Clinical Trial Protocol: APD811-003

Study Title:	A Randomized, Double-blind, Parallel-group, Placebo-controlled Phase 2 Trial of APD811, an Oral IP Receptor Agonist, in Patients with Pulmonary Arterial Hypertension
Study Number:	APD811-003
Study Phase:	2
Product Name:	APD811
IND Number:	109021
Indication:	Pulmonary Arterial Hypertension
Investigators:	Multicenter
Sponsor:	Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, CA 92121
Sponsor Contact:	[redacted]

	Date
Original Protocol:	04 December 2014
Amendment 1:	17 June 2014
Amendment 2:	15 August 2014

SYNOPSIS

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Study Phase:	2
Name of Drug:	APD811
Indication:	Pulmonary Arterial Hypertension
Sponsor:	Arena Pharmaceuticals, Inc. 6154 Nancy Ridge Drive San Diego, California 92121
Name of Sponsor Contact:	[redacted]
Name of Principal Investigator:	Multicenter
Medical Monitor:	[redacted]
Scientific Expert:	[redacted]
Dosage:	The starting dose of APD811 will be 0.01 mg b.i.d. The dose of APD811 will be titrated according to patient tolerability. Available dosage forms include 0.01, 0.02, 0.03, 0.04 mg, and 0.10 mg. If the initial dose is tolerated (0.01 mg b.i.d.), then the dose will be increased in the following fashion at subsequent visits: 0.02 mg b.i.d., 0.03 mg b.i.d., 0.04 mg b.i.d., 0.06 mg b.i.d., 0.08 mg, 0.1 mg b.i.d.,

	0.2 mg b.i.d and 0.3 mg b.i.d. The dose may be escalated to a possible maximum total daily dose of 0.6 mg (0.3 mg b.i.d.) pending tolerability. If a dose is not tolerated, the study drug may be decreased to the previous dose level. If the initial dose of 0.01 mg b.i.d. is not tolerated, dosing may be decreased to 0.01 mg q.d.
Concurrent Control:	Matching placebo
Route and Formulation:	Oral, liquid-filled, hard-gelatin capsules
Objectives:	Primary: The primary objective of the study is to assess the hemodynamic effects of APD811 and the effect of APD811 on 6MWD in patients with PAH after 22 weeks of treatment including an initial dose titration period of up to 9 weeks. Secondary: The secondary objectives of the study are: • to assess the safety and tolerability of APD811 • to assess the effect of APD811 on clinical worsening Exploratory: Exploratory objectives of the study are: • to assess the effect of APD811 on levels of BNP and NT-proBNP after 22 weeks of treatment • to assess change in WHO/NYHA functional class • to evaluate the pharmacokinetics (C_{min} and presumptive C_{max}) of oral APD811 • to evaluate the effects of APD811 on systemic vascular resistance (SVR)
Study Design:	The study will be conducted as a placebo-controlled, randomized (2:1, APD811:placebo), 22 week double-blind study which will include a dose titration period of up to 9 weeks. An additional transition period of 3 weeks (±1 week) will occur for those patients who elect to enroll into the open-label extension study, APD811-007. Patients that do not continue in the extension study will have a 3-week follow-up visit. Approximately 60 patients with PAH will be enrolled. Safety will be assessed by the Safety Monitoring Committee (SMC). The SMC will review safety data including adverse events, blood pressure and heart rate periodically, in order to ensure patient safety and determine an appropriate dose titration regimen.

	To be eligible to enroll in the extension study APD811-007, patients must complete study APD811-003. Additionally, placebo treated patients who discontinue study drug treatment due to clinical worsening in APD811-003 will be permitted to enroll in APD811-007, upon approval of the medical monitor, provided that all end of study procedures including right heart catheterization are performed per protocol. Patients will be receiving concomitant oral disease-specific PAH therapy consisting of an endothelin receptor antagonist (ERA) and/or an agent acting on the nitric oxide pathway, a PDE5 inhibitor or a soluble guanlyate cyclase stimulator, provided the dose has remained stable for at least 3 months prior to the start of Screening. Patients should continue the same dose and regimen of these medications for the duration of the study. The use of the following therapies, which may affect PAH, are permitted: • Vasodilators (including calcium channel blockers), digoxin, spironolactone, or L-Arginine supplementation; if on a stable dose for at least 1 month prior to the start of Screening and should remain unchanged during the study. - Doses of spironolactone and digoxin may be held or reduced as necessary to protect the patient's safety. Doses may not be increased in the month before Day 1 and during the controlled study. • Diuretics may be dosed as clinically indicated throughout the study. • Intravenous inotropes within 1 month of starting Screening are not permitted. In an attempt to maintain balance across treatment groups, the following stratification factor will be utilized during patient randomization: • Baseline WHO/NYHA Functional Class (Class II vs. III or IV) If a patient's participation in the study is discontinued early, all end of study (EOS) safety and efficacy evaluations are to be performed as part of the Week 22/Early Termination visit. The EOS visit for early terminations will be followed by a follow-up visit to ensure appropriate patient safety at Week 25. If the patient is unable to return for the follow-up visit, AE and concomitant medication follow-up may be conducted by telephone.

Study Site:	Multiple centers in United States, Europe, and Australia.
Patient Population:	Up to 60 patients with PAH will be studied. All women, regardless of childbearing potential, must have a negative pregnancy test at Screening (serum hCG) and on Day 1 (urine dipstick) of the dose titration period and periodically throughout the study (serum hCG). Males and females of childbearing potential must use adequate means of contraception and must agree not to participate in a conception process (i.e., active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization) for 1 month after the last dose of study drug.
Eligibility:	Key Inclusion Criteria: • Males or females aged 18-75 years, inclusive • Symptomatic WHO Group 1 PAH classified by one of the following subgroups: - Idiopathic pulmonary arterial hypertension (IPAH); - Heritable pulmonary arterial hypertension (HPAH); - Drugs and toxins induced; - Associated with (APAH); specifically connective tissue diseases, HIV infection and congenital heart disease • Has had the diagnosis of PAH confirmed by cardiac catheterization • Has WHO/NYHA functional class II- IV symptomatology • Previously diagnosed with PAH and on stable oral disease-specific PAH therapy with either an ERA and/or an agent acting on the nitric oxide pathway, i.e. a PDE5 inhibitor or a soluble guanlyate cyclase stimulator. Stable is defined as no change in dose within **3 months** of the start of Screening and for the duration of the study. • Has 6MWT distances of 100-500 m, and within 15% of each other on 2 consecutive tests done on different days at Screening • Has pulmonary function tests (PFTs) within 6 months prior to the start of Screening with no evidence of significant parenchymal lung disease • Has a ventilation-perfusion (V/Q) lung scan or pulmonary angiogram within 5 years prior to Screening and concomitant with or following diagnosis of PAH that shows no evidence of thromboembolic disease

	• If on vasodilators (including calcium channel blockers), digoxin, spironolactone, or L-Arginine supplementation; the patient must be on a stable dose for at least 1 month prior to the start of Screening Key Exclusion Criteria: • Newly diagnosed with PAH and on no disease-specific PAH therapy • Previous participation in any clinical study with an investigational drug, biologic, or device within **2 months** prior to the Screening visit • Acutely decompensated heart failure within **1 month** prior to start of Screening • Systolic blood pressure <90 mm Hg at Screening • Evidence or history of left-sided heart disease and/or clinically significant cardiac disease • Use or chronic administration (defined as >30 days) of a prostacyclin or prostacyclin analogue within **3 months** of Screening • Any previous use of a prostacyclin or prostacyclin analogue that was stopped for safety or tolerability issues associated with pharmacology/mechanism of action • Other severe acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study
Duration per Patient:	~29 weeks: 4 weeks for screening, a 22 week treatment period including a dose titration period of up to 9 weeks, followed by a 3 week follow-up visit. Patients will stay on treatment through the follow-up visit if continuing into the open-label extension study. For patients not continuing into the open-label extension study, treatment will be discontinued at the end of the treatment period.
Patient Assignment:	Patients will be randomly allocated to APD811 or placebo in a 2:1 ratio.
Sample Size:	Up to 60 patients.
Efficacy Endpoints:	Efficacy will be assessed by measurement of pulmonary vascular resistance (PVR) obtained on RHC, measurement of B-type natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and six-minute walk test (6MWT).

	Primary: • Change from baseline in PVR • Change from baseline in 6MWD **Secondary:** • Percent change from baseline in PVR • Proportion of subjects who exhibit clinical worsening **Exploratory:** • Change from baseline in BNP/NT-proBNP • Change from baseline in WHO/NYHA functional class • Change from baseline in other hemodynamic parameters (e.g. SVR)
Pharmacokinetic Assessments:	Dose Titration Period: Pharmacokinetic (PK) blood samples will be collected pre-dose and at 4 hours post-dose at each dose escalation, and one week after the last dose escalation. Treatment Phase: PK blood samples will be collected pre-dose and at 4 hours post-dose at each visit during the treatment phase. An additional blood sample for PK analysis will be collected if possible at the time of any intolerable AE or SAE.
Safety Assessments:	• Clinical laboratory tests (to include hematology, coagulation parameters [PT/PTT, INR], serum chemistry, and urinalysis) • Vital signs • Physical examinations • 12-lead electrocardiograms (ECGs) • Adverse events
Data Analyses:	The primary efficacy hypothesis regarding the superiority of APD811 to placebo will be assessed in a stepwise manner. First, the statistical significance of APD811 versus placebo result will be determined for the change from baseline in PVR at the end of 22 weeks of treatment. If the result is significant ($p < 0.05$, two-sided), the primary hypothesis will be considered satisfied and this study will be declared positive. Subsequently, the change from baseline in 6MWD will only be tested if the change from baseline in PVR is significant. This testing procedure preserves the overall Type I error rate for testing the primary efficacy hypothesis. An analysis of covariance (ANCOVA) model with baseline PVR as a covariate and treatment and baseline WHO/NYHA functional class as factors will be used to assess the effect of APD811. Appropriate transformations will be applied if necessary (i.e., log transformation). 6MWD and other continuous efficacy endpoints will be analyzed

	using the above ANCOVA method described for PVR, substituting the relevant baseline measurement as the covariate. For the APD811 versus placebo comparison, 28 patients in the APD811 group and 14 patients in the placebo group will have 90% power to detect a between-treatment difference of 350 dyn·s· cm^{-5} in PVR. This calculation was based upon the pooled SD estimate of 320.3 dyn·s·cm^{-5} for the mean change from baseline in PVR at Week 17 observed in the selexipag phase 2 study. Assuming that up to 30% of patients may drop out of the trial before a post-randomization RHC is performed, 40 patients will be randomized to the APD811 group and 20 patients will be randomized to the placebo group. For 6MWD, 40 patients in APD811 group and 20 patients in the placebo group will have 80% power to detect a between-treatment difference of 50 meters in 6MWD assuming pooled SD estimate of 65 meters. Safety and tolerability will be assessed by a review of all safety parameters including adverse events (AEs), laboratory safety parameters, vital signs and ECG.
Original Protocol Date:	04 December 2014
Amendment 01 Date:	17 June 2014
Amendment 02 Date:	15 August 2014

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PROTOCOL AMENDMENT SUMMARY

The following is a list of **major** changes made to the APD811-003 Protocol Amendment 01 dated 17 June 2014. These changes are incorporated in Protocol Amendment 02 dated 15 August 2014.

Section(s) Amended	Page No(s).	Description of Changes Made
Header/Footer, Title Page, and TOC	All	Added "Amendment 02", updated date to reflect final amended protocol, updated pagination and TOC
Protocol Amendment Summary	13-14	Updated table to include summary of changes to the Amendment 02 protocol
Table 1. Schedule of Procedures and Visits: Dose Titration Period	29-30	• Added footnote to indicate that all references to pre-dose and post-dose activities in this schedule applies to the morning dose of study drug • Added ECG assessments to all dose-titration period visits (Weeks 1-9), to be completed pre-dose and 2 hours post-dose. • Added footnote to indicate WHO/NYHA functional class assessment should be completed pre-dose • Footnote "o" incorrectly notes a 6 MWT distance of ≥50 meters and ≤500 meters and within 15% of each other on 2 consecutive tests on different days during Screening Corrected to read: 6MWT distance requirement of 100-500 m, and within 15% of each other on 2 consecutive tests done on different days at Screening
Table 2. Schedule of Procedures and Visits: Treatment Period	31-32	• Added footnote to indicate that all references to pre-dose and post-dose activities in this schedule applies to the morning dose of study drug • Added or corrected footnotes to indicate procedures or assessments to be completed pre-dose
Section 4.2 Inclusion Criteria #8	34	Corrected requirement for 6 MWT distance at screening Previously: "Has a 6MWT distance of **≥50 meters and ≤500 meters**, and within 15% of each other on 2 consecutive tests on different days during Screening" Corrected: "Has a 6MWT distance of **≥100 meters and ≤500 meters**, and within 15% of each other on 2 consecutive tests on different days during Screening"
Section 4.3 Exclusion Criteria #21	37	Removed exclusion criteria of positive drug test at screening
6.2 Medical and Social History	43	Added collection of history of alcohol or substance (drug/solvent) abuse per exclusion #21
6.16 Allowable Visit and Procedure	55	Revised for clarity, adjusted window for PK sampling from ± 5 min to ± 15 min

Section(s) Amended	Page No(s).	Description of Changes Made
Windows		
Section 7.4.1 Pre-dose Procedures for Dose Titration Visits and 7.4.2 Post-dose Procedures for Dose Titration Visits	58	Added safety ECG assessments to all dose-titration visits (Weeks 1-9) to be completed pre-dose and 2 hours post-dose

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

6MWT	six-minute walk test
6MWD	six-minute walk distance
ADL	activities of daily living
AE	adverse event
ALK-P	alkaline phosphatase
ALT	alanine aminotransferase (SGPT)
ANCOVA	analysis of covariance
AST	aspartate aminotransferase (SGOT)
ATS	American Thoracic Society
AUC	area under the time-concentration curve
b.i.d.	twice daily
BNP	B-type natriuretic peptide
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
Cl/F	apparent oral clearance
C_{last}	last measured concentration
C_{max}	maximum plasma drug concentration
C_{min}	minimum plasma drug concentration
CNS	central nervous system
CO	cardiac output
CRF	case report form
CRO	Contract Research Organization
CT	computerized tomography
CTCAE	common terminology criteria for adverse events
EC_{50}	median effective concentration
ECG	Electrocardiogram
EDTA	ethylenediaminetetraacetic acid
ERA	endothelin-receptor antagonist
FDA	Food and Drug Administration
FiO2	venous oxygen saturation
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	good laboratory practice

GMR	geometric mean ratio
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
Hct	Hematocrit
HCV	hepatitis C virus
hERG	human Ether-à-go-go-Related Gene
Hgb	Hemoglobin
HIV	Human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	international normalized ratio
IRB	Institutional Review Board
kg	Kilogram
LDH	lactic dehydrogenase
LOCF	last observation carried forward
LVEDP	left ventricular end diastolic pressure
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MITT	modified intent-to-treat
month	1 month = 30 days
MTD	maximum tolerated dose
N/A	not applicable
nM	Nanomolar
NOAEL	no observed adverse effect level
NT-proBNP	N-terminal-pro-BNP
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PCWP	pulmonary capillary wedge pressure
PDE-5i	phosphodiesterase type 5 inhibitor
PGI_2	prostaglandin I_2
PH	pulmonary hypertension
PI	principal investigator
PK	Pharmacokinetic

