline ECG abnormalities that preclude accurate surface ECG assessment of ventricular repolarization (eg, bundle branch block).

11.12.5. Vital Signs

Descriptive statistics for vital signs (SBP, DBP, HR, respirations, and body temperature) will be presented by treatment group.

11.12.6. Physical Examination

Clinically significant physical examination abnormalities will be included in medical history or recorded and summarized as an AE.

12. ETHICAL CONSIDERATIONS

12.1. Ethical Conduct of the Study

This study shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP, ICH guidelines, and other applicable regulatory requirements (eg, local requirements).

12.2. Institutional Review Board or Independent Ethics Committee Approval

Before initiating a study, the Investigator must have written and dated approval from the IRB/IEC for the study protocol, written ICF, subject recruitment materials and procedures (eg, advertisements or websites), and any other written information to be provided to subjects. Approval from the committee must be documented in a letter to the Investigator specifying the protocol number, protocol version, documents reviewed, and the date on which the committee met and granted the approval.

All documents subject to review during the study, including any modifications made to the protocol after receipt of IRB/IEC approval, must also be submitted to the committee for approval prior to implementation. The Investigator must also provide periodic reports as required and promptly report important safety information (ie, SAEs) and protocol violations, as appropriate, to the IRB/IEC.

As part of the Investigator's written application to the IRB/IEC, the Investigator should provide the committee with a current copy of the IB. If the IB is updated during the study, the Investigator should supply an updated copy to the committee.

12.3. Informed Consent

The Investigator will fully inform the subject of all pertinent aspects of the study, including the approval of the study by the IRB/IEC. Before informed consent may be obtained, the Investigator should provide the subject ample time and opportunity to inquire about details of the study and to decide whether to participate.

Prior to a subject's participation in the study, the IRB/IEC-approved ICF must be signed and personally dated by the subject and by the person who conducted the informed consent discussion. If a subject is unable to read, an impartial witness will be present during the entire informed consent discussion.

The written ICF and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written ICF or study materials to be available and/or supplied to subjects should receive the IRB/IEC's approval in advance of use. The subject will be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

12.4. Confidentiality

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is provided from the sponsor.

Prior to study participation, the Investigator shall inform the subject that the monitor(s), auditor(s), IRB/IEC, and the regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, and that, by signing a written ICF, the subject is authorizing such access.

In addition, prior to study participation, the subject must be informed that the records identifying the subject will not be made publicly available; if the results of the study are published, the subject's identity will remain confidential.

12.5. Protocol Compliance

The Investigator/institution will conduct the study in compliance with the protocol agreed to by the sponsor and regulatory authorities (if applicable) and that was approved by the IRB/IEC. The

Investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

The Investigator should not implement any deviation from, or changes to, the protocol without agreement by the sponsor and prior review and documented approval from the IRB/IEC of an amendment, except where necessary to eliminate immediate hazard(s) to study subjects or when the change involves only logistical or administrative aspects of the study (eg, change in monitor, change of telephone number).

When an important deviation from the protocol is deemed necessary for an individual subject, the Investigator must contact the Clinical Lead for the study. Such contact must be made as soon as possible to permit a review by the sponsor to determine the impact of the deviation on the subject's participation and/or the assessment of safety or efficacy in the study. Any significant protocol deviations affecting subject eligibility and/or safety must be reported by Investigator or site delegate to the IRB/IEC and regulatory authorities, as applicable, prior to implementation.

The Investigator should document and explain any deviation from the approved protocol.

13. QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance and quality control systems shall be implemented and maintained with written SOPs to ensure that the study is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s). Quality control shall be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

An agreement must be secured from all involved parties to ensure direct access to all study-related sites, source documents, and reports for the purpose of monitoring and auditing by the sponsor and inspection by regulatory authorities.

13.1. Training of Study Site Personnel

Prior to study activities being initiated at the study site, the sponsor or designee will train study site personnel on the protocol and applicable procedures. Training should be documented.

Note: If new study site personnel are assigned to the study after the initial training, study sites should contact the study monitor to coordinate training. Qualified study personnel may conduct training, as appropriate. Training of new study personnel should also be documented.

