Statistical Analysis Plan

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

Protocol Number: APD811-003

Product Name: APD811

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TABLE OF CONTENTS

List of In-Text Tables

List of Appendices

LIST OF ABBREVIATIONS

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
Clast	last measured concentration
Cmax	maximum plasma drug concentration
Cmin	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
EC50	median effective concentration
ECG	Electrocardiogram
EDTA	ethylenediaminetetraacetic acid
ERA	endothelin-receptor antagonist
FC	functional class
FDA	Food and Drug Administration
FiO2	venous oxygen saturation
GCP	Good Clinical Practice
GEE	generalized estimating equations
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
ITT	Intent-to-treat

kg	Kilogram
LDH	lactic dehydrogenase
LOCF	last observation carried forward
LS	least squares
LVEDP	left ventricular end diastolic pressure
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MI	Multiple imputation
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
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)
WHODRUG	World Health Organization Drug Dictionary
WHO/NYHA	World Health Organization/New York Heart Association

SYNOPSIS (PROTOCOL AMENDMENT #2, 15 AUGUST 2014)

Protocol Number:	APD811-003
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 Phase:	2
Name of Drug:	APD811
Indication:	Pulmonary Arterial Hypertension
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 Objective:** 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 Objectives:** The secondary objective of the study is to assess the effect of APD811 on clinical worsening. **Safety Objectives:** The safety objective of this study is to determine the safety profile and tolerability of APD811. **Exploratory Objectives:**

	The 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 (Cmin and presumptive Cmax) of oral APD811 • to evaluate the effects of APD811 on systemic vascular resistance (SVR)
Hypotheses:	Primary: • 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. Safety: • In patients with PAH who receive 22 weeks of treatment, APD811 will be safe and well tolerated. Secondary: • In patients with PAH who receive 22 weeks of treatment, APD811 compared with placebo will provide fewer events of clinical worsening. Exploratory: • 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.
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.
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 Assessments:	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 patients 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 APD811to 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, baseline WHO/NYHA functional class and class of PAH therapy at baseline (ERA alone, nitric oxide (NO) pathway (i.e. PDE5, soluble guanylate cyclase, sGC) +/- ERA) 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.

1 INTRODUCTION

1.1 Objective of the Statistical Analysis Plan

This statistical analysis plan (SAP) provides the statistical rationale and methods that will be applied to data gathered in clinical trial Protocol APD811-003[1] (Amendment #2, 15 August 2014) in order to assess the safety and efficacy of APD811 in patients with pulmonary arterial hypertension. Section 9 of this SAP discusses the changes from analysis planned in protocol. This SAP is finalized prior to database lock and data analysis start. Major changes of analysis that are made after database lock will be documented in the Clinical Study Report with the rationales and details.

1.2 Description of the Study and Objectives/Hypotheses

1.2.1 Summary of Study Design

APD811-003 is a 22 week, randomized, double-blind, placebo controlled study which includes 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 Appendix 1). 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.

1.2.2 Efficacy Assessments

1.2.2.1 Six Minute Walk Test (6MWT)

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”. Technicians performing the test will be trained according to published procedures. Tests will be performed at approximately the same time of day for each test in order to minimize intraday variability. The 6MW distance will be analyzed at Day 1 prior to study drug administration, and at, Weeks 5, 10, 14, 18 and 22.

1.2.2.2 WHO/NYHA Functional Class

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. 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. The four functional classes are described below.

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.

The WHO/NYHA functional class will be analyzed at Day 1, Weeks 5, 10, 14, 18 and 22.