PT	prothrombin time
PTT	partial thromboplastin time
PVR	pulmonary vascular resistance
q.d.	once daily
RAP	right atrial pressure
RBC	red blood cell (count)
RHC	right heart catheterization
RVP	right ventricular pressure
SAE	serious adverse event
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SMC	Safety Monitoring Committee
SOP	standard operating procedure
SVR	systemic vascular resistance
TEAE	treatment emergent adverse event
TLC	total lung capacity
t_{max}	time to maximum plasma concentration
US	United States
V/F	apparent volume of distribution
WBC	white blood cell (count)
WHO	World Health Organization
WHODRUG	World Health Organization Drug Dictionary
WHO/NYHA	World Health Organization/New York Heart Association

1 INTRODUCTION

APD811 is an orally available, potent and selective, non-prostanoid, prostaglandin I_2 (PGI_2, prostacyclin, IP) receptor agonist. The IP receptor is a rhodopsin-like transmembrane spanning G protein-coupled receptor which is expressed on platelets and on the smooth muscle cells of several tissues including the lung, heart, aorta, liver, and kidneys. Activation of the IP receptor results in vasodilation and inhibits platelet aggregation.[1]

APD811 is being developed to treat World Health Organization (WHO) Group 1 pulmonary hypertension, designated as pulmonary arterial hypertension or PAH. Elevated pulmonary artery pressure in PAH is thought to result from primary pathological alterations in pulmonary arterioles. PAH is a rare, progressive disease characterized by elevated pulmonary vascular resistance that leads to right ventricular failure and ultimately death. Prior to the development of effective therapies for PAH, the median survival of patients with idiopathic PAH was approximately 2.8 years without effective treatment.[2] Though the median survival of a more recent, large US cohort has improved to approximately 7 years[3] from time of diagnosis, PAH remains a severe, often fatal condition. Pulmonary arterial hypertension is associated with alterations in prostacyclin and thromboxane A_2 activity, the balance of which plays a major role in maintaining normal pulmonary vascular tone.[2,4] Prostacyclin, released by endothelial cells, promotes vasodilation and inhibits platelet aggregation by binding to G protein-coupled receptors on nearby smooth muscle cells and platelets. Prostacyclin also has antiproliferative effects on vascular smooth muscle. In direct opposition, thromboxane A_2 promotes vasoconstriction and platelet aggregation. An imbalance in this homeostasis towards vasoconstriction, *in situ* thrombosis, and remodeling of the small pulmonary arteries results in pulmonary hypertension.[4,5]

Studies indicate that patients with pulmonary hypertension (PH) have decreased levels of prostacyclin.[4,6] Epoprostenol, an intravenous prostanoid which binds to the IP receptor, is the only therapy to demonstrate improved survival compared to conventional therapy, supporting utility of the IP receptor as a target for PAH therapy.[7] Epoprostenol requires continuous infusion through a portable pump, is unstable at room temperature, and is associated with catheter related infections and thrombosis. Subsequent forms of prostanoids have been developed to address some of the limitations of epoprostenol and have demonstrated efficacy through improved exercise capacity and/or delay in clinical worsening. There is a need for effective oral agents targeting the prostacyclin pathway.

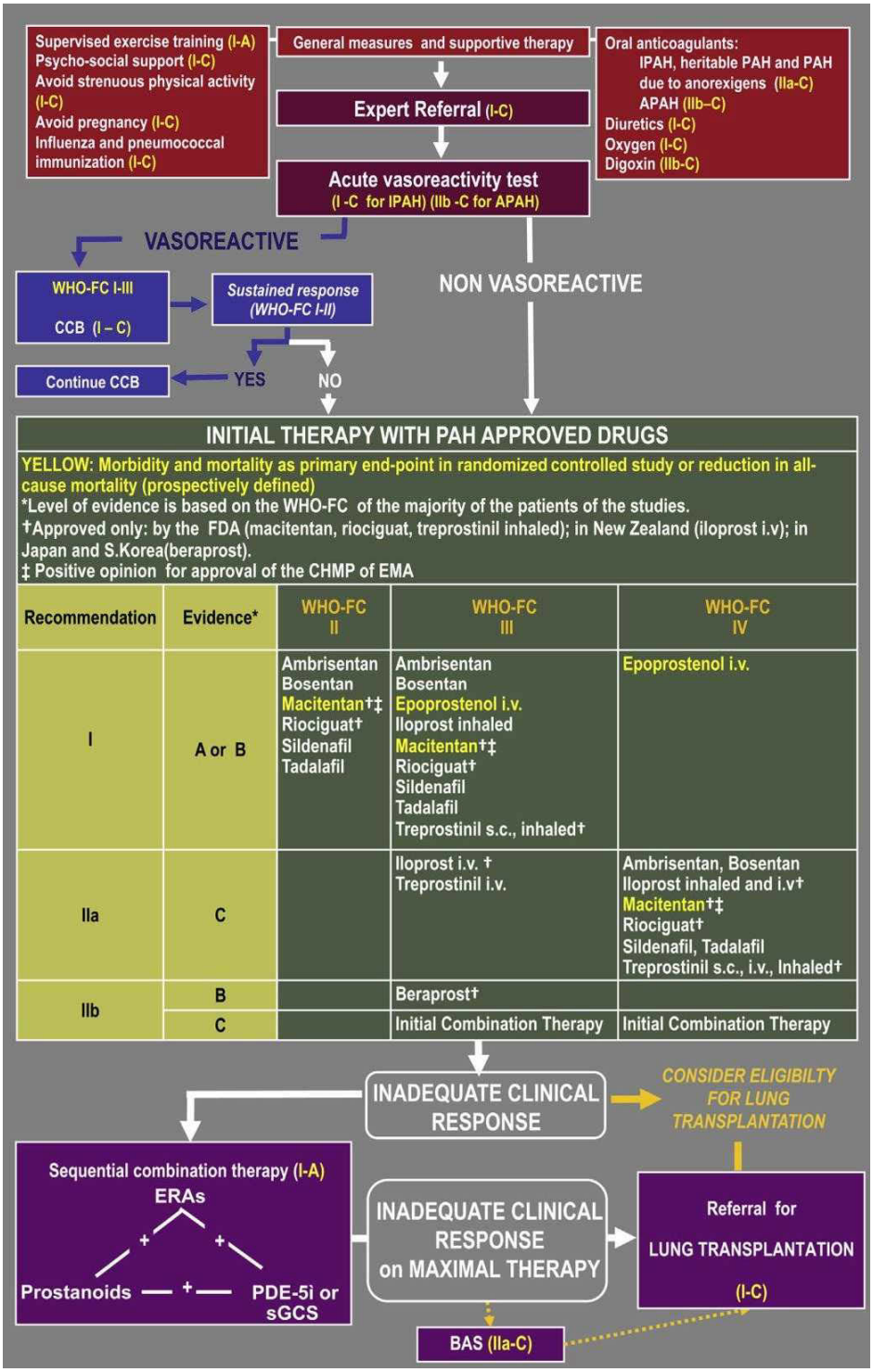
The clinical definition of PH requires confirmation by right heart catheterization (RHC) demonstrating a mean pulmonary artery pressure (PAP) >25 mm Hg. The diagnosis of PAH requires a normal (≤15 mm Hg) pulmonary capillary wedge pressure (PCWP) and an increase in pulmonary vascular resistance (PVR) in addition to an elevated mean PAP. The latest clinical classification by the 4th World Symposium on Pulmonary Hypertension divides pulmonary hypertension into five categories based on similarities in clinical presentation, pathogenesis, and response to treatments.[8] PAH is the first category (Group 1) and is further divided into subgroups reflecting associated conditions. All of the subgroups in Group 1 PAH share similar clinical characteristics and virtually identical histopathology in the pulmonary arteriolar circulation.

There is a wide variation in the reported prevalence of PAH; 15-50 cases/million with a higher female preponderance (~3:1).[9,10,11] The range in reported prevalence is likely due to the difficulty in diagnosing early PAH. Patients are usually asymptomatic in the earliest stages of the disease and presenting symptoms, which include exertional dyspnea, fatigue, peripheral edema, and syncope, can be indistinguishable from other cardiorespiratory diseases. The majority of patients are not diagnosed until they have developed symptoms of World Health Organization (WHO) [modification of the New York Heart Association (NYHA) classification for pulmonary hypertension] functional class III.

The current evidence-based recommended treatment algorithm emerged from the Fifth World Symposium on Pulmonary Hypertension[12] and is summarized in Figure 1. The majority of patients who undergo acute vasoreactivity testing are classified as non-responders, and are therefore candidates for treatment with an endothelin receptor antagonist (ERA), a phosphodiesterase-type 5 (PDE-5) inhibitor or a prostacyclin receptor agonist, depending upon the severity of symptoms. Patients with inadequate response to initial medical therapy may progress to combination drug therapy or ultimately to surgical procedures that could include lung transplantation. The efficacy of prostacyclin receptor agonists has been demonstrated for monotherapy in patients with functional class II or greater symptoms, and for combination therapy with an ERA or with a PDE-5 inhibitor.

Due to availability of oral dosage forms, almost all patients initiate therapy with ERA or PED5 inhibitors. The report from the Fifth World Symposium on PH points out that the clinical role of aggressive early therapy with prostacyclin receptor agonists remains unknown, since in randomized controlled trials the available agents were evaluated primarily in patients with more advanced disease. Multiple attempts at developing an IP receptor agonist for oral administration have been limited by molecules with unfavorable pharmacokinetic properties. One analog of prostacyclin (PGI_2) has been recently approved by the FDA for oral administration, Orenitram™ (treprostinil), but was effective only as monotherapy and not as add-on therapy in phase 3 studies. Thus, there is a need for additional effective oral agents targeting the prostacyclin pathway.

Figure 1. Evidence-based Treatment Algorithm for PAH



APAH=associated pulmonary arterial hypertension; BAS=balloon atrial septostomy; CCB=calcium channel blockers; ERA=endothelin receptor antagonist; sGCS=soluble guanylate cyclase stimulators; IPAH=idiopathic pulmonary arterial hypertension; i.v.=intravenous; PDE-5i=phosphodiesterase type-5 inhibitor; s.c.=subcutaneous; WHO-FC=World Health Organization functional class.

Source: World Symposium on Pulmonary Hypertension[12]

1.1 Background Information

1.1.1 Rationale for Proposed Clinical Study

Despite recent advancements in treatment options, PAH remains a fatal disease with approximately 15% mortality within 1 year[15] and a 3-year survival rate between 35-75% depending on PAH etiology and co-morbid conditions.[4,15] There is a significant need for alternative treatments for this disease. APD811, an oral non-prostanoid IP receptor agonist, could be an effective and convenient treatment option.

APD811 has been characterized in both single and multiple dose studies in a healthy volunteer population. The safety profile suggests that dose-related pharmacology at the IP receptor is occurring within the dose range of 0.01 – 0.2 mg with adverse effects consistent with those reported for IP agonists. The pathophysiology of PAH may be associated with changes in prostacyclin receptors within the pulmonary vascular circulation, and lead to differing responses than in healthy volunteers. This study is being undertaken to define the appropriate dose titration regimen and assess the hemodynamic effects of APD811 in PAH patients.

1.1.2 Summary of Preclinical Data

The efficacy of APD811 was demonstrated in male rat monocrotaline models of PH. In one study, APD811 improved survival and prevented the development of PH in monocrotaline treated rats.[16] In another study APD811 blocked the progression of established PH in monocrotaline treated rats.[17]

The most sensitive species for toxicology findings is monkey. The no observed adverse effect level (NOAEL) was determined to be 0.1 mg/kg in a 4-Week Good Laboratory Practice (GLP) study.[18] The NOAEL corresponds to Day 28 C_{max} values of 22.1 and 15.5 ng/mL in male and female monkeys, respectively.[18] In a pilot 14-day repeat dose range finding study, a "slight convulsion" was observed in one male monkey at 0.2 mg/kg after four once daily doses and one convulsion in one female monkey at 0.5 mg/kg after two once daily doses.[20] Plasma concentrations were only measured on Day 1 and Day 14 during this study. Thus plasma levels were not determined at the time of the convulsions. However C_{max} on Day 1 and Day 14 for the male monkey with a "slight convulsion," administered 0.2 mg/kg, was 119 ng/mL and 64.1 ng/mL, respectively. A NOAEL could not be determined for this study. It is not clear whether the reported incidences of convulsions were due to indirect effects such as hypotension, or to a direct CNS effect. Convulsions were not observed in the GLP repeat dose toxicity studies of 4-weeks, 3-months and 9-months in duration where doses of 0.02, 0.06, 0.10, 0.20, or 0.40 mg/kg/day were administered to monkeys.[18,19] APD811 was better tolerated in the chronic (9-month) monkey study with no adverse findings reported.

A single 0.2 mg/kg dose of APD811 substantially decreased mean arterial pressure and pulse pressure from 40 to 70 minutes after dosing in a single dose, oral, cardiovascular GLP study in monkeys.[21] The NOAEL for this study was also 0.1 mg/kg.

Much higher doses and exposures of APD811 were tolerated in rats, consistent with a substantial reduction in potency (EC_{50} 529 nM) at the rat IP receptor as compared to monkey (EC_{50} = 0.15 nM). In a 4-week GLP repeat-dose toxicity study, APD811 was administered to rats at doses of 10, 30, and 100 mg/kg/day by oral gavage. It was well tolerated up to 100 mg/kg/day for males and 30 mg/kg/day for females. The NOAEL was 100 mg/kg/day for males, corresponding to Day 28 C_{max} and AUC_{last} values of 45.1 µg/mL and 475 hr•µg/mL, respectively, and 30 mg/kg/day for females, corresponding to Day 28 C_{max} and AUC_{last} values of 18.5 µg/mL and 190 hr•µg/mL, respectively. In the chronic 6-month toxicity study in rats, the NOAEL was established at 30 mg/kg/day for both sexes.

1.1.3 Summary of Clinical Data

The starting dose of 0.1 mg for the first-in-man study (APD811-001) was determined in accordance with the FDA Guidance Document "Estimating the Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers" (July 2005) and was based on the monkey NOAEL of 0.1 mg/kg/day, using a safety factor of 20, and assuming a 60 kg human subject.[22]

In the first human study (APD811-001), up to 9 single ascending dose cohorts of 8 subjects each (6 active, 2 placebo) were planned. The administration of single doses of 0.03, 0.05 and 0.1 mg were generally tolerated in healthy male and female subjects. The administration of a single dose of 0.2 mg APD811 was not well tolerated by subjects and resulted in discontinuation of further dose escalation in the study due to nausea and vomiting of severe intensity. The maximum tolerated dose in this clinical study was therefore 0.1 mg. The adverse events most commonly experienced included headache, vomiting, nausea and jaw pain.