13.2. Monitoring

Study site monitoring is conducted to ensure the study is progressing as expected, the rights and well-being of human subjects are protected, the reported study data are accurate, complete, and verifiable, and the conduct of the study is in compliance with the currently approved protocol, with GCP and with applicable regulatory requirements. Protocol deviations identified will be documented.

Details of study site monitoring are documented in the study Clinical Monitoring Plan (CMP) or similar document. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed (eg,

targeted and/or risk based), and the distribution of monitoring reports. Monitoring may include a study site selection visit, which may be conducted in person or via communication media (eg, teleconference, online meeting) or may be waived in accordance with policy and procedures being followed for the study, if appropriate. Monitoring will include a study site initiation visit, interim monitoring visit(s), and a study site closeout visit. An interim monitoring visit may be combined with a closeout visit, if applicable.

13.3. Audit

An audit of one or more participating study sites may be performed independently of, and separately from, routine monitoring to evaluate clinical study conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Management

14.1.1. Case Report Forms

An eCRF must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to the sponsor and regulatory authorities, as applicable.

The documentation related to the validation of the eCRFs will be maintained in the Trial Master File (TMF). The TMF will be maintained by the CRO and the sponsor.

The Investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by study site personnel. All data entered into the eCRF will be supported by source documentation.

The Investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All changed information, including the date and person performing the corrections, will be available via the audit trail, which will be part of the electronic data capture system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness and acceptability by sponsor personnel (or their representatives). The sponsor (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to the eCRFs as evidence thereof.

14.1.2. Source Documents

Per regulatory requirements, the Investigator or designee will maintain accurate and up-to-date study documentation, including source documentation for each study subject. Source documents are defined as original documents, data, and records. These may include, but are not limited to, hospital records, clinical and office charts, endoscopy reports, laboratory data/information, evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, ECGs, X-rays, ultrasounds, RHC reports, ECHOs. Data collected during this study must be recorded on the appropriate source documents.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspection(s) and will provide direct access to the source data.

14.2. Study Documentation and Records Retention

The Investigator and study staff have the responsibility of maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be available for inspection by the sponsor, representatives of the sponsor, the IRB/IEC, and regulatory authorities (ie, Food and Drug Administration [FDA] or international regulatory authorities) at any time, and should consist of the following elements:

- Subject files: Containing the completed eCRFs (if applicable), supporting source documentation including medical records, laboratory data, and signed ICFs.
- Regulatory files: Containing the protocol with all amendments and Investigator signature pages, copies of all other regulatory documentation, all correspondence between the study site and the IRB/IEC and sponsor, and drug accountability files, including a complete account of the receipt and disposition of the study treatment.

Records will be available for 2 years after marketing application approval, or if the application is not approved or never submitted, 2 years after the last shipment and delivery of the study treatment and the appropriate competent regulatory authorities are notified. The sponsor will provide written notification when it is appropriate for the Investigator to discard the study-specific documents referenced above.

During the record retention period, the Investigator or designee must inform the sponsor or designee (eg, CRO), of the following:

- Location of study documentation
- If the custody of documentation will be transferred or moved to another location
- If the Investigator is unable to retain documentation for the specified period

14.3. Clinical Study Report

Whether the study is completed or prematurely terminated, a clinical study report will be prepared and provided to the regulatory agencies according to applicable regulatory requirement(s).

14.4. Disclosure of Study Results

The sponsor will post the results of the study in a publicly accessible database in accordance with the applicable laws and regulations.

15. RESPONSIBILITIES

15.1. Investigator Responsibilities

The Investigator must comply with this protocol and the conduct of all study procedures. The Investigator will disclose to the sponsor sufficient, accurate, financial information to allow the

sponsor to submit accurate disclosure statements to the FDA per 21 Code of Federal Regulations (CFR) Part 54 (Financial Disclosure by Clinical Investigators) or to other regulatory authorities that have similar requirements. The Investigator is responsible for compliance with applicable sections of ICH GCP requirements. The investigator may also be responsible for compliance with 21 CFR Part 312, Subpart D, (*Responsibilities of Investigators*) and other, federal, and local laws, applicable to conducting drug studies.