1.2.2.3 Right Heart Catheterization (RHC)

RHC measurements will be obtained prior to study Day 1 of the dose titration period and at Week 22. 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 hemodynamic values will be obtained and recorded:

Pulmonary Vascular Resistance (PVR) will be calculated using the following formula:

$$PVR\ (dyn.sec/cm^5) = 80*(mPAP-PCWP) \div CO \text{ where}$$

mPAP = mean Pulmonary Artery Pressure (mmHg)
PCWP = Pulmonary Capillary Wedge Pressure (mmHg)
CO = Cardiac Output (L/min)

Pulmonary Vascular Resistance Index (PVRI) will be calculated using the following formula:

$$PVRI\ (dyn.sec\ m^2/cm^5) = 80*(mPAP-PCWP) \div CI \text{ where}$$

mPAP = mean Pulmonary Artery Pressure (mmHg)
PCWP = Pulmonary Capillary Wedge Pressure (mmHg)
CI = Cardiac Index (L/min/m2)

Cardiac Output (CO)

Thermodilution or the Fick method, however the same method of testing should be used in the same subject throughout the study.

Cardiac Index will be calculated using the following formula:

CI (L/min/m^2) = CO ÷ BSA where

CO = Cardiac Output (L/min)
BSA = Body Surface Area (m2) = 0.007184 * (weight0.425)* (height0.725) with weight expressed in kg and height recorded in cmPulmonary Artery Pressure, PAP (systolic, diastolic, and mean)
Heart Rate (HR)
Mean right atrial pressure (mRAP)
Pulmonary capillary wedge pressure (PCWP)

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 is acceptable.

Right ventricular pressure (RVP)

Systemic Vascular Resistance (SVR) will be calculated using the following formula:

SVR (dyn.sec/cm^5) = 80*(MAP- mRAP) ÷ CO where

MAP = Mean Arterial Pressure (mmHg)
mRAP = mean Right Atrial Pressure (mmHg)
CO = Cardiac Output (L/min)

Systemic Vascular Resistance Index (SVRI) will be calculated using the following formula:

SVRI (dyn.sec m^2/cm^5) = 80*(MAP-mRAP) ÷ CI where

MAP = Mean Arterial Pressure (mmHg)
mRAP = mean Right Arterial Pressure (mmHg)
CI = Cardiac Index (L/min/m2)

Systolic Blood Pressure (sBP) (mmHg)
Diastolic Blood Pressure (dBP) (mmHg)
Mixed venous oxygen saturation (SvO_2)
Arterial oxygen saturation (SaO_2) (if Fick method for CO is used)

Stroke volume will be calculated as Cardiac output ÷ heart rate.

1.2.2.4 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. BNP/NT-proBNP will be measured at Day 1, Weeks 10 and 22.

1.2.2.5 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.

1.2.3 Objectives

Primary Objective: T 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 Objectives: To assess the effect of APD811 on clinical worsening

Safety Objective: To assess the safety and tolerability of APD811

Exploratory Objectives:

- 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)

1.2.4 Hypotheses

1.2.4.1 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.

1.2.4.2 Secondary Hypothesis

In patients with PAH who receive 22 weeks of treatment, APD811 compared with placebo will provide fewer events of clinical worsening

1.2.4.3 Safety Hypothesis

In patients with PAH who receive 22 weeks of treatment, APD811 will be safe and well tolerated.

1.2.4.4 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 better improvement in SVR and/or other hemodynamic parameters.

2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

All baseline patient characteristics of demographic data (age, height, and weight), social history, medical history (abnormalities only), physical examination (abnormalities only), and concomitant medications at study entry will be listed for all patients. Demographic and baseline characteristics of the safety population will be summarized by treatment group and for the overall population. Baseline for the demographic variables will be the last pre-randomization value. 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. No formal statistical testing comparing treatment groups will be performed.

The following variables will be summarized by treatment group:

1. Continuous baseline demographic variables: age (years) - the years between the date of informed consent and the date of birth
2. Categorical baseline demographic variables: sex (female or male), ethnicity (Hispanic/Latino or Not Hispanic/Not Latino) and race (American Indian or Alaska Native, Asian, Black or African-American, Native Hawaiian or Other Pacific Islander, White or Caucasian, or Other).
3. Pulmonary Arterial Hypertension history include:

    - Duration of PAH (in years): the years between the date of PAH diagnosis and the date of randomization, the incomplete date with be calculated by year.
    - PAH Classification (Idiopathic PAH, Heritable PAH, Drugs or toxin induced, Associated PAH)
    - PAH Disease Specific Concomitant Medication by category
        - With ERA vs. without ERA
        - With PDE5 vs. without PDE5
        - With sGC vs. without sGC
        - Monotherapy ERA
        - Monotherapy PDE5
        - Monotherapy sGC
        - Combination therapy ERA + PDE5
        - Combination therapy ERA + sGC
    - Baseline WHO/NYHA Function Classification
    - Baseline PVR
    - Baseline 6-Minute Walk Test
    - Baseline BNP/NT-proBNP

3 PATIENT DISPOSITION

The number of patients enrolled in the study by investigator and treatment group will be tabulated. Tables showing study participant accounting will be provided. Tables will indicate number of patients who were randomized into the study, the number of patients who completed the study, and the number of patients who discontinued prematurely (early termination) for any of the following reasons:

- Clinical worsening
- Deviation/noncompliance with the protocol or study drug
- Adverse event(s)
- Investigator decision
- Sponsor decision
- Patient withdrawal of consent
- Patient lost to follow up
- Death
- Other

4 EFFICACY ANALYSES

4.1 Efficacy Endpoints

A table is provided in Appendix 3 summarizing the efficacy variables and their analysis populations.

Primary Endpoints

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.

Secondary Endpoints

Secondary efficacy variables include:

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

Exploratory Endpoints

The exploratory efficacy endpoints are listed below:

- Change from baseline in BNP and NT-proBNP after 22 weeks of treatment
- Change from baseline in SVR and other hemodynamic parameters (listed in Section 1.2.2.3) after 22 weeks of treatment
- Change from baseline in WHO/NYHA functional class in numeric scale after 22 weeks of treatment
- Proportion of patients in categorical change of WHO/NYHA function class after 22 weeks of treatment. Three ordinal categories are defined as Improved, No Change, and Deteriorated, in comparison with baseline
- Longitudinal change from baseline in 6 MWD up to 22 weeks
- Longitudinal change from baseline in WHO/NYHA functional class in numeric scale up to 22 weeks
- Time to first event of clinical worsening, the duration is defined as from randomization to first occurrence of clinical worsening, otherwise it will be censored at the last record date of clinical worsening event assessment or end of study, whichever is latest.

4.2 Analysis Population

The primary analysis of the efficacy endpoint, PVR, will be conducted using the intent to treat population.

Intent-to-Treat Population (ITT):

This population consists of all patients randomized who receive at least one dose of study drug, and have a baseline PVR 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. The primary endpoint, PVR change from baseline at Week 22, will use this population for analysis.

Unless otherwise specified, the analyses of all other 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 Population (MITT):

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 (CP):

This population consists of all patients who completed the study treatment at Week 22. No missing data will be imputed for this analysis. Any substantial differences between conclusions based on the ITT, MITT and the completers' populations will be investigated.

Safety Population (SP):

The Safety Population will include all randomized patients who received at least one dose of study medication.

4.3 Approaches to Efficacy Analysis

4.3.1 Primary Efficacy Analysis

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 formally 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.

In this first-in-patient Phase 2 study in PAH patients, there is a clinical rationale to specify two important primary endpoints: the key hemodynamic parameter, PVR; exercise capacity as measured by 6MWD. Right heart catheterization from which PVR is derived only takes place at Screening and Week 22; 6MWD is measured at Screening, baseline, and at 5 post-baseline specified time points.

In cases of missing data occurring at Week 22, the following missing data handling rules will apply.

For PVR, assessments measured at Week 22 or at time of early withdrawal will be included in the analysis. Missing data at Week 22 will be imputed using the method of multiple imputation as outlined in Section 7.4 and detailed in Appendix 4. For 6MWD, missing values will be imputed with the last observation carried forward (LOCF), 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. Baseline assessments will not be carried forward.

To further assess missing data impacts on primary analyses, the completers analyses without data imputation will be performed and compared with additional sensitivity analyses specified in Section 7.4.