No consistent effects were seen on blood pressure, but pulse rate appeared to increase more in APD811 subjects than placebo subjects (delta ~ 10 bpm) at the 3 highest doses. Consequently, uncorrected QT interval decreased, but rate corrected QT interval (QTcF) was increased from baseline at t_{max} in non-dose responsive fashion, by means and medians ranging from 3 to 9 msec at the two highest doses. An effect on QT interval is not supported by preclinical findings (hERG IC_{50} >20 µM, and no effect on QTc in a primate cardiovascular study at 3-4 times the C_{max} achieved in this phase 1 study). No dose response on QT interval was seen, and the significance of the findings in this limited study is unclear.

A subsequent multiple ascending dose study was conducted in healthy volunteers (APD811-002). The safety and tolerability of two different dosing regimens was evaluated: a once-daily regimen in Cohorts 1 and 2 (run concurrently) began at an initial dose of 0.05 mg and was escalated as tolerated to doses of 0.1 mg, 0.2 mg, 0.3 mg and 0.4 mg at 5-day intervals, and a twice-daily regimen in Cohort 3 began at an initial dose of 0.01 mg b.i.d. and was escalated as tolerated to doses of 0.02 mg, 0.03 mg, 0.04 mg, 0.05 mg, and 0.07 mg b.i.d. at 5-day intervals. In Cohorts 1 and 2, a total of 30 subjects were dosed, with 20 receiving APD811 and 10 receiving placebo. In Cohort 3, a total of 25 subjects were dosed, with 20 receiving APD811 and 5 receiving placebo.

Overall tolerability for both dosing regimens was similar; when comparing the total daily dose taken by subjects for at least 3 consecutive days, 40% of subjects tolerated a total daily dose of 0.1 mg or higher with either q.d. or b.i.d. regimens. The specific adverse events observed were similar for each of the dosing regimens and included headache, nausea, vomiting, jaw pain and flushing; nausea and vomiting occurred more frequently with the once-daily dosing regimen. The AEs observed in the study were similar to the AE profile seen with other IP agonists. As this study was designed to titrate to individual tolerability, it was not surprising that the majority of AEs for subjects on active drug were moderate in intensity and were considered by the Investigator to be probably related to study drug.

One serious adverse event (SAE), transient atrial fibrillation, occurred in a single patient during the first portion of the study after receiving 5 days of 0.05 mg q.d. Study drug was discontinued. The subject was admitted overnight to a hospital, treated with metoprolol and subcutaneous heparin and spontaneously converted to sinus rhythm. No further episodes of atrial fibrillation occurred after several additional days of monitoring, or after discharge. The investigator considered the event to be of moderate intensity and possibly related to study drug. The patient was subsequently evaluated in a cardiology clinic, with no etiology identified for the resolved bout of atrial fibrillation.

For all cohorts, the majority of AEs experienced by subjects in the active treatment group were those that coded to the System Organ Classes (SOCs) Nervous System Disorders, Gastrointestinal Disorders, and Musculoskeletal and Connective Tissue Disorders (MedDRA v. 13.1). Headache, nausea, pain in jaw, and vomiting were the most commonly reported preferred terms. There were no deaths reported in the study.

APD811 appears to be associated with a vasodilatory effect at lower doses, and reflex tachycardia at higher doses. These hemodynamic effects were not limiting for dose escalation. These observations are consistent with the expected pharmacology of APD811 and are also consistent with observations for other IP agonists.

Intensive ECG monitoring was undertaken in this study to better understand possible effects of APD811 on QT interval and to evaluate risk for QT effects. APD811 in the dose range administered in this study is not likely to be associated with QT prolongation. Mean ΔΔQTcF was below 5 msec for plasma levels up to the highest levels achieved, approximately 10 ng/mL, with an upper bound of the 90% CI below 10 msec, the threshold of regulatory concern.

Results of the pharmacokinetic measurements of APD811 demonstrate that the median time to reach maximum plasma concentration (t_{max}) for APD811 was similar between doses and occurred between 1.0 to 1.5 hours post-dose. The half-life of APD811 was consistent across doses and was between 20.5 to 26.4 hours. The apparent oral clearance (Cl/F) was low compared to hepatic blood flow. The apparent volume of distribution (V/F) was moderate (~2-fold that of total body water). Clearance and volume of distribution were dose independent.

APD811-004 was conducted as an open-label, randomized, single dose, two-treatment crossover study to assess the pharmacokinetic properties of APD811at a dose of 0.03mg in

the fed and fasted state. The t_{max} in the fed state was delayed compared to the fasted state (from 1 to ~4 hours), the C_{max} reduced (estimated GMR ~0.6), and the AUC largely maintained (estimated GMR ~0.8). These results support dosing of APD811 with food.

1.2 Ethics and Regulatory Considerations

The study will be conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki on biomedical research involving human volunteers (2008 Version), the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) E6, 21CFR Part 312 and applicable regulatory requirements, the study protocol, and where applicable, sponsor and/or Contract Research Organization (CRO) Standard Operating Procedures (SOPs). The protocol and informed consent will be submitted for consideration by the appropriate IRB/IEC and written approval from the Chair or designated deputy of the IRB/IEC is required before clinical activities of the study can commence.

The IRB/IEC must be notified promptly by the investigator of the following:

- Deviations from, or changes in, the protocol to eliminate immediate hazards to the trial patients
- Changes increasing the risk to patients and/or affecting significantly the conduct of the trial
- All AEs that meet the definition of a SAE
- New information that may affect adversely the safety of the patients or the conduct of the trial

Any changes to the protocol will be made by means of a formal written protocol amendment. All amendments will require IRB/IEC approval before implementation except when changes to the protocol are required immediately due to a safety concern.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of the study is to assess the hemodynamic effects of APD811 and the effect of APD811 in 6MWD in patients with PAH after 22 weeks of treatment, including an initial dose titration period of up to 9 weeks.

2.2 Secondary Objectives

The secondary objectives of the study are:

- to assess the safety and tolerability of APD811
- to assess the effect of APD811 on clinical worsening

2.3 Exploratory Objectives

Exploratory objectives of the study are:

- to assess the effect of APD811 on levels of BNP and NT-proBNP after 22 weeks of treatment
- to assess change in WHO/NYHA functional class
- to evaluate the pharmacokinetics of oral APD811
- to assess the effects of APD811 on systemic vascular resistance

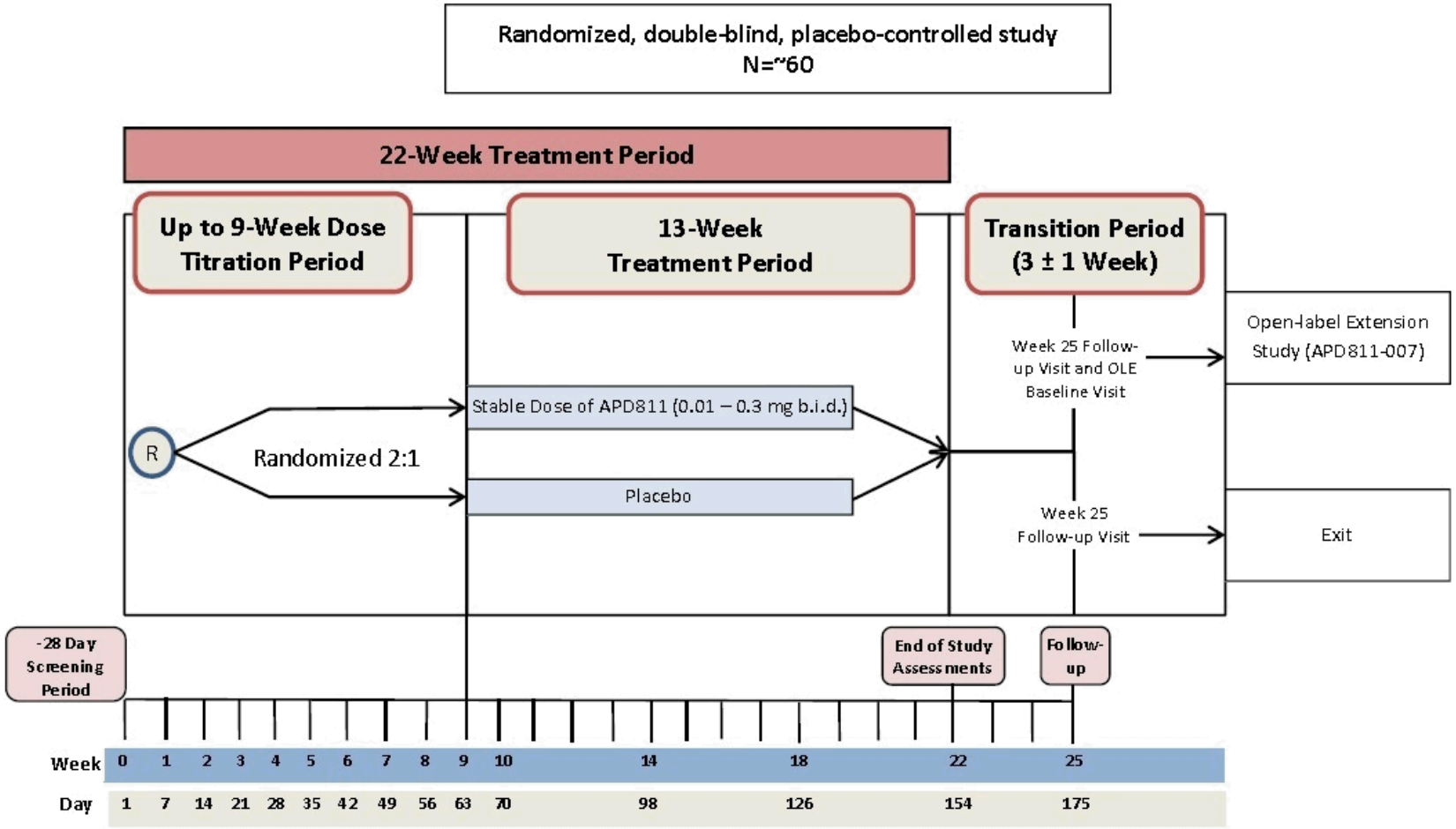
3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

APD811-003 will be conducted as a 22 week, randomized, double-blind, placebo controlled study which will include a dose titration period of up to 9 weeks. An additional transition period of 3 weeks (±1 week) will occur for those patients who elect to enroll into the open-label extension study, APD811-007. Patients that do not continue in the extension study will have a 3-week follow-up visit. Patients will be randomized 2:1 active to placebo. Approximately 60 patients with PAH will be enrolled. At the end of the treatment period, all patients that choose to continue in the open-label extension study (OLE: APD811-007) will remain on study treatment until the follow-up visit at Week 25. This visit will serve as the baseline visit for the open-label extension study if the patient is eligible and chooses to participate (see Figure 2). Patients who do not choose to participate in the OLE will discontinue treatment at the end of the treatment period.

Safety will be assessed by the Safety Monitoring Committee (SMC) as documented in the SMC Charter. The SMC will review safety data including adverse events, blood pressure and heart rate periodically during the dose titration period and the treatment period, in order to ensure patient safety and determine an appropriate dose titration regimen.

Figure 2. Schematic of APD811-003 Study Design



3.2 Study Duration and Dates

All patients will undergo screening procedures within 28 days of dosing.

All patients will receive doses of APD811 according to the dose titration scheme outlined in Section 5.6. The dose titration will take up to 9 weeks. After dose titration is completed, patients will enter a treatment period where the optimal (i.e. maximally tolerated) dose of APD811 will be continued. The schedule of procedures and visits for the dose titration period and the treatment period are provided in Table 1 and Table 2, respectively.

The SMC will review safety and tolerability and recommend any changes to the dose titration scheme.

3.3 Rationale for Study Design and Control Group

The study is designed to evaluate the safety and tolerability of APD811 in patients with PAH, and to assess the hemodynamic effects in patients with WHO Group 1 PAH after 22 weeks of treatment at an individually optimized dose. The safety evaluation will include standard evaluations of vital signs, adverse events, clinical laboratory values, and ECG measurements.

Based on the history of other IP agonists, the dose range for PAH patients may differ from that which has been observed in healthy volunteers. The study is designed to test the hemodynamic effects of APD811 in PAH patients. Based on the pharmacological action, APD811 is expected to have vasodilatory effects as well as effects on vascular smooth muscle remodeling.

Optimal dosing of IP agonists in PAH patients requires titration on an individualized basis, as tolerability improves with continued exposure and individual tolerability varies. A dose titration scheme will therefore be employed in the first part of the study (dose titration period).[15] It is anticipated that the starting dose of 0.01 mg b.i.d. will be tolerated by most, if not all patients. Data from the previous phase 1 dose titration study suggests that there are individual differences in tolerability of APD811 in healthy volunteers, consistent with findings with other prostacyclin receptor agonists.

Twice daily dosing and dosing after meals is being employed in this study to decrease peak-to-trough variability and maintain exposure, as these may be important in minimizing adverse events while maintaining activity at the IP receptor. A phase 1 study demonstrated that a high fat meal increased t_{max} from ~1 to 4 hours and decreased C_{max} by ~ 30% while preserving total drug exposure (AUC).

Table 1. Schedule of Procedures and Visits: Dose Titration Period

Evaluation[a]	Screen[b]	Dose Titration Period									
Study Week		**0**	**1[b]**	**2[b]**	**3**	**4**	**5[c]**	**6**	**7**	**8**	**9[b]**
Day	**-28**	**1**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**56**	**63**
Informed consent	X										
Medical and social history	X										
PAH history[d]	X										
Physical exam[e]	X										
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X
Safety ECG (12-lead)[g]	X	X	X	X	X	X	X	X	X	X	X
WHO/NYHA functional class assessment[h]	X	X	X	X	X	X	X	X	X	X	X
Assessment of clinical worsening		X	X	X	X	X	X	X	X	X	X
Clinical laboratory tests[i]	X	X[j]		X[j]			X[j]				X[j]
HIV, HBsAg, HCV[k]	X										

[a] Reference to pre-dose and post-dose activities in this schedule apply to the morning dose of study drug.
[b] All screening activities are to be completed within 28 days, or less, prior to dosing on Day 1.
[c] If a patient reaches the highest dose tolerated prior to Week 9, and no additional dose escalations are planned, the visit schedule may be amended at the investigator's discretion. However, visits at Weeks 1, 2, 5, and 9 of the dose titration period are mandatory.
[d] Full history of PAH diagnosis, medications, and associated illness and disease
[e] Including height and weight
[f] Vital sign measurements (blood pressure, heart rate, respirations, body temperature, and pulse oximetry (SpO_2), taken in supine position after 5-minute rest) will be taken at Screening, pre-dose on Day 1, and pre-dose during each visit in which dose escalation is planned. In addition, blood pressure and heart rate will be taken approximately every hour for the first 4 hours following dose escalation. Vital sign measurements should be taken first if they coincide with the timing of a required blood draw.
[g] Safety ECG measurements to be completed at Screening, Day 1, and at Weeks 1 - 9, unless the patient's visit schedule is amended due to reaching highest tolerated dose [see footnote c, ECGs will still be required at mandatory visits (Weeks 2, 5, and 9)]; ECGs will be completed pre-dose and 2 hours post-dose.
[h] WHO/NYHA functional class will be assessed **pre-dose** at all visits.
[i] Clinical laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis and will be taken at Screening, Day 1 and Weeks 2, 5, and 9.
[j] To be completed **pre-dose**.
[k] Patients with HIV-associated PAH may be included in the study with the approval of the medical monitor.