The Investigator is responsible for ensuring an investigation is conducted according to the signed Investigator statement, the investigational plan, and applicable regulations; for protecting the rights, safety, and welfare of subjects under the Investigator's care; and for the control of drugs under investigation. An Investigator shall, in accordance with the provisions of ICH GCP guidelines and/or 21 CFR Part 50, obtain the informed consent of each human subject to whom the drug is administered.

15.2. Sponsor Responsibilities

The sponsor is responsible for compliance with applicable sections of ICH Guideline E6(R2) and 21 CFR Part 312, Subpart D (*Responsibilities of Sponsors*). The sponsor is responsible for selecting qualified Investigators. Sponsors are also responsible for providing them with the information they need to conduct an investigation properly, and ensuring proper monitoring of the investigation(s). Sponsors are also responsible for ensuring the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the Investigational New Drug (IND) application (or equivalent), maintaining an effective IND (or equivalent) with respect to the investigations, and ensuring the FDA (and/or other regulatory authorities as applicable), and all participating Investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

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APPENDIX 1: SCHEDULE OF ASSESSMENTS

Table 4: Study APD418-201 Schedule of Assessments: Part A and Part B

Study Day	**–21 to 1 (Part A) –14 to 1 (Part B)[a]**	**Day 1**										**Day 2**					**Day 9 (± 2)**
Study Period	**Screen**	**Predose Period[b]**	**Baseline[c]**	**Dosing Period[d]**								**Postdose Period[e] and Discharge[f]**					**Follow-Up[g]**
Time from Initiation of Study Treatment (hours)	**NA**	**> –2**	**–2 to 0**	**0.5**	**1**	**2**	**3**	**4**	**5**	**6[h]/EEOI[i]**	**6.5**	**7**	**8**	**10**	**18 (+ 3 h)**	**24 (+ 6 h)**	**NA**
Informed consent	X																
Inclusion/Exclusion criteria	X	X	X														
Demographics	X																
Medical/surgical history	X	X															
Prior/concomitant medications	X	→															X
Height and weight	X	X[j]										X[j]				X[j]	
Meals[k]		X				X											
Physical examination[l]	X	X														X	
Vital signs[m]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[n]	X	X	X	X	X	X		X		X			X		X	X	
ECHO[o]	X		X							X			X			X	
RHC assessments[p]			→														
Cardiac biomarkers[q]	X	X	X		X	X		X		X			X	X	X	X	
Markers of renal function[r]	X		X			X		X		X			X	X	X	X	
Urine output[s]			→													X	
DNA for genetic testing (optional)			X														

Study Day	**−21 to 1 (Part A)** **−14 to 1 (Part B)**[a]	**Day 1**										**Day 2**						**Day 9 (± 2)**
Study Period	**Screen**	**Predose Period**[b]	**Baseline**[c]	**Dosing Period**[d]								**Postdose Period**[e] **and Discharge**[f]						**Follow-Up**[g]
Time from Initiation of Study Treatment (hours)	**NA**	**> −2**	**−2 to 0**	**0.5**	**1**	**2**	**3**	**4**	**5**	**6**[h]**/EEOI**[i]		**6.5**	**7**	**8**	**10**	**18 (+ 3 h)**	**24 (+ 6 h)**	**NA**
Hematology, serum chemistry, and coagulation	X[t]		X							X							X	
Inflammation and endothelial biomarkers			X							X							X	
Serum pregnancy test[u]	X[t]																	
Urine pregnancy test[u]		X																
Urinalysis	X[t]	X								X							X	
Urine drug screen[v]		X																
Randomization			X															
Administer Study Tx[w]				→														
PK blood sample[x]			X	X	X	X	X	X	X	X		X	X	X	X	X	X	
PK urine samples[y]			→															
Adverse events	X	→																X

[a] Screening period for Part A is up to 21 days prior to (and including) Day 1. Screening period for Part B is up to 14 days prior to (and including) Day 1.

[b] Predose assessments are performed on Day 1 prior to RHC insertion (Hours > −2), including certain assessments for confirmation of eligibility.

[c] Baseline assessments are performed over at least 2 hours from RHC insertion to start of study treatment administration (Hours −2 to 0), including confirmation of hemodynamic eligibility criteria and randomization, followed by all other assessments ending with Baseline hemodynamic parameters measurements.