Evaluation[a]	Screen[b]	Dose Titration Period									
Study Week		0	1[b]	2[b]	3	4	5[c]	6	7	8	9[b]
Day	-28	1	7	14	21	28	35	42	49	56	63
DNA Sample[l]		X									
Pregnancy test[m]	X	X					X				
BNP/NT-proBNP[n]		X									
Six-minute walk test[o]	X[p]	X					X				
VQ Scan[q]	X										
Pulmonary function test	X[r]										
Echocardiogram[s]	X[t]										
Right heart catheterization[u]	X										
Study drug administration[v]		X	X	X	X	X	X	X	X	X	X
Pharmacokinetic blood sample[w]		X	X	X	X	X	X	X	X	X	X
Adverse event monitoring	←	—	—	—	—	—	—	—	—	—	→
Concomitant medication monitoring	←	—	—	—	—	—	—	—	—	—	→

[l] Optional blood sample (4mL) for DNA testing, to be taken pre-dose on Day 1.

[m] Serum hCG pregnancy test required at Screening and at Week 5; urine pregnancy test at Day1.

[n] Blood sample for BNP/NT-proBNP to be taken after 1-hour rest and prior to administration of 6MWT.

[o] 6MWT should be completed pre-dose at approximately the same time of day at each designated visit.

[p] Two 6MWTs are required during Screening and each test must be performed on a separate day. The distance walked during each test must be ≥100 meters and ≤500 meters, and within 15% of each other in order to be eligible for the study.

[q] Thromboembolic disease assessment to include a V/Q scan or spiral/helical/electron beam computed tomography utilizing an angiography protocol, or selective pulmonary angiogram, unless performed within 5 years prior to Screening.

[r] Pulmonary function test (PFT) to be completed at screening. A PFT completed within 6 months prior to Screening may be acceptable (see inclusion criteria #9).

[s] See exclusion criteria #10

[t] Transthoracic or transesophageal ECHO, unless performed within 12 months prior to Screening.

[u] A Baseline RHC is required. Patients who have had a RHC performed within 30 days of screening and meet study entry requirements are not required to have a repeat screening RHC.

[v] Should be taken with food.

[w] Blood samples for PK will be collected at pre-dose and at 4 hours post-dose during every visit in which dose escalation occurs and one week after the last dose escalation. An additional blood sample for PK analysis will be collected if possible at the time of any intolerable AE or SAE.

Table 2. Schedule of Procedures and Visits: Treatment and Dose Transition Periods

Evaluation[a]	Treatment Period			Transition Period	
				End of Study (EOS) Visit	Follow-up Visit (start of OLE) ±1 week[b]
Study Week	**10**	**14**	**18**	**22[c]**	**25**
Day	**70**	**98**	**126**	**154**	**175**
Physical exam				X	X
Safety ECG (12-lead)[d]	X	X	X	X	X
Clinical laboratory tests[e]	X	X	X	X	X
Serum pregnancy test[f]	X	X	X	X	X
Vital signs[g]	X	X	X	X	X
Study drug administration[h,i]	◄———	———	———	———[j]	——— ►
Six-minute walk test[k]	X	X	X	X	X
Right heart catheterization				X[l]	

[a] Reference to pre-dose and post-dose activities in this schedule apply to the morning dose of study drug.

[b] For patients who terminate early from the study and is unable to return for the follow-up visit at Week 25, AE and concomitant medication follow-up may be conducted by telephone.

[c] Patients should have all assessments including RHC, 6MWT and BNP/NT-proBNP completed prior to entering the transition period.

[d] Safety ECGs should be completed **pre-dose**.

[e] Clinical laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Clinical laboratory tests will be completed **pre-dose**.

[f] Serum pregnancy test will be completed **pre-dose** at each visit during the treatment period.

[g] Vital sign measurements (blood pressure, heart rate, respirations, body temperature, and pulse oximetry, taken in supine position after 5-minute rest) will be taken **pre-dose**.

[h] Study drug should be taken with food.

[i] On days with scheduled study visits, patients should **not** take their morning dose of study medication at home in order to complete pre-dose study procedures.

[j] Patients entering the APD811-007 study will remain on current dose through the transition period. Patients who do not continue into the APD811-007 study will discontinue study medication at Week 22 visit but not prior to undergoing the final RHC, and will return for follow-up visit at Week 25; if the patient is unable return for the follow-up visit, AE and concomitant medication follow-up may be conducted by telephone.

[k] 6MWT should be completed **pre-dose** at approximately the same time of day at each designated visit.

Evaluation[a]	Treatment Period			Transition Period	
				End of Study (EOS) Visit	Follow-up Visit (start of OLE) ±1 week[b]
Study Week	**10**	**14**	**18**	**22[c]**	**25**
Day	**70**	**98**	**126**	**154**	**175**
BNP/NT-proBNP[m]	X			X	X
Pharmacokinetic blood sample[n]	X	X	X	X	
WHO/NYHA functional class assessment[o]	X	X	X	X	X
Assessment of clinical worsening	X	X	X	X	X
Adverse event monitoring	←	—	—	—	→
Concomitant medication monitoring	←	—	—	—	→

[l] RHC will be performed as part of Week 22 end-of-study procedures.

[m] Blood sample for BNP/NT-proBNP to be taken after 1-hour rest and prior to administration of 6MWT.

[n] PK blood samples will be collected **prior to the morning dose** and 4 hours post-dose at every visit; an additional blood sample for PK analysis will be collected if possible at the time of any intolerable AE or SAE.

[o] WHO/NYHA functional class will be assessed **pre-dose** at all visits.

4 STUDY POPULATION SELECTION

4.1 Study Population

The study population will consist of adult male and female patients diagnosed with pulmonary arterial hypertension (symptomatic WHO Group 1 PAH) aged 18 to 75 years, inclusive. Up to 60 patients with PAH will be studied.

Eligible patients must meet all entry criteria prior to being randomized to receive study medication as outlined below. Any patient specific concerns or questions regarding these criteria must be discussed with the medical monitor or Arena Pharmaceuticals, Inc. prior to the patient being randomized.

4.2 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be eligible for enrollment into the study.

1. Males or females aged 18-75 years, inclusive
2. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study prior to initiation of any patient-mandated procedures
3. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures
4. Has a diagnosis of symptomatic WHO Group 1 PAH classified by one of the following subgroups:
   a. Idiopathic pulmonary arterial hypertension (IPAH);
   b. Heritable pulmonary arterial hypertension (HPAH);
   c. Drugs and toxins induced;
   d. Associated with pulmonary arterial hypertension (APAH); specifically:
      i. connective tissue disease (CTD)
      ii. HIV infection (see section 6.10.2)
      iii. Congenital systemic-pulmonary shunt (must have undergone surgical correction at least 1 year prior to screening)
5. Has had a RHC prior to Screening and at screening that is consistent with the diagnosis of PAH meeting **all** of the following criteria:
   a. mPAP ≥25 mmHg (at rest); **and**
   b. PCWP ≤15 mmHg;

      If PCWP is not available, then mean left atrial pressure (mLAP) or left ventricular-end diastolic pressure (LVEDP) ≤15 mmHg in the absence of left atrial obstruction; and

c. PVR >3 mmHg/Liter (L)/minute (min) or 240 dyn.sec/cm^5

d. Patients who have had a RHC performed within 30 days of screening and meet study entry requirements are not required to have a repeat screening RHC as long as the results meet study entry criteria

6. Has WHO/NYHA functional class II- IV symptomatology
7. Be on stable oral disease-specific PAH therapy with either an ERA and/or an agent acting on the nitric oxide pathway, PDE5 inhibitor or a soluble guanlyate cyclase stimulator

   a. Stable is defined as no change in dose within **3 months** of the start of Screening and for the duration of the study

   b. If the patient's disease-specific PAH therapy does not include a PDE-5i, the use of PDE-5i as needed for erectile dysfunction (ED) is permitted as long as the patient has not taken a dose within 48-hours of any Baseline or study related efficacy assessment. In addition, the patient must not take more than 8 sildenafil tablets, 6 vardenafil, or 4 tadalafil tablets per month for ED.

   c. Patients may be on **one** agent active in the NO pathway, either a PDE5i or a sGCs at stable dose (but not both)

8. Has a 6MWT distance of ≥100 meters and ≤500 meters, and within 15% of each other on **2 consecutive tests on different days during Screening**
9. Has PFTs within 6 months prior to the start of Screening with no evidence of significant parenchymal lung disease. PFTs will be performed as part of screening procedures, if data within 6 months of Screening is not available. Significant evidence of parenchymal lung disease is defined as:

   a. Forced expiratory volume in 1 second (FEV_1) ≤70% (predicted) (pre-bronchodilators); or

   b. Forced expiratory volume in 1 second/forced vital capacity ratio (FEV_1/FVC) ≤70% (pre-bronchodilators); or

   c. Total lung capacity (TLC) <70% (predicted).

10. Has no evidence of thromboembolic disease (i.e. should note "normal" or "low probability" for pulmonary embolism) as determined by ventilation-perfusion (V/Q) lung scan or pulmonary angiogram within 5 years prior to Screening

    - V/Q scanning is preferred, but if unavailable, spiral/helical/electron beam computed tomography (CT) angiography is acceptable in patients with NO history of venous thromboembolic disease
    - If V/Q scan is unavailable and patient has a prior history of venous thromboembolic disease, then selective pulmonary angiography is required to exclude chronic thromboembolic disease
    - If a V/Q scan is abnormal (i.e. anything other than "normal" or "low probability"), then a selective pulmonary angiography must be conducted to exclude chronic thromboembolic disease

- All required tests must be performed prior to Screening or such tests may be requested if clinically indicated to exclude chronic thromboembolic pulmonary hypertension

11. If on the following therapies, which may affect PAH: vasodilators (including calcium channel blockers), digoxin, spironolactone, or L-Arginine supplementation; the patient must be on a stable dose for at least 1 month prior to the start of Screening and the dosage maintained throughout the study.
12. Patients with obstructive sleep apnea must be asymptomatic and on stable therapy for 6 months prior to the start of Screening and no changes in therapy are anticipated for the duration of the study
13. Eligible female subjects will be:
    a. non-pregnant, evidenced by a negative serum human chorionic gonadotropin (hCG) pregnancy test at Screening and a urine dipstick pregnancy test on Day 1
    b. non-lactating
    c. surgically sterile or postmenopausal, or agree to continue to use an accepted method of birth control for at least **3 months** prior to first dose, during, and for at least **30 days** after last study medication administration
        - Acceptable methods of birth control are: hormonal contraceptives; double barrier method; intrauterine device; surgical sterility for at least **6 months** prior to screening for tubal ligation performed laparoscopically; surgical sterility for at least **6 months** prior to screening by hysterectomy and/or bilateral oophorectomy; and/or postmenopausal status (defined as at least **2 years** without menses). Intended abstinence is not considered an acceptable method of birth control for this study; subjects must agree to use an acceptable method of birth control should they become sexually active during the study or within **30 days** after the last dose of study medication.
    d. Eligible male subjects will either be:
        - Surgically sterile (i.e., vasectomy), for at least **3 months** prior to screening

    or

        - Agree to use a condom with spermicide when sexually active with a female partner who is not using an acceptable method of birth control during the study and for **30 days** after last study medication administration

14. Eligible male and female subjects must agree not to participate in a conception process (i.e. active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization) during the study and for **30 days** after the last dose of study drug
15. Body weight of at least 45 kg at Screening
16. Patients ages >60 years **or** for whom screening PCWP is >12 mmHg **must** be discussed with and approved by the medical monitor prior to randomization

Note: 1 month = 30 days

4.3 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study.

1. Newly diagnosed with PAH and on no disease-specific PAH therapy
2. Prior participation in any study of APD811
3. Previous participation in any clinical study with an investigational drug, biologic, or device within **2 months** prior to the Screening visit
4. Male patients with a QTc >450 msec on screening ECG
5. Female patients with a QTc >470 msec on screening ECG
6. Participation in a cardio-pulmonary rehabilitation program based upon exercise within **1 month** prior to Screening and/or during study participation
7. Acutely decompensated heart failure within **1 month** prior to Screening
8. Has uncontrolled systemic hypertension as evidenced by sitting systolic blood pressure (BP) >160 mmHg or sitting diastolic blood pressure >100 mmHg at Screening
9. Systolic BP <90 mmHg during Screening
10. Evidence or history of left-sided heart disease and/or clinically significant cardiac disease, including but not limited to any of the following:
    a. Echocardiogram (ECHO) within 12 months prior to Screening demonstrating significant left-sided heart disease including LV ejection fraction <40%
    b. History of coronary artery disease
    c. History of significant valvular heart disease
    d. Restrictive or congestive cardiomyopathy
    e. History of cardiac arrhythmia, including atrial fibrillation or ventricular arrhythmia
    f. Clinically significant conduction disorder (PR interval greater than or equal to 210 msec, QRS interval ≥120, second degree block)
11. Use of chronic administration (defined as >30 days) of a prostacyclin or prostacyclin analogue within 3 months of Screening.
12. Any previous use of a prostacyclin or prostacyclin analogue that was stopped for safety or tolerability issues associated with pharmacology/mechanism of action. Previous use of prostacyclin for acute vasodilator testing during cardiac catheterization is permitted.
13. History of atrial septostomy within **6 months** prior to start of Screening
14. Diagnosis of Down Syndrome
15. History of portal hypertension or chronic liver disease, including hepatitis B and/or hepatitis C
16. Chronic renal insufficiency as defined by serum creatinine >2.5 mg/dL or has an estimated Glomular Filtration Rate (eGFR) <30 mL/min at screening, or requires dialytic support.

17. Hemoglobin (Hgb) concentration <8.5 g/dL at screening
18. Requirement of intravenous inotropes within **1 month** prior to start of Screening
19. For patients with HIV associated PAH, any of the following:
    a. Concomitant active opportunistic infections within 6 months prior to Screening;
    b. Detectable viral load within 3 months of Screening;
    c. Cluster designation 4 (CD4+) T-cell count <200 mm^3 within 3 months of Screening;
    d. Changes in antiretroviral regimen within 3 months of Screening;
    e. Use of inhaled pentamidine.
20. Malignancy within **5 years** of the screening visit (with the exception of basal cell skin cancer excised with curative intent)
21. Recent history (within **2 years** prior to the screening visit) of alcohol or drug/solvent abuse.
22. Documented sensitivity to gelatin (APD811 will be contained in gelatin capsules)
23. Other severe acute or chronic medical or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study including, but not limited to the following:
    a. Clinically significant new illness in the **1 month** before screening based on the investigator's discretion
    b. History of severe drug or excipient allergy or hypersensitivity
    c. History of severe allergies (i.e., anyone with a known history of anaphylaxis to medication[s] or allergens and/or asthma requiring hospitalization)
    d. Significant blood loss within **6 months** of dosing
    e. Plasma donation within **1 week** prior to dosing
    f. A psychiatric, addictive or other disorder that compromises the ability to give informed consent for participating in this study
    g. History of cerebrovascular disease
    h. History of epilepsy or other seizure disorder
    i. History of unexplained syncope
    j. History of organ transplantation

Note: 1 month = 30 days

5 STUDY TREATMENTS

5.1 Test Article

Arena Pharmaceuticals will provide adequate supplies of APD811 and placebo capsules. Placebo and active drug capsules will have the same appearance. APD811 will be provided as 0.01, 0.02, 0.03, 0.04 mg, and 0.10 mg dose strengths.

5.2 Treatments Administered

The APD811 formulation is a liquid-filled, size 4, hard-gelatin capsule containing APD811, polyoxyl 40 hydrogenated castor oil (Kolliphor® RH40) NF, butylated hydroxytoluene (BHT) NF, and colloidal silicon dioxide NF. The placebo formulation is a liquid-filled, size 4, hard-gelatin capsule containing Kolliphor® RH40 NF, BHT NF, and colloidal silicon dioxide NF.

APD811 used for the capsules was manufactured under Current Good Manufacturing Practices (CGMP) compliance at Arena Pharmaceuticals, San Diego, CA. The APD811 and placebo capsules will be manufactured under CGMP compliance by Arena Pharmaceuticals, San Diego, CA, and shipped to the clinical study site prior to the study start.

5.3 Packaging, Labeling and Storage

For each dosage strength, 74 capsules will be bulk packaged in 40 cc high-density polyethylene bottles with a heat induction seal and child resistant screw caps. These bottles should be stored under refrigeration at 2ºC (36 ºF) to 8ºC (46 ºF); the bottles should not be frozen.

5.4 Test Article Accountability

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

5.5 Investigational Product Retention at Study Site

At completion of the study, all study medication will be reconciled by the Arena monitor or contracted designee and then returned at the direction of Arena to either Arena or a third party contractor to be retained or destroyed according to applicable country regulations and investigative site standard operating procedures. Prior to any action being taken with study medication after the study is completed, the investigator will contact Arena (or contracted CRO) for approval of such action.

5.6 Dosage and Administration

Investigational product will be dispensed in a blinded fashion to the patients under the supervision of the investigator or his/her designee as determined by the randomization schedule. Patients should not crush, break, chew, or dissolve the capsules. Patients should wash hands with soap and water after handling drug product.

Capsules should be taken with food.

5.6.1 Dose Titration Period (up to 9 Weeks)

There will be a total of approximately 60 patients randomized to either active treatment or placebo in a 2:1 ratio. The starting dose is 0.01 mg APD811 twice daily (b.i.d.) or placebo. Thus, the identity of study drug (active or placebo) will be blinded, but the dose level is not. Patients will be observed for at least 4 hours after the initial dose of APD811 and after each subsequent dose escalation. A pre-dose and a 4-hour post-dose PK sample will be collected at each study visit in which dose escalation is planned. Adverse events, blood pressure, and heart rate will be monitored during the observation period. The observation period may be extended based on the judgment of the investigator. If deemed necessary by the investigator, the patient may be monitored as an in-patient for the initial dose and/or subsequent increases in dose. The medical monitor should be notified in any instance that prolonged observation and/or in-patient monitoring is anticipated or required.

If a dose is not tolerated, the study drug may be decreased to the previous dose level. If the initial dose of 0.01 mg b.i.d. is not tolerated, dosing may be decreased to 0.01 mg q.d.

If the initial dose is tolerated (0.01 mg b.i.d.), the dose will be increased in the following fashion at subsequent visits: 0.02 mg b.i.d., 0.03 mg b.i.d., 0.04 mg b.i.d., 0.06 mg b.i.d., 0.08 mg b.i.d., 0.1 mg b.i.d., 0.2 mg b.i.d and 0.3 mg b.i.d. The dose may be escalated to a maximum total daily dose of 0.6 mg (0.3 mg b.i.d.) depending on tolerability.

Prolonged dosing may result in tolerance to some adverse effects and thus, more than 1 week between dose escalations may be required. However, Investigators are encouraged to dose escalate to the highest possible dose within the 9-week dose titration period. If a particular dose is not tolerated, treatment may be reduced to a previous dose as directed by the investigator. The dose may be decreased for safety reasons at any time, but may not be increased without assessment in the clinic.

Table 3 indicates the dosing regimen during the 9-week dose titration period. This dosing regimen (starting dose, dose increments, dosage forms, duration) may be modified during the course of the study by the Safety Monitoring Committee based on cumulative patient experience. In order to simplify dose titration, the 0.01 mg dose strength will be used during the initial portion of the dose titration.

If a patient reaches the highest dose tolerated prior to Week 9, and no additional dose escalations are planned, the visit schedule may be amended at the investigator's discretion. However, visits at Weeks 1, 2, 5, and 9 of the dose titration period are mandatory.

Table 3. Possible Dosing Regimen during 9-Week Dose Titration Period

Dose (mg)	Supplied by	Total daily dose
0.01 q.d.	1 x 0.01 mg once daily	0.01 mg
*0.01 b.i.d.	1 x 0.01 mg twice daily	0.02 mg
0.02 b.i.d.	2 x 0.01 mg twice daily	0.04 mg
0.03 b.i.d.	3 x 0.01 mg twice daily	0.06 mg
0.04 b.i.d.	4 x 0.01 mg twice daily	0.08 mg
0.06 b.i.d.	3 x 0.02 mg twice daily	0.12 mg
0.08 b.i.d.	4 x 0.02 mg twice daily	0.16 mg
0.1 b.i.d.	5 x 0.02 mg twice daily	0.2 mg
0.2 b.i.d.	2 x 0.1 mg twice daily	0.4 mg
0.3 b.i.d.	3 x 0.1 mg twice daily	0.6 mg

* starting dose

5.6.1.1 Treatment Period

The optimal dose achieved for each patient at the end of the dose titration period will be maintained throughout the treatment period. Table 4 indicates the possible dosing regimens to be used during the remainder of the treatment period according to each individual patient's optimally defined dose.

Table 4. Possible Dosing Regimen during the 16-Week Treatment/Transition Period

Dose (mg)	Supplied by	Total daily dose
0.01 q.d.	1 x 0.01 mg once daily	0.01 mg
0.01 b.i.d.	1 x 0.01 mg twice daily	0.02 mg
0.02 b.i.d.	1 x 0.02 mg twice daily	0.04 mg
0.03 b.i.d.	1 x 0.03 mg twice daily	0.06 mg
0.04 b.i.d.	1 x 0.04 mg twice daily	0.08 mg
0.06 b.i.d.	2 x 0.03 mg twice daily	0.12 mg
0.08 b.i.d.	2 x 0.04 mg twice daily	0.16 mg
0.1 b.i.d.	1 x 0.1 mg twice daily	0.2 mg
0.2 b.i.d.	2 x 0.1 mg twice daily	0.4 mg
0.3 b.i.d.	3 x 0.1 mg twice daily	0.6 mg

5.6.2 Study Transition Period

At the end of the treatment period and after all Week 22 study assessments are performed, patients who are eligible and who elect to enroll in the APD811-007 study, will continue current treatment through the 3 week (±1 week) follow-up visit (Week 25). During this 3-week (±1 week) period, the individual patient database will be locked allowing for

subsequent unblinding of the individual patient and enrollment into the APD811-007 OLE. The Week 25 visit will serve as the baseline visit for the APD811-007 OLE study.

For patients who do not enter the extension study, study drug is stopped after the treatment period at the Week 22, End of Study Visit.

5.7 Safety Monitoring Committee

The roles and responsibilities of the SMC will be outlined in a separate charter. The SMC will include the following members: at least 2 physicians, representing expertise in clinical care of patients with PAH, and expertise in drug development; and a biostatistician. The SMC will oversee the safe conduct of the trial, and in particular, guide dose titration in order to determine a suitable scheme to achieve the optimal dose within the 9-week titration period while maintaining patient safety. Based on review of safety and tolerability information, the SMC may recommend a higher starting dose, different dose increments (escalation scheme), different dosage strengths, and/or duration.

5.8 Method of Assigning Patients to Treatment Groups

At the beginning of the dose titration period, eligible patients will be randomly assigned to receive 1 of 2 study treatments, either APD811 or placebo in a 2:1 ratio. Patient randomization numbers will be assigned after successful completion of all screening procedures.

5.9 Randomization

5.9.1 Randomization

Approximately 60 patients will be randomized for entry into the study using an Interactive Web Randomization System (IWRS). Patients will be randomized to either APD811 or placebo in a 2:1 ratio.

5.9.2 Maintenance of Randomization Codes and Code-break Procedures

The sponsor, patients, and personnel involved with the conduct of the study will be blinded to the identity of study medication, with the exception of the independent statistician responsible for generating the randomization code and interacting with the SMC, and a representative from the bioanalytical lab conducting the pharmacokinetic (PK) analysis. All other personnel directly related to this study (i.e., investigators, site personnel, monitors, CRO personnel, Arena personnel) will remain blinded until patient completion of the study and the patient's data in the clinical database is locked, at which time the randomization code will be broken for the individual patient. The CRO will obtain written consent from Arena prior to breaking the code.

Breaking of the randomization code without Arena permission is expressly forbidden except in the event of a medical emergency where the identity of the study medication must be known in order to properly treat the patient. In the event of a medical emergency, it is requested that the Investigator make every effort to contact the study monitor or designee

prior to breaking the code. If the blind is broken, the individual responsible should document the date, time, and reason for breaking the blind. A written report should be sent to Arena **within one working day**.

6 STUDY PROCEDURES

6.1 Informed Consent

The investigator will obtain and document the volunteer ICF for each patient screened for this study. All patients will be informed in writing of the nature of the protocol and investigational therapy, its possible hazards, and their right to withdraw at any time, and will sign a form indicating their consent to participate prior to the initiation of study procedures. The patient's medical record should contain written documentation indicating that informed consent was obtained. The ICF must be reviewed and approved by the investigator's designated IRB/IEC and by the sponsor. The ICF should include all the elements as outlined in Section 4.8.10 of the ICH guideline for GCP (E6).

6.2 Medical and Social History

At screening, relevant and clinically significant medical and social history will be collected by patient interview. History will include tobacco, alcohol, and caffeine use, and any history of alcohol or substance (drug/solvent) abuse. Concomitant medications, recent blood donations, illnesses, and participation in other investigational drug studies will also be recorded.

6.2.1 History of PAH

A complete patient history of PAH, including diagnosis, associated illness and diseases, and medications will be collected by chart review and patient interview.

6.3 Physical Examination

The physical examination will include measurement of height (screening only) and weight and should be performed in a consistent manner throughout the study with each body system assessed and changes/no changes noted as compared to Baseline.

6.4 Vital Signs

Supine blood pressure (BP), heart rate (HR), body temperature, respiratory rate (RR) and pulse oximetry will be measured after the patient has been resting for 5 minutes according to Table 1 and Table 2.

or following early termination of the study. Vital signs will be measured prior to any blood draw that occurs at the same time point.

Proper technique should be utilized during the measurement of BP to include the following:

- Subjects should be allowed a 5-minute rest period before each assessment.
- Readings should be taken on the subject's non-dominant arm consistently throughout the study.
- The subject's arm should be bare and supported at heart level.

- An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be utilized. Subject's legs should not be crossed during the evaluation.

In addition, subjects should be queried concerning caffeine or tobacco use, neither of which is permitted within 30 minutes prior to BP measurements.

It is also critical that standard, consistent, definitions of systolic BP (sBP) and diastolic BP (dBP) be utilized. Systolic BP is the point at which the first of 2 or more sounds are heard. Diastolic BP is the point before the disappearance of sounds. The results of the measurement of sBP and dBP should not be rounded.

6.5 Electrocardiography

6.5.1 ECG Equipment

6.5.2 Safety ECG Equipment

Safety ECGs will be recorded from an ECG machine (12-lead). Safety ECGs will be printed and reviewed on site by the PI or designee. Safety ECGs will be captured, recorded, and analyzed according to the Centralized ECG Procedure Manual.

6.5.3 ECG Acquisition

The safety ECG equipment will be set according to the procedure manual. The operator will enter certain patient demographic information prior to obtaining the ECG. Every attempt will be made to ensure that patient ECG readings throughout the study will be obtained from the same machine. Patient information will be entered into the machine according to the ECG procedure manual and may include the following:

- Patient initials (example: XYZ or X-Z)
- Patient identifier (screening and/or randomization number)
- Patient gender
- Patient date of birth (DDMMMYYYY)
- Study day and time

ECGs will be recorded with patients in the recumbent position and resting. Patients will have been in this resting position for 10 minutes prior to ECG recording and performed prior to any blood draw that occurs at the same time point.

In case of baseline tremor, measures will be taken to eliminate this as it may interfere significantly with the quality of the interpretation. Prior to electrode placement, the anatomical sites will be prepared to allow for proper skin/electrode interface. Patients with excessive hair will be dry shaven, as needed.

Intervals to be provided on the confirmed read for each safety ECG are: RR, PR, QRS, QT, QTc, QTcB, and QTcF.

6.5.4 ECG Assessment

Safety ECGs will be performed as outlined in Table 1 and Table 2, or following early termination of the study. Post-screening ECGs will be compared with screening ECG.

The PI or sub-investigator (physician) will be responsible for review and interpretation of safety ECGs on site and determining if the ECG is normal, abnormal clinically insignificant or abnormal clinically significant. Findings will be documented in the CRF. This information will be used in the ongoing safety review during the conduct of the trial.

6.6 Six-minute Walk Test

The 6MWT will be conducted the according to the modified guidelines issued by the American Thoracic Society, "ATS Statement: Guidelines for the Six-minute Walk Test".[24] Technicians performing the test will be trained according to published procedures (Appendix 1). Tests will be performed at approximately the same time of day for each test in order to minimize intraday variability.

6.7 WHO/NYHA Functional Class Assessment

PAH will be classified according to a system originally developed for heart failure by the New York Heart Association (NYHA) and then modified by the World Health Organization (WHO) for patients with PAH.[12] The severity of PAH will be graded according to the functional status of the patient and assessed at every visit. The grades range from Functional Class (FC) I, where the patient's disease does not affect their day-to-day activities, to FC IV, where patients are severely functionally impaired, even at rest (see Appendix 2).

The same Investigator or designee should complete the WHO/NYHA functional class evaluation at the patient's first visit and for the duration of the study when possible. See Appendix 2.

6.8 Right Heart Catheterization

RHC measurements will be obtained prior to study Day 1 of the dose titration period and at Week 22. At Week 22, it is recommended that every effort should be made to take the measurements approximately 4 hours after the last dose of study drug. RHC should be performed when a patient terminates from the study early. Patients who have had a RHC performed within 30 days of screening and who meet study entry requirements are not required to have a repeat screening RHC.

The following values will be obtained and recorded: PAP (systolic, diastolic, and mean), HR, right atrial pressure (RAP), pulmonary capillary wedge pressure (PCWP) right ventricular pressure (RVP) and cardiac output (CO), pulmonary vascular resistance (PVR), arterial and mixed venous oxygen saturation, FiO2 (if applicable). Systemic vascular resistance (SVR) will be estimated from blood pressure measurements. Further specifications will be provided in a separate study manual.