[d] Dosing Period to occur over 6 hours from start to end of IV infusion (Hours 0 to 6).

[e] Postdose Period to occur over 18 to 24 hours from end of IV infusion (Hours 6 to 24 [+ 6 hours]).

[f] Subjects are discharged at the Investigator's discretion based upon clinical presentation (if the patient's clinical state allows) and after all scheduled assessments at Hour 24 (+ 6 hours) have been completed.

[g] Follow-Up phone contact to occur on Day 9 (± 2 days) to assess for AEs and any changes to concomitant medications. Site staff will work with Early Termination subjects to obtain as much follow-up data as possible.

[h] Assessments can occur within 60 minutes of Hour 6, with priority on the RHC assessments occurring as close as possible to 6 hours after start of IV infusion/EOI. The following order of assessments should be followed, if possible: 12-lead ECG, ECHO, vital signs, RHC hemodynamic parameter measurements, blood sampling, EOI, urine sampling.

[i] Subjects who discontinue study treatment prior to the end of the full 6-hour IV infusion will immediately, if possible, complete the EEOI assessments followed by all Postdose Period/Follow-Up assessments. In such situations, order of assessments specified in footnote "h" can be modified, but the priority should be given to RHC hemodynamic parameter measurements, vital signs, and blood sampling occurring as close as possible to EOI.

[j] Only weight. The weight collected during the Predose Period will be used to calculate the subject's dose.

[k] Subjects are allowed a light meal 2 hours prior to RHC insertion (at least 4 hours prior to Baseline hemodynamic parameters measurements). Another light meal is provided after the 2-hour assessments are completed. After the end of RHC measurements, the meals can be provided per the site's SOC.

[l] Physical examination is performed per the site's SOC at Screening and abbreviated physical examination is performed during the Predose Period. A symptom-based physical examination is performed prior to Discharge.

[m] Vital signs include BP, HR, respiratory rate, and temperature. Temperature and respiratory rate are collected only at the following timepoints: Baseline, Hour 6, and Hour 24. During RHC assessments, vital signs (BP and HR) are collected within ± 5 minutes of hemodynamic parameter measurements.

[n] If applicable, it is recommended to collect ECGs at least 30 minutes after the end of the subject's most recent meal.

[o] ECHO is performed at Screening to confirm eligibility (LVEF ≤ 35%).

[p] RHC measurements for confirmation of hemodynamic eligibility criteria (CI ≤ 2.5 L/min/m^2 and PCWP ≥ 15 mm Hg) are performed at Baseline no less than 1 hour following RHC insertion. After at least 2-hour stabilization period, Baseline hemodynamic parameters measurements are performed prior to start of study treatment administration. During the Dosing and Postdose Periods, hemodynamic parameters measurements are performed at specified timepoints (at 0.5, 1, 2, 3, 4, 5, and 6 hours during Dosing Period, and at 0.5 and 1 hour during Postdose Period).

[q] Cardiac biomarkers include NT-pro-BNP and hs-cTnT. Only cardiac troponin is required at Screening and Predose for eligibility purposes (hs-cTnT, hs-cTnI, cTnT, or cTnI), and it is collected and reported locally at Predose and at Screening if required per Section 10.3.5.

[r] Renal function assessments include eGFR, BUN, cystatin C, urine protein/creatinine ratio, and urinary sodium excretion. Subjects are encouraged to provide urine sample at these timepoints. Only eGFR is required at Screening for eligibility purposes, and may be collected and reported locally if required per Section 10.3.4.

[s] Urine output is assessed during prespecified intervals by having the subject empty his/her bladder and capturing the urine volume at indicated timepoints. Any spot urine samples collected during the intervals will be accounted for in the total volume for that specific interval. Urine output is assessed during the following intervals in relation to the start of the IV infusion: Baseline (within 2 hours prior to study treatment administration), every 2 hours during the IV infusion (at Hours 2, 4, and 6), and during the Postdose Period at 6 to 10 hours and 10 to 24 hours intervals.

[t] Local laboratory assessments may be used for determining eligibility at Screening under certain circumstances; refer to Sections 10.2.8, and 10.2.9 for clinical laboratory assessments (and serum pregnancy) and urinalysis, respectively.