6.9 Assessment of Clinical Worsening

The Investigator will evaluate the patient for potential clinical worsening throughout the study. If clinical worsening is suspected, additional clinic evaluations may be required to make a final determination as to whether clinical worsening has been met. Clinical worsening is defined as one of the following:

- Death, or onset of treatment-emergent AE with a fatal outcome occurring less than or equal to 14 days after study treatment discontinuation; **or**
- Hospitalization for heart-lung or lung transplant, or atrial septostomy; **or,**
- The patient requires the addition (or change in dose if applicable) of any of the following PAH specific medications:
    - Prostacyclin/prostacyclin analogue (intravenous, subcutaneous, oral or inhaled)
    - Phosphodiesterase type-5 inhibitors
    - Soluble guanylate cyclase stimulator
    - Endothelin receptor antagonist, **or**
- The combined occurrence of the events listed below.
    - A decrease in 6MWT by at least 20% from Baseline, confirmed on two 6MWTs, on different days; **and**
    - Increase (worsening) in WHO/NYHA FC from Baseline; **and**
    - Appearance of or worsening of signs/symptoms of right heart failure that did not respond to optimized oral diuretic therapy.

In cases of clinical deterioration, the investigator must assess carefully if the deterioration of the patient's condition (e.g. worsening functional class) is related to the underlying pulmonary hypertension or can be explained by an alternative cause (e.g. transient infection, musculoskeletal disease, surgical or medical intervention other than PH related, exacerbation of a concomitant lung disease, lacking compliance of medication intake). Only persistent clinical deteriorations caused by the underlying pulmonary arterial hypertension and confirmed as per the above criteria, will be considered clinical worsening.

Transient deteriorations of clinical status requiring hospitalization, treatable by, for example, short-time application of intravenous diuretics, positive inotropic agents or non-invasive ventilation and allowing patients discharge within 48 hours, are not considered to meet the criteria for clinical worsening. Patients should be discontinued only if any of the above criteria exceed 48 hours.

Patients who meet the criteria for clinical worsening should be discontinued from study drug, and should undergo procedures for early termination. Patients who meet the criteria for clinical worsening do not qualify for entry into the extension study APD811-007 with the exception of placebo-treated patients.

Placebo-treated patients who discontinue study drug treatment due to clinical worsening in APD811-003 will be permitted to enroll in APD811-007, upon approval of the medical monitor, provided that all end of study procedures including right heart catheterization are performed per protocol.

6.10 Clinical Laboratory Tests

All details regarding clinical laboratory sample collection, preparation, and shipment are included in the laboratory manual provided by the local or central laboratory and the PK manual provided by the sponsor.

In the event of abnormal clinical laboratory values, the physician will make a judgment whether or not the abnormality is clinically significant.

6.10.1 Laboratory Parameters

Clinical laboratory tests will include the following:

Serum Chemistry
Albumin (ALB)
Alkaline phosphatase (ALK-P)
Alanine aminotransferase (ALT; SGPT)
Amylase
Aspartate aminotransferase (AST; SGOT)
Bicarbonate
Blood urea nitrogen (BUN)
Calcium (Ca)
Chloride (Cl)
Creatinine
Creatine kinase and MB subtype (if elevated)
Gamma-glutamyl transferase (GGT)
Glucose
Lactate dehydrogenase (LDH)
Lipase
Magnesium
Phosphate
Potassium (K)
Sodium (Na)
Total bilirubin
Total cholesterol
Total protein
Triglycerides

Hematology
Hematocrit (Hct)
Hemoglobin (Hb)
Mean corpuscular hemoglobin (MCH)
Mean corpuscular volume (MCV)
Platelet count
Red blood cell count (RBC)
White blood cell count (WBC) with differential

Coagulation
Prothrombin time (PT)
Activated partial thromboplastin time (PTT)
International normalized ration (INR)

Additional tests
Serum human chorionic gonadotropin (hCG)
B-type natriuretic peptide (BNP)
N-terminal pro-brain natriuretic peptide (NT-proBNP) levels

6.10.2 Virology

Human immunodeficiency virus (HIV antibody), hepatitis B (HBsAg), and hepatitis C virus (RIBA 2 or 3) screening tests will be performed at screening only. Patients with HIV-associated PAH may be included in the study with the approval of the medical monitor.

6.10.3 Urinalysis

Urinalysis parameters for clinical laboratory tests include the following:

- appearance
- bilirubin
- color
- glucose
- ketones
- leukocyte esterase
- occult blood
- pH
- protein
- specific gravity
- urobilinogen

6.10.4 Sample Collection, Storage, and Shipping

Blood samples for hematology, coagulation parameters, serum chemistry, HIV and hepatitis screens, and serum hCG will be collected according to the laboratory manual provided by the local or central laboratory and according to the schedule of events presented in Table 1.

6.10.5 Blood Volume

Total blood volume for clinical laboratory tests will be approximately 130 mL.

6.11 Pharmacokinetic and Pharmacodynamic Assessments

Blood samples will be processed for collection of plasma fractions for determination of APD811 plasma concentrations. PK blood samples will be collected pre-dose and at 4 hours post-dose during the dose titration period at each study visit where dose escalation is planned and during each study visit within the treatment period.

An additional blood sample for PK analysis will be collected if possible at the time of any intolerable AE or SAE. No urine samples will be collected.

At each PK time point, approximately 3 mL of blood will be collected, and the plasma will be harvested. Plasma samples will be shipped to the analytical lab for analysis. A PK sample collection manual will be provided to instruct the type of anticoagulant, the material supplies, sample processing, storage and shipping procedures.

6.12 BNP/NT-proBNP

As mean pulmonary artery pressure increases, so do BNP and NT-proBNP levels as long as left ventricular function is intact. In idiopathic pulmonary artery hypertension, BNP and NT-proBNP levels are related to functional impairment.

As BNP/NT-proBNP may be affected by recent exercise, patients must be allowed to rest for a minimum period of **one hour** following arrival at the clinic, prior to obtaining this blood sample. Similarly, this sample must be taken prior to the 6MWT. This sample should be taken with the patient in the same position at all appropriate visits, e.g., sitting or semi-recumbent.

A 3 mL blood sample will be collected at the required visits to provide at least a 1.5 mL plasma sample for this assay. Detailed instructions will be provided in a separate sample collection manual.

6.13 Adverse Events Assessments

AEs will be recorded and reported in accordance with ICH Good Clinical Practice (GCP). The definitions of AEs and SAEs will be as given in the ICH Topic E2A, ICH Guideline "Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting."

6.13.1 Adverse Event Reporting

Patients will be instructed that they may report AEs at any time. AEs will be regarded as 'pre-treatment' if they occur between Screening and the time of administration of the first dose of APD811. All events reported following study medication administration will be recorded as treatment emergent AEs (TEAE).

Monitoring of AEs will be continued **up to 30 days** after study medication administration. In the event that 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 close-out the event in the database if no further follow-up is necessary.

For this study, an AE is defined as: "Any untoward medical occurrence in a study patient administered any dose of study medication (APD811 or placebo) and which does not necessarily have to have a causal relationship with this treatment." An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study medication, whether or not related to the product. Worsening of underlying disease (section 6.9) will not be considered to be an adverse event.

AEs can be 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 observed in a patient in the course of a clinical study

- Pre-existing conditions which worsen in severity or frequency or which have new signs/symptoms associated with them

Adverse events will be elicited at the time indicated in the schedule by asking the question: "Since you were last asked, have you felt unwell or different from usual in any way?" Any adverse or unexpected events, signs and symptoms, will be fully recorded on the Adverse Event Form including details of intensity, onset, duration, outcome and relationship to the drug as determined by the PI. Whenever possible, a constellation of signs and symptoms should be recorded as a unifying diagnosis (e.g., self-limited fever, runny nose, cough, and scratchy throat should be captured as an upper respiratory infection rather than by the individual signs and symptoms). AEs may also be reported at any time. The type and duration of follow-up of patients after AEs will be documented.

6.13.2 Serious Adverse Events and Expedited Reporting of Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose results in the following outcomes:

- Death
- Is Life-Threatening
- Required/Prolonged Hospitalization
- Disability/Incapacity
- Congenital Anomaly/Birth Defect
- Important Medical Event

SAEs will be captured from the time of screening to 30 days after the dose of study drug, and will be monitored until resolution or stabilization.

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such a medical event includes allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

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

All SAEs, whether or not considered related to study treatment, must be reported to the sponsor Contact within 24 hours of becoming aware of the event. In addition, a completed report using the sponsor's SAE form must be submitted within 24 hours of notification to:

Arena Drug Safety and Pharmacovigilance
Arena Pharmaceuticals, Inc.
6154 Nancy Ridge Drive
San Diego, California 92121

Other situations as defined in ICH Topic E2A, 21 CFR§ 312.32, and EU Volume 10 also qualify for expedited reporting. In these situations the process will be as detailed for SAEs above:

- Serious adverse events which could be associated with the trial procedures;
- Serious adverse events and adverse events of special interest that could materially influence the benefit-risk assessment of a medicinal product, such as: a clinically important increase in the rate of a serious suspected adverse reaction over that listed in the investigator brochure.

Patients who become pregnant during the study will be discontinued immediately. Although not considered a SAE or AE, pregnancies occurring during the period of study drug administration (Day 1 of the dose titration period to Week 25/ Follow-up) until 30 days after the last dose of study drug should be reported to the sponsor Contact and IRB/IEC in the same manner as a SAE.

Pregnancies will be followed every trimester through the first well baby visit. For female partners who become pregnant by male study patients during the course of the study, reasonable efforts will be made to collect information on the partner's pregnancy through the first well baby visit as provided by the male study patient.

6.13.3 Assessment of Adverse Event Severity

The severity of each AE will be assessed at onset by a nurse and/or physician. When recording the outcome of the AE the maximum severity of the AE experienced will also be recorded. The severity of the AE will be graded according to the CTCAE v4.03[23] definitions, listed below:

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 (ADL)*.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.13.4 Assessment of Adverse Event Relationship to Study Medication

The relationship of an AE to investigational product(s) will be classified using modified WHO criteria (Edwards and Biriell, World Health Organization Collaborating Centre for International Drug Monitoring 1994) as follows.

Related: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition; or an event that could also be explained by concurrent disease or other drugs or chemicals where information on drug withdrawal may be lacking or unclear.

Not related: a clinical event, including laboratory test abnormality, with sufficient evidence to accept that there is no causal relationship to drug administration (e.g., no temporal relationship to drug administration, because the drug was administered after onset of event; investigation shows that the drug was not administered; proof of other cause; etc.); or an event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

6.13.5 Assessment of Adverse Event Outcome

Outcome of AEs will be defined according to ICH Topic E2B, ICH Guideline.

- Recovered/Resolved
- Recovering/Resolving
- Not Recovered/Not Resolved
- Recovered/Resolved with Sequelae
- Fatal
- Unknown

6.13.6 Action Taken for Adverse Event

Action taken for AEs will be documented according to the following:

- Concomitant medication or other treatment
- Withdrawal from the study

6.13.6.1 Action Taken for Study Drug

Any action taken with study drug will be defined according to ICH Topic E2B, ICH Guideline and documented in the CRF according to the following:

- Drug Withdrawn
- Dose Reduced
- Dose Increased
- None (not changed)
- Dose Interrupted
- Unknown
- Not Applicable

6.13.7 Collection of Extra Laboratory Samples/Investigations

In the event of a clinically important AE, a suitable blood sample may be collected for additional laboratory tests. The investigator must ensure that the sample is properly labeled and stored. The investigator and others responsible for care of the patients should institute any supplementary investigations of significant AEs based on the clinical judgment of the likely causative factor. This may include seeking a further opinion from a specialist in the field of the AE. The company may suggest special tests based on expert advice.

6.13.8 Follow-up of Adverse Events Present at Last Scheduled Study Visit

Adverse events present at the last study day (Week 25/Follow-up) that require follow-up or a repeat laboratory test will be followed-up initially for 30 days according to the CRO's procedures for AE follow-up. AEs that have not resolved or stabilized at 30 days after the last patient's last study dose, will be reviewed with the sponsor on an individual basis to determine whether the database will be locked and subsequently updated once the events of ongoing AEs are resolved or whether database lock will be held.

6.14 Concomitant Medication Assessments

All concomitant medications (OTC and prescribed) taken by patients during the screening period and during the study will be recorded in the CRF with indication, start date/time and stop date/time, if known.

Patients will be permitted oral disease-specific PAH therapy consisting of an endothelin receptor antagonist (ERA) and/or an agent acting on the nitric oxide pathway, PDE5 inhibitor or a soluble guanlyate cyclase stimulator at a stable dose for at least **3 months** prior to the start of Screening, and should continue the same dose and regimen of these medications for the duration of the study.

The use of the following therapies, which may affect PAH, are permitted if on a stable dose for at least **1 month** prior to Screening and should remain unchanged during the study:

- vasodilators (including calcium channel blockers)
- digoxin
- spironolactone
- L-Arginine supplementation

Previous administration of a prostacyclin or prostacyclin analogue is not permitted if treatment was stopped for a safety or tolerability issue. In addition, intravenous inotropes within **1 month** of Screening are not permitted.

Diuretics may be dosed as clinically indicated throughout the study.

Additionally, the use of PDE-5i as needed for erectile dysfunction (ED) is permitted as long as the patient has not taken a dose within **48-hours** of any Baseline or study related efficacy assessment. In addition, the patient must not take more than 8 sildenafil tablets, 6 vardenafil, or 4 tadalafil tablets **per month** for ED.

6.15 Removal of Patients from the Trial or Study Drug

The study will be terminated early if, in the opinion of the sponsor, investigator, or IRB/IEC, an unacceptable risk to the safety and welfare of patients is posed by the continuation of the study in light of review of the key safety data.

Patients will be informed that they are free to withdraw from the study at any time for any reason should they so wish. The PI may remove a patient if, in his/her opinion, it is in the best interest of the patient. A patient may be withdrawn from the study for any of the following reasons:

- Clinical worsening as defined in Section 6.9
- Deviation/noncompliance with the protocol,
- A serious or intolerable AE occurs,
- The sponsor or investigator terminates the study, or
- Withdrawal of consent - any patient may withdraw his/her consent from the study at any time. The investigator should make a reasonable attempt to document the specific reason why consent is withdrawn.

6.15.1 Handling of Withdrawals

Although a patient is not obliged to give his/her reason for withdrawing prematurely, the investigator will make a reasonable effort to obtain the reason while fully respecting the patient's rights. If there is a medical reason for withdrawal, the patient will remain under the

supervision of the study physician until in satisfactory health. Reasonable efforts will be made to contact a patient who fails to attend any follow-up appointments, in order to ensure that he/she is in satisfactory health.

If a patient is prematurely discontinued from this study, every attempt will be made to follow the Week 22/ EOS visit procedures described in Section 7.4.3.1.

6.15.2 Replacements

Patients who terminate early from the study will not be replaced.

6.16 Allowable Visit and Procedure Windows

The following are the allowable windows for specific study visits and procedures during the 9-week dose titration period:

- Screening: within 28 days prior to dosing on Day 1
- Study visits (Weeks 1-9): ± 1 day
- Study visits (Weeks 10-22): ± 3 days
- Week 25 follow-up visit: ± 1 week
- Vital signs: ± 15 min
- Blood pressure and heart rate: ± 15 min
- Safety labs (excluding urinalysis): - 15 min
- Baseline ECG: within 2 hours prior to dosing on Day 1
    - all other ECGs: ± 15 min
- Blood draws for PK samples:
    - time points up to 4 hours: ± 15 min

7 STUDY ACTIVITIES

7.1 Screening Visit (Days -28 to -1)

At the initial screening visit, potential patients will have a detailed oral presentation of the nature, purpose, risks, and requirements of the study in addition to receiving detailed written information. They will have adequate opportunity to ask the appropriate person of the clinical staff (i.e., principal investigator or designee) presenting the study about any aspect of the study. Once the patient is satisfied that he/she is willing to participate in the study, he/she will be asked to sign the study ICF. The clinical personnel obtaining written consent from the patient will also sign the form to confirm consent has been obtained. Once signed, the investigator will retain the original for the patient's study records and provide the patient with a signed copy. The investigator will verify that informed consent has been obtained from each patient prior to admission into the study and prior to the patient undergoing any study-related procedures. If it is standard practice at the site to conduct a few general non-invasive study procedures (i.e., medical/social history, collection of concomitant medications, etc.) before a patient can be considered for a specific study, the study center must have a written SOP detailing the procedure, and also ensure that each patient signs a general consent prior to undergoing the general procedures.

A unique patient screening number will be assigned upon completion of the ICF.

Within 28 days before administration of the study medication, or sooner, all screening activities subsequent to obtaining informed consent will be conducted and consist of the following**:**

- Review of all inclusion and exclusion criteria
- Collection of demographic data (sex, age, race/ethnicity)
- Completion of medical and social history (to include tobacco, alcohol, and caffeine use)
- PAH medical history
- Physical examination, including height, weight, and vital signs (i.e., supine blood pressure, heart rate, respirations, body temperature and pulse oximetry (SpO_2) after a 5 minute rest)
- 12-lead safety ECG
- WHO/NYHA functional class assessment
- Clinical laboratory tests to include hematology, coagulation parameters (prothrombin time [PT] and activated partial thromboplastin time [PTT], international normalized ratio [INR]), serum chemistry, and urinalysis), and virology screen (HBsAg, HIV antibodies, and HCV antibodies).
- Serum hCG pregnancy test (females only)
- 6MWTs – 2 consecutive tests done on different days
- Thromboembolic disease assessment to include a ventilation-perfusion lung scan (VQ Scan) or spiral/helical/electron beam computed tomography utilizing an

angiography protocol, or selective pulmonary angiogram, unless performed within 5 years prior to Screening

- Pulmonary function testing including measurement of total lung capacity (TLC), unless performed within 6 months prior to Screening
- Transthoracic or transesophogeal ECHO unless performed within 12 months prior to Screening
- Right heart catheterization performed within 1 month prior to Day 1 Patients who have had a RHC performed within 30 days of screening and who meet study entry requirements are not required to have a repeat screening RHC
- Record concomitant medications
- Record adverse events

7.2 Screening Failures

A screening failure is defined as a patient who has signed the ICF, does not meet all the entry criteria as outlined in this protocol and has not been randomized or received study medication. A screening log will be maintained by the Investigator or designee, indicating the reason for the screening failure.

7.3 Study Procedures

7.3.1 Study Procedures for Dose Titration Period

Patients who meet all the entry criteria and are eligible for the study will report to the clinical study unit to confirm eligibility for the study and complete all Day 1 baseline procedures and receive study medication and instructions. The study medication will be given in the morning at the study site on Day 1. The patient should be observed for at least 4 hours after the dose.

Clinic visits will occur for each escalation of study drug dose. Visits should be entered based on the study week as noted in Table 1. There should be at least one study visit each week during the dose titration period. Beyond this visit, any additional visit during the dose titration period will be documented as an ‘unscheduled’ visit.

If a patient reaches the highest dose tolerated prior to Week 9, and no additional dose escalations are planned, the visit schedule may be amended at the investigator’s discretion. However, visits at Weeks 1, 2, 5, and 9 of the dose titration period are mandatory.

7.3.1.1 Pre Day 1 Procedure

RHC measurements for baseline measurement will be performed within **30 days** of screening. Any AE related to study procedures will be recorded. A RHC measurement will be performed as part of end of study assessments.

7.4 Baseline/Day 1 Visit (Week 1)

Once Screening and Baseline procedures are completed, and the patients' urine pregnancy test (if applicable) has been confirmed as negative, the patient will be given the first dose of study drug (Day 1). Study drug should be given with food. The date of initial drug administration is Day 1 and must be on the same day that the Baseline evaluations are performed.

7.4.1 Pre-dose Procedures for Dose Titration Visits

- Vital signs pre-dose according to Table 1
- Safety ECG pre-dose on Day 1 and Weeks 1- 9 according to Table 1
- WHO/NYHA functional class assessment
- Assessment of clinical worsening
- Clinical laboratory tests (to include hematology, coagulation parameters [PT/PTT, INR], serum chemistry, and urinalysis) according to Table 1
- Optional blood sample for DNA testing according to Table 1
- Pregnancy test according to Table 1
- BNP/NT-proPNP: blood sample to be taken after 1-hour rest and prior to administration of 6MWT according to Table 1
- 6MWT according to Table 1
- PK blood draw: pre-dose according to Table 1
- Record adverse events
- Record concomitant medications

7.4.2 Post-dose Procedures for Dose Titration Visits

- Study drug administration
- Safety ECG 2 h post dose on Day 1 and Weeks 1- 9 according to Table 1
- Vital signs: every hour through the first 4 hours
- PK blood draw: 4 h post dose according to Table 1
- Record adverse events
- Record concomitant medications

7.4.3 Study Procedures for Treatment Phase —Week 10, Week 14, Week 18

- Safety ECG
- Clinical laboratory tests (to include hematology, coagulation parameters [PT/PTT, INR], serum chemistry, and urinalysis)
- Serum hCG pregnancy test (females only)
- Vital signs

- 6MWT
- BNP/NT-proBNP pre-dose according to Table 2
- Study drug administration according to Table 2
- PK blood draw: pre-dose and 4 h post dose
- Assessment of clinical worsening
- WHO/NYHA functional class assessment
- Record adverse events
- Record concomitant medications

7.4.3.1 End of Study (EOS) Assessments —Week 22

- All assessments as noted for Week 10; plus a physical exam and a right heart catheterization

7.4.3.2 Week 25* Follow-up Visit (±1 week)

Following a 3 week (±1 week) transition period, the following assessments will be done:

- Physical exam
- Safety ECG
- Clinical laboratory tests (to include hematology, coagulation parameters [PT/PTT, INR], serum chemistry, and urinalysis)
- Serum hCG pregnancy test (females only)
- Vital signs
- Study drug administration (current dose) for patients continuing into the APD811-007 OLE study
- 6MWT
- BNP/NT-proBNP pre-dose according to Table 2
- Assessment of clinical worsening
- WHO/NYHA functional class assessment
- Record adverse events
- Record concomitant medications

*If appropriate, patients will 'switch' to the long-term open label extension study (APD811-007), thus Week 25 will also serve as the baseline visit for the APD811-007 OLE study.

8 DATA MANAGEMENT

8.1 Data Collection

All data (ECGs, clinical laboratory data, and all other study-related data) will be collected according to the sponsor or CRO's SOPs.

Upon database lock, to include resolution of all queries, the CRO, if applicable, will provide statistical analysis software (SAS) transfer datasets to the sponsor and to the biostatistician for analysis using secure electronic data transfer per the sponsor's specifications.

8.2 Data Coding

8.2.1 Adverse Events

Adverse events will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA) and tabulated, including categorical information of interest such as onset and resolution times, time of onset relative to dose, severity at onset, maximum severity, causal relationship to study medication, and action taken. Whenever possible, a constellation of signs and symptoms should be recorded as a unifying diagnosis (e.g., self-limited fever, runny nose, cough, and scratchy throat should be captured as an upper respiratory infection rather than by the individual signs and symptoms). AEs will be regarded as 'pre-treatment' if they occur between Screening and the time of administration of the first dose of APD811. All other AEs that occur after the first dose of study medication will be considered to be 'treatment-emergent'.

8.2.2 Concomitant Medications

Due to the variability in how medications are recorded, a standard naming convention is required in order to tabulate this data effectively. A common method of standardization is to categorize medications by their Preferred Term. In order to do this, medications will be coded using the World Health Organization Drug Dictionary (WHODRUG).

9 STATISTICAL METHODS AND DATA ANALYSIS

9.1 Responsibility for Analyses

The statistical analysis of the data obtained from this study will be the responsibility of the sponsor. Details of the statistical analyses will be included in a separate analysis plan (SAP) which will be finalized before database lock of the first patient completing the study. If, after the study has been unblinded, changes are made to the pre-specified statistical analysis plan, the changes will be listed along with an explanation as to why they occurred in the Clinical Study Report.

9.2 Hypotheses

9.2.1 Primary Hypotheses

- In patients with PAH who receive 22 weeks of treatment, APD811 compared with placebo will provide a greater reduction in PVR.
- In patients with PAH who receive 22 weeks of treatment, APD811 compared with placebo will provide a greater improvement in 6MWD.

9.2.2 Secondary Hypotheses

- In patients with PAH who receive 22 weeks of treatment, APD811 will be safe and well tolerated.
- In patients with PAH who receive 22 weeks of treatment, APD811 compared with placebo will provide fewer events of clinical worsening

9.2.3 Exploratory Hypotheses

- In patients with PAH who receive 22 weeks of treatment with APD811 compared with placebo will provide greater improvement on levels of BNP and NT-proBNP.
- In patients with PAH who receive 22 weeks of treatment with APD811 compared with placebo will provide a greater reduction in SVR.

9.3 Sample Size and Power Calculations

For the APD811 versus placebo comparison, 28 patients in the APD811 group and 14 patients in the placebo group will have 90% power to detect a between-treatment difference of 350 dyn·s· cm-5 in PVR. This calculation was based upon the pooled SD estimate of 320.3 dyn·s·cm-5 for the mean change from baseline in PVR at Week 17 observed in the selexipag phase 2 study. Assuming that up to 30% of patients may drop out of the trial before a post-randomization repeat RHC is performed, 40 patients will be randomized to the APD811 group and 20 patients will be randomized to the placebo group. For 6MWD, 40 patients in APD811 group and 20 patients in the placebo group will have 80% power to detect a

between-treatment difference of 50 meters in 6MWD assuming pooled SD estimate of 65 meters.

9.4 Analysis Populations

The analyses of all efficacy variables will use the modified intent to treat (MITT) population as primary. The completers population will be used as a secondary analysis population.

Modified Intent-to-treat (MITT) Population:

This population consists of all patients randomized who received at least one study dose, have a baseline measurement, and have a post-randomization measurement. Under this approach, patients are counted in the treatment group to which they were randomized, regardless of the treatment received during the course of the trial.

Completers Population:

This population consists of all patients that completed the study. No missing data will be imputed for this analysis. Any substantial differences between conclusions based on the MITT population and the completers population will be investigated.

Safety Population:

This population will include all randomized patients who received study medication.

9.5 Statistical Methods

9.5.1 Statistical Analysis of Pharmacokinetic Variables

APD811 plasma concentrations are limited to pre-dose (C_{min}) and 4 hours post-dose.

APD811 plasma steady-state will be determined by regressing C_{min} values over time and the resultant slope tested for its difference from zero.

APD811 will be administered in the trial as a liquid-filled, hard-gelatin capsule formulation provided as 0.01, 0.02, 0.03, 0.04, and 0.10 mg dose strengths.

Individual APD811 plasma concentrations at specified time points will be listed for each patient by treatment group. Individual plasma concentration-time points of APD811 will be plotted on both a linear and a semi-logarithmic scale for each dose level.

9.5.2 Statistical Analyses of Efficacy Measurements

9.5.2.1 Primary Efficacy Analysis

The primary endpoints are listed below:

- Change from baseline in PVR after 22 weeks of treatment
- Change from baseline in 6 MWD after 22 weeks of treatment.

The primary efficacy hypothesis regarding the superiority of APD811 to placebo will be assessed in a stepwise manner. First, the statistical significance of APD811 versus placebo result will be determined for the change from baseline in PVR at the end of 22 weeks of treatment. If the result is significant ($p < 0.05$, two-sided), the primary hypothesis will be considered satisfied and this study will be declared positive. Subsequently, the change from baseline in 6MWD will only be tested if the change from baseline in PVR is significant. This testing procedure preserves the overall Type I error rate for testing the primary efficacy hypothesis.

An analysis of covariance (ANCOVA) model with baseline PVR as a covariate and treatment and baseline WHO/NYHA functional class as factors will be used to assess the effect of APD811 on change from baseline in PVR. Missing values will be imputed using the last observation carried forward (LOCF) method. Assumptions for the analysis of covariance will be checked, and if not satisfied, parametric analyses will be corroborated with nonparametric analyses or with appropriate data transformations if necessary (i.e., log transformation).

Six minute walking distance (6MWD) will be analyzed using the above ANCOVA method described for PVR, substituting the relevant baseline measurement as the covariate. Missing values will be imputed with last observation carried forward, except if any patient withdraws early due to death or due to clinical worsening without a 6MWT being measured at a termination visit, a worst value of 0 for 6MWD will be imputed.

Note that testing for secondary and exploratory endpoints will proceed only if the comparison for the change from baseline in PVR is significant.

9.5.2.2 Secondary Efficacy Analysis

The secondary efficacy endpoints are listed below:

- Percent change from baseline in PVR after 22 weeks of treatment
- Proportion of patients who progress to clinical worsening

The percent change from baseline in PVR will be analyzed using the above ANCOVA method described for change from baseline in PVR. Missing values will be imputed using the last observation carried forward (LOCF) method. For the proportion of patients who progress to clinical worsening, the effect of APD811 will be compared to placebo using a logistic regression model with model with terms for treatment and baseline WHO/NYHA functional class.

9.5.2.3 Exploratory Efficacy Analysis

- Change from baseline in BNP and NT-proBNP after 22 weeks of treatment
- Change from baseline in SVR after 22 weeks of treatment
- Change from baseline in WHO/NYHA functional class after 22 weeks of treatment

Other continuous efficacy endpoints will be analyzed using the above ANCOVA method described for PVR, substituting the relevant baseline measurement as the covariate. Missing values will be imputed with last observation carried forward.

9.5.3 Safety Analysis

All patients who receive study medication will be evaluated for safety. Safety and tolerability will be assessed by a review of all safety parameters including adverse experiences (AEs), laboratory safety parameters, vital signs, and ECG. Summary tabulations (N, mean [or median], SD, mean [or median] change/percent change) will be obtained for the safety parameters. Adverse experiences will only be presented as summary tabulations.

9.5.3.1 Demographics and Baseline Characteristics

All baseline patient characteristics of demographic data (age, height, weight, race), social history (smoking status, caffeine intake, alcohol intake), medical history (abnormalities only), physical examination (abnormalities only), and concomitant medications at study entry will be listed for all patients. Demographic data will be summarized and tabulated. Continuous variables will be summarized using number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be reported for all categorical data.

9.5.3.2 Adverse Events

Adverse events will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA) and tabulated, including categorical information of interest such as onset and resolution times, time of onset relative to dose, severity at onset, maximum severity, causal relationship to study medication, and action taken. AEs will be regarded as 'pre-treatment' if they occur between Screening and the time of administration of the first dose of APD811.

All other AEs that occur after the first dose of study medication will be listed by patients and by treatment and will be summarized per treatment and expressed in terms of maximum severity and relationship to study medication.

9.5.3.3 Physical Examinations

Physical examination results (abnormalities only) at Screening, Day 1 of the dose titration period and Week 22/EOS visit will be listed.