[u] Serum pregnancy test is performed for female subjects of childbearing potential to determine eligibility at Screening. Urine pregnancy test is performed and a negative result is required to be documented for female subjects of childbearing potential at Day 1 prior to randomization to confirm eligibility. In case of positive urine pregnancy test, serum pregnancy test should be performed before the subject can be enrolled in the study.

[v] It is not required to result the urine drug screen prior to randomization. If a urine drug screen cannot be obtained prior to study treatment administration due to the timing of events as required by subject safety considerations, then it can be obtained after study treatment administration and prior to discharge.

[w] Continuous 6-hour IV infusion.

[x] Blood samples for plasma PK are collected as denoted in the table above. In addition to the timepoints denoted in the table above, blood samples for plasma PK are collected during the Postdose Period at 6.083, 6.167, 6.25 hours. The collection at Hour 6 should be done within 10 minutes before EOI.

[y] Urine samples for PK analysis are collected during the following intervals in relation to the start of the IV infusion: Baseline (within 2 hours prior to study treatment administration), 0 to 6 hours, 6 to 10 hours, and 10 to 24 hours.

AE, adverse event; BP, blood pressure; BUN, blood urea nitrogen; CI, cardiac index; DNA, deoxyribonucleic acid; ECHO, echocardiogram; ECG, electrocardiogram; EEOI, early end of infusion; eGFR, estimated glomerular filtration rate; EOI, end of infusion; HR, heart rate; hs-cTnT, high-sensitive cardiac troponin T; IV, intravenous; LVEF, left ventricular ejection fraction; NA, not applicable; N-pro-BNP, N-terminal pro b-type natriuretic peptide; PK, pharmacokinetic; PCWP, pulmonary capillary wedge pressure; RHC, right heart catheterization; SOC, standard of care; Tx, treatment

APPENDIX 2: INVESTIGATOR SIGNATURE

Study title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Hemodynamic Effects, Safety, Tolerability, and Pharmacokinetics of APD418 in Subjects with Heart Failure with Reduced Ejection Fraction

Study number: APD418-201

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Investigator Signature	**Date**

Investigator Name and Credentials - Printed
Institution Name - Printed

APPENDIX 3: COUNTRY-SPECIFIC REQUIREMENTS

SPONSOR SIGNATURE

Study title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Hemodynamic Effects, Safety, Tolerability, and Pharmacokinetics of APD418 in Subjects with Heart Failure with Reduced Ejection Fraction

Study number: APD418-201

This document is signed electronically; the electronic signature is the signature of record in countries and regions that recognize electronic signature. This signature page is provided to meet signature requirements in countries that do not recognize electronic signature; the hand-written signature on this page is the signature of record in countries and regions that do not recognize electronic signature.

PPD , MD, MBA

PPD

PPD

Sponsor Signature **Date**

PPD

Name: Clinical Study Protocol: APD418-201 Amendment 3.0
Description: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlle

User Nam PPD Capacity: PPD	Meaning: Approval Task Date: 26-Apr-2022 15:48:26 GMT+0000

Note to File, Addendum

Date:	13 January 2023
To:	TMF
From:	PPD
Protocol No.:	APD418-201
Subject:	Addendum to APD418-201 NTF to document the status of select post-database lock outline plan for pharmacokinetic analyses

Background:

On 25 August 2022, the decision was made to discontinue development of the Arena cardiovascular programs, which includes APD418.

As a result of the immediate termination, the biostatistics aspects related to finalizing documents (e.g., statistical analysis plan [SAP]) and other downstream activities pertaining to pharmacokinetic analyses were either draft and/or have not been established. These tasks would have taken significant time and resources by both the Arena and Medpace team to finalize, which was not feasible given the accelerated study close-out timeline, including the database lock (DBL) which occurred on 24 October 2022. The document here serves as the addendum to APD418-201 NTF (approved on 21 October 2022) to outline the plans for select post-database lock pharmacokinetic analyses.

Final Status:

Pharmacokinetic (PK) Analysis

- As per draft statistical analysis plan (SAP) v0.3
- Final pharmacokinetic analysis completed on Nov 14

Pharmacokinetics-Pharmacodynamics Analysis

- Development has not begun

OATP1B Analysis

- Raw genotyping data received on 25 October 2022
- Development has not begun

Deliverables & Analyses:

Alternative solutions were utilized to provide post-DBL pharmacokinetic analyses. PK parameters were estimated as per stated in SAP (v0.3) by Medpace clinical pharmacologists. Following DBL, the raw datasets, both eCRF (EDC) and external non-CRF, were made available to Medpace for production of unblinded pharmacokinetic outputs. PK TLFs were produced as presented in Appendix I of this Note to File, Addendum. Arena utilized this existing report structure in place of SAP-based TLFs for the final report.

Signatures:

REASON: I approve this document.

PPD

14 Jan 2023 00:48:040-0500

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PPD

Distribution:

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Appendix A – Table of Contents of Pharmacokinetic Analysis Final Report

Note to File, Addendum

Date:	13 Jan 2023
To:	TMF
From:	PPD
Protocol No.:	APD418-201
Subject:	Addendum to APD418-201 NTF to document the status of biometrics-related documents/processes and outline plan for select post-database lock safety and efficacy analyses

Background:

On 25 August 2022, the decision was made to discontinue development of the Arena cardiovascular programs, which includes APD418. Enrollment into the ongoing clinical trial APD418-201 was terminated and study team activities were reprioritized to focus and accelerate study close-out activities. For this study, the biostatistics, data management, and statistical programming deliverables and activities are outsourced to the clinical research organization (CRO) Medpace.

As a result of the immediate termination, the biostatistics aspects related to finalizing documents (e.g., statistical analysis plan [SAP]) and other downstream activities are either immature and/or have not been established. These tasks would take significant time and resources by both the Arena and Medpace team to finalize, which is not feasible given the accelerated study close-out timeline, which includes the database lock (DBL) which occurred on 24 October 2022. The original note to file (date: 21 October 2022), is amended here to re-number the outputs included in the appendix to be ICH consistent for CSR reporting and added Table 14.3.3.6.

Final Status:

Statistical Analysis Plan

- Draft SAP (v0.4)

Statistical Analysis Plan: Table, Listing, and Figure (TLF) Shells

- Development has not begun.

CDISC Specifications and Datasets (aCRF/SDTM/ADaM)

- aCRF (dbCRF; based on protocol amendment v3.0)
- SDTM: Specifications and datasets by 18 November 2022
- ADaM: Draft specifications (Development not yet begun)

Statistical Analysis Plan: Table, Listing, and Figure (TLF) Programming

- Development has not begun for output programming

Define.xml

- Development has not begun for either SDTM or ADaM Defines

Reviewer's Guide (SDTM/ADaM)

- Development has not begun for either SDTM or ADaM Reviewer's Guides

Unblinding Procedure:

Following completion of the DBL sign-off form, the Medpace project statistician will circulate the Unblinding form for signature by Arena (Lead Study Statistician, Head of Biostatistics and Data Management) and by appropriate Medpace team members. The Medpace project statistician will then present both the signed DBL and Unblinding forms to the IRT group to document that the unblinded treatment assignments could be shared with the Biostatistics team for incorporation into the final database. The signed DBL and Unblinding forms will be included in TMF.

Deliverables & Analyses:

Since the SAP, CDISC ADaM data development, and statistical programming (e.g., dataset level, table level) will not be finalized, alternative solutions are being utilized to provide post-DBL safety and efficacy analyses.

As outlined in the Study APD418-201 protocol (Section 11.9), a Dose Escalation Committee is utilized. The Dose Escalation Charter outlines a list of outputs (presented in Appendix I of this Note to File) produced following each cohort in Part A of the study. Arena will be utilizing this existing report structure in place of SAP-based TLFs for the final report.

Following DBL, the raw datasets, both eCRF (EDC) and external non-CRF, will be made available to Medpace for production of unblinded safety and efficacy outputs for Part A Cohort 1 (N = 7; reproduction for data completeness) and Part A Cohort 2 (N = 15). A pooled placebo treatment group (Cohort 1 + Cohort 2 will also be presented in tables and figures).

Signatures:

PPD

REASON: I approve this document.

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PPD

Distribution:

☒ TMF or applicable document repository

ARENA PHARMACEUTICALS

Appendix A – Table of Contents of Final Report

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