9.5.3.4 Vital Signs

Individual vital sign measurements will be listed by treatment and measurement time, and summarized using descriptive statistics. Summary statistics will also be provided for change from baseline in vital sign measurements by treatment groups.

9.5.3.5 Clinical Laboratory Values

Individual lab values will be listed by treatment and visit, and summarized using descriptive statistics. Summary statistics will also be provided for change from baseline in lab values. Shift tables from baseline to last double-blind visit will also be produced for the laboratory assessments based on the categories of Low, Normal, and High. A clinically significant change from baseline may be recorded as an AE if deemed appropriate by the PI or sponsor.

9.5.3.6 Safety ECGs

Individual ECG values will be listed by treatment and visit, and summarized using descriptive statistics. Intervals to be provided for each ECG are: RR, PR, QRS, QT, QTc, QTcB, and QTcF. Post-screening ECGs will be compared with the baseline ECG. Any clinically significant change from baseline may be recorded as an AE if deemed appropriate by the PI or sponsor.

9.6 Multiplicity

The principal evaluation of the efficacy of APD811 will be based on testing the primary hypotheses for PVR and 6MWD. The testing procedure specified in the Statistical Methods section preserves the overall Type 1 error rate for testing the primary hypotheses. Comparisons involving other efficacy endpoints and time points are considered supportive or exploratory and will be made at α=0.050 level (two-sided). No multiplicity adjustment will be made for these other comparisons.

9.7 Interim Analysis

No interim analysis is planned for this study.

10 REGULATORY REQUIREMENTS

10.1 Pre-Study Documentation

The sponsor must receive the following documentation prior to initiation of the trial:

- Protocol signature page signed by the principal investigator (PI)
- FDA form 1572 signed by the PI
- Curriculum vitae of the PI and sub-investigators, updated within 2 years
- Current medical licenses for the PI and all sub-investigators
- Financial disclosure form signed by the PI and all sub-investigators listed on the FDA Form 1572
- Copy of the IRB/IEC approval letter for the study and approved ICF
- IRB/IEC Membership List.

Additional country specific documentation may be required per international regulatory authorities. Documents should be sent (via fax, email or other pre-specified) to the sponsor Contact at the following address:

Arena Pharmaceuticals, Inc.
6154 Nancy Ridge Drive
San Diego, California 92121

10.2 Investigator Obligations

The PI is responsible for ensuring that all study site personnel, including sub-investigators and other study staff members, adhere to all FDA regulations and guidelines regarding clinical trials, including guidelines for GCP (including the archiving of essential documents), both during and after study completion. The PI will be responsible for the patient's compliance to the study protocol. The PI is responsible for providing the sponsor an adequate final report shortly after he/she completes participation in the study, in accordance with ICH Guidelines E6, E2A and E8.

10.3 Patient Confidentiality

All information obtained during the conduct of the study with respect to the patients' state of health will be regarded as confidential. This is detailed in the written information provided to

the patient. An agreement for disclosure of any such information will be obtained in writing and is included in both copies of the ICF signed by the patient. The study data shall not be disclosed to a third party without the written consent of the sponsor.

10.4 Informed Consent

According to the ICH guideline for GCP (E6), the investigator will obtain and document informed consent for each patient screened for this study. All patients will be informed in writing of the nature of the protocol and investigational therapy, it's possible hazards, and their right to withdraw at any time, and will sign a form indicating their consent to participate prior to the initiation of study procedures. The patient's medical record should contain written documentation indicating that informed consent was obtained. The ICF must be reviewed and approved by the investigator's designated IRB/IEC and by the sponsor. The ICF should include all the elements as outlined in Section 4.8.10 of the ICH guideline for GCP (E6).

10.5 Institutional Review Board

This protocol and relevant supporting data are to be submitted to the appropriate IRB/IEC for review and approval before the study can be initiated. Amendments to the protocol will also be submitted to the IRB/IEC prior to implementation of the change. The sponsor must receive a letter documenting the IRB/IEC approval prior to initiation of the study. The PI is also responsible for informing the IRB/IEC of the progress of the study and for obtaining annual IRB/IEC renewal. The IRB/IEC must be informed at the time of completion of the study and should be provided with a summary of the results of the study by the PI. The PI must notify the IRB/IEC in writing of any SAE or any unexpected AE according to ICH guidelines.

11 PROTOCOL MANAGEMENT AND ADMINISTRATIVE CONSIDERATIONS

11.1 Study Documentation

The PI and study staff has 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 (i.e., FDA or international regulatory authorities) at any time, and should consist of the following elements:

Patient files, containing the completed CRFs, supporting source documentation from the medical record including laboratory data and the ICF;

Regulatory files, containing the protocol with all amendments and investigator signature pages, copies of all other regulatory documentation, and all correspondence between the site and the IRB/IEC and sponsor; and Drug accountability files, including a complete account of the receipt and disposition of the study medication (test article).

Records are to 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 material 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.

11.2 Protocol Interpretation and Compliance

To ensure accurate interpretation and implementation of the study, the procedures and endpoints defined in the protocol will be carefully reviewed by the PI and his or her staff prior to the time of study initiation. The sponsor and PI will follow all reasonable means to resolve any differences of opinion of matters of eligibility, toxicity and other endpoints. In the event that a resolution cannot be reached then one or both parties may seek to terminate the study following the provisions outlined in the Clinical Trials Agreement.

11.3 Study Monitoring

The sponsor or a contracted monitor will visit the study center periodically to monitor adherence to the protocol, compliance with ICH guidelines, adherence to applicable FDA regulations, and the maintenance of adequate and accurate clinical records. Case reports forms will be reviewed to ensure that key safety and efficacy data are collected and recorded as specified by the protocol. The monitor will be permitted to access patients' complete medical records, laboratory data, and other source documentation as needed to monitor the trial appropriately.

12 PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I agree to conduct the study as outlined in the protocol entitled, "A Randomized, Double-blind, Parallel-group, Placebo-controlled Phase 2 Trial of APD811, an Oral IP Receptor Agonist, in Patients with Pulmonary Arterial Hypertension" in accordance with the guidelines and all applicable government regulations per country, including Part 54: Financial Disclosure by Clinical investigators. These guidelines and regulations include, but are not limited to:

- Permission to allow the sponsor, or designee, and the FDA or other country specific regulatory agencies to inspect study facilities and pertinent records at reasonable times and in a reasonable manner that ensures patient confidentiality. If this study is to be inspected by a regulatory agency, the sponsor and CRO should be notified as soon as possible.
- Submission of the proposed clinical investigation, including the protocol and the consent form, to a duly constituted IRB/IEC for approval, and acquisition of written approval for each prior to the use of the study drug.
- Use of written informed consent that is obtained prior to administration of study drug or any non-routine procedures that involve risk, and that contains all the elements of consent as specified in the federal regulations and has been previously approved by the sponsor and the IRB/IEC.
- Submission of any proposed change in the protocol to the IRB/IEC using a signed formal amendment document approved by the sponsor. Any proposed changes to the protocol require that the informed consent also reflect such changes and that the revised informed consent be approved as determined by the IRB/IEC.
- Documentation and explanation of individual protocol deviations on the appropriate CRF page or in letters to the sponsor.
- Reports of SAEs to Arena Pharmaceuticals, Inc. within 24 hours by telephone and a written report of the SAE within 24 hours after the investigator's initial receipt of the information.
- Submission of reports of SAEs, as outlined in the protocol, to the IRB/IEC within 15 calendar days of their disclosure.
- Submission of timely progress reports to the IRB/IEC and sponsor at appropriate intervals on a schedule determined by the IRB/IEC.
- Maintenance of appropriate records: Federal regulations require an investigator to prepare and maintain adequate and accurate case histories designed to record all observations and other data (such as study drug accountability) pertinent to the investigation on each individual enrolled in the study. These records must be maintained by the investigator until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

In addition, I agree to provide all the information requested in the CRF in a manner to assure legibility and accuracy. To this end, I shall carefully follow the instructions for completing CRFs.

I also agree that all information provided to me by the sponsor, including protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be related in confidence to the IRB/IEC. I also understand that reports of information about the study or its progress will not be provided to anyone not involved in the study other than to the PI, or in confidence to the IRB/IEC or to the FDA or other legally constituted authority.

Principal Investigator **Date**

Printed Name

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Appendix 1 Guidelines for the Six-minute Walk Test

(Adapted from American Thoracic Society (ATS) Statement: Guidelines for the Six-Minute Walk Test. www.atsjournal.org

Location

The 6MWT should be performed indoors preferably, along a long, flat, straight, hallway with a hard surface that is seldom traveled. **The walking course must be 15-50 meters in length**. Turnaround points should be marked with a brightly colored cone. A starting line, which marks the beginning and end of each lap, should be marked on the floor with brightly colored tape. If possible, the subject should use the same 6MWT location for each test and same pair of shoes.

Safety Issues

1. Testing should be performed in a location where a rapid, appropriate response to an emergency is possible. The appropriate location of a crash cart should be determined by the physician supervising the facility.
2. Supplies that should be available include oxygen, sublingual nitroglycerine, aspirin, and albuterol (eg, a beta agonist by metered dose inhaler or nebulizer). A telephone or other means should be in place to enable a call for help.
3. The technician should be certified in cardiopulmonary resuscitation with a minimum of Basic Life Support and American Health Association-approved cardiopulmonary resuscitation course (or equivalent). Advanced cardiac life support certification is desirable. Training, experience, and certification in related health care fields (registered nurse, registered respiratory therapist, certified pulmonary function technician, etc) are also desirable. A certified individual should be readily available to respond if needed.
4. Physicians are not required to be present during all tests. The physician ordering the test or supervising a laboratory physician may decide whether physician attendance at a specific test is required.

Reasons for immediately stopping a 6MWT include the following: (1) chest pain, (2) intolerable dyspnea, (3) leg cramps, (4) staggering, (5) diaphoresis, and (6) pale or ashen appearance.

Technicians must be trained to recognize these problems and the appropriate responses. If a test is stopped for any of these reasons, the subject should sit or lie supine as appropriate depending on the severity or the event and the technician's assessment of the severity of the event and the risk of syncope.

Equipment in the Vicinity

1. O_2 saturation equipment + forehead probes.
2. Countdown timer or stopwatch.
3. Mechanical lap counter.

4. Two small cones to mark the turnaround points.
5. A chair that can be easily moved along the walking course.
6. Worksheets.
7. A source of oxygen.
8. Telephone.
9. Automated electronic defibrillator.

Subject Preparation

1. Comfortable clothing should be worn.
2. Appropriate shoes for walking should be worn preferably the same pair for each test.
3. A subject should use his or her usual walking aids during the test (cane, walker, etc).
4. The subject's usual medical regimen should be continued and study drug taken in the morning before the commencement of the 6MWT.
5. A light meal is acceptable before early morning or early afternoon tests.
6. Subjects should not have exercised vigorously within 2 hours of beginning the test.

Measurements

1. Repeat testing should be performed about the same time of day to minimize intra-day variability.
2. A "warm-up" period before the test should not be performed.
3. The subject should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications and make sure that clothing and shoes are appropriate. Record all pertinent information surrounding the test (ie, starting location, length of hallway, direction the subject will be walking, time of test, subject's general condition/feeling on the day of the test, and any other physical or medical information that may potentially influence the results of the test).
4. Subjects who require supplemental oxygen must breathe a stable oxygen dose for at least 15 minutes prior to the measurement of SpO2 and until the end of the 6MWT (see below for SpO2 requirements). It is critical that if oxygen was utilized during the Screening 6MWTs, that it be utilized during all subsequent on-study tests and that it is delivered in the same manner with the same flow. Note whether the oximeter signal quality is acceptable.
5. Set the lap counter to 0 and the time to 6 minutes. Assemble all necessary equipment (lap counter, timer, worksheets, etc.) and move to the starting point.
6. Instruct the subject as follows:

   The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow

down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able.

You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation.

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog.

Start now or whenever you are ready.

7. Position the subject at the starting line. You should also stand near the starting line during the test. Do not walk with the subject. As soon as the subject starts to walk, start the timer.
8. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the subject. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, click the lap counter once (or mark the lap on the worksheet). Let the participant see you do it. Exaggerate the click using body language, like using a stopwatch at a race.

   After the first minute, tell the subject the following (in even tones): *You are doing well. You have 5 minutes to go.*

   When the timer shows 4 minutes remaining, tell the subject the following: *Keep up the good work. You have 4 minutes to go.*

   When the timer shows 3 minutes remaining, tell the subject the following: *You are doing well. You are halfway done.*

   When the timer shows 2 minutes remaining, tell the subject the following: *Keep up the good work. You have only 2 minutes left.*

   When the timer shows 1 minute remaining, tell the subject: *You are doing well. You have only 1 minute to go.*

   Do not use other words of encouragement (or body language) to speed the subject up.

   If the subject stops walking during the test and needs a rest, say this: *You can lean against the wall if you would like: then continue walking whenever you feel able.* Do not stop the timer. If the subject stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the subject to sit on, discontinue the walk and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

   When the timer is 15 seconds from completion, say this: *In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you.*

When the time rings (or buzzes), say this: *Stop!* Walk over to the subject. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

9. Record the number of laps from the counter (or tick marks on the worksheet).
10. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides (or use a tape measure). Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.
11. Congratulate the subject on good effort and offer a drink of water.

CONTRAINDICATIONS

Absolute contraindications for the 6MWT include the following: unstable angina during the previous month and myocardial infarction during the previous month. Relative contraindications include a resting HR of more than 120, a sBP of more than 180 mmHg, and a dBP of more than 100 mmHg.

Subjects with any of these findings should be referred to the physician ordering or supervising the test for individual clinical assessment and a decision about the conduct of the test. The results from a resting electrocardiogram done during the previous 6 months should also be reviewed before testing. Stable exertional angina is not an absolute contraindication for a 6MWT, but subjects with these symptoms should perform the test after using their antiangina medication, and rescue nitrate medication should be readily available.

Rationale
Subjects with the previously mentioned risk factors may be at increased risk for arrhythmias or cardiovascular collapse during testing. However, each subject determines the intensity of their exercise, and the test (without electrocardiogram monitoring) has been performed in thousands of older persons and thousands of subjects with heart failure or cardiomyopathy without serious adverse events. The contraindications listed previously here were used by study investigators based on their impressions of the general safety of the 6MWT and their desire to be prudent, but it is unknown whether adverse events would occur if such subjects performed a 6MWT; they are, therefore, listed as relative contraindications.

Appendix 2 World Health Organization Functional Classification

Class I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near-syncope.

Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near-syncope.

Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes undue dyspnea or fatigue, chest pain or near-syncope.

Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Appendix 3 Protocol Signature Page

Protocol Title: A Randomized, Double-blind, Parallel-group, Placebo-controlled Phase 2 Trial of APD811, an Oral IP Receptor Agonist, in Patients with Pulmonary Arterial Hypertension

This study will be conducted in accordance with the International Conference on Harmonization (ICH) guideline for Good Clinical Practice (GCP) (E6), applicable Food and Drug Administration (FDA) guidelines, and the ethical principles that have their origins in the Declaration of Helsinki (2008 Version).

Protocol Number: APD811-003

Arena Pharmaceuticals, Inc. Signatures:

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Meaning: Approval
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