An analysis of covariance (ANCOVA) model with baseline PVR as a covariate and treatment and baseline WHO/NYHA functional class (II vs, III or IV) and baseline background PAH therapy (With ERA vs. Without ERA) as factors will be used to assess the effect of APD811 on change from baseline in PVR. LSMeans for the treatments and the treatment effect and LSMean difference between treatment will be displayed with 95% CIs and the two-sided p-value will be displayed. The normality of the model residuals will be assessed using Shapiro-Wilks test. Assumptions for the analysis of covariance will be checked, and if not satisfied, parametric analyses will be corroborated with appropriate nonparametric analyses, such as the Wilcoxon rank sum test stratified by baseline WHO/NYHA functional class (II vs, III or IV) and baseline background PAH therapy (With ERA vs. Without ERA). The Hodges-Lehmann estimation of location shift and confidence interval will be produced. If the model residuals is not normally distributed, ANCOVA analysis based on log-transformed data will be performed.

Six minute walking distance (6MWD) will be analyzed using the above ANCOVA method described for PVR, substituting the 6MWD baseline measurement as the covariate. Assumptions for the analysis of covariance will be checked, and if not satisfied, parametric analyses will be corroborated with nonparametric analyses, such as the Wilcoxon rank sum test stratified by baseline WHO/NYHA functional class (II vs, III or IV) and baseline background PAH therapy (With ERA vs. Without ERA). The Hodges-Lehmann estimation of location shift and confidence interval will be produced.

Note that formal testing for secondary and exploratory endpoints will proceed only if the comparison for the change from baseline in PVR is significant. In the event that the treatment effect for PVR is non-significant all subsequent testing of other endpoints will be interpreted only in an exploratory, rather than confirmatory manner.

4.3.2 Secondary Efficacy Analyses

The percent change from baseline in PVR will be analyzed using the method described for change from baseline in PVR.

In addition, the PVR data (absolute value instead of change from baseline) will be natural log-transformed (ln) prior to analysis. The dependent variable of the model is the change from baseline for the log-transformed endpoint value (i.e., ln(Week 22 value)-ln(baseline value)) or equivalently the log-transformed ratio change from baseline (i.e., $\ln(\frac{Week\ 22\ value)}{baseline\ value}$)). Resultant LS mean estimates will be exponentiated to yield the geometric mean estimates of ratio changes from baseline; resultant LS mean difference estimates from placebo will be exponentiated to derive the geometric mean ratio estimates of ratio changes from baseline that is relative to placebo.

For the proportion of patients who progress to clinical worsening, number (%) of patients progressed in each treatment group and 95% CI will be reported; difference in proportion with 95% CI between treatment groups will be estimated using the method of Miettinen and Nurminen, 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 (II vs, III or IV), and odds ratio and 95% CI will be reported.

4.3.3 Exploratory Efficacy Analyses

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 at Week 22.

Change from baseline in BNP and NT-proBNP after 22 weeks of treatment will be summarized analysed using ANCOVA in the same way as for PVR (using the respective baseline as a covariate instead of baseline PVR). In the event that the normality assumption is violated the analysis will be repeated after the data has been log-transformed.

Categorical change from baseline in WHO/NYHA functional class after 22 weeks of treatment is an ordinal categorical endpoint with 3 categories (Improved, No Change, Deteriorated). It will be analyzed using Cochran-Mantel-Haenszel (CMH) method adjusted baseline WHO/NYHA functional class stratum, and using modified ridit scores to compute the test statistic and p-value for the between-treatment comparison.

For longitudinal change from baseline in 6MWD and WHO/NYHA functional class, a mixed-effects model repeated measures (MMRM) analysis with baseline WHO/NYHA functional class stratum, treatment, week and treatment-by-week interaction as factors and baseline value as covariate will be used to assess the effect of APD811. An unstructured covariance will be used for the within-patient correlation. Appropriate transformations in 6MWD will be applied if necessary (i.e., log transformation). An analysis of categorical WHO/NYHA functional class over time using generalized estimating equations (GEE) proportional odds model will be performed to assess treatment effect on function class shift during entire study period. The GEE model will include appropriate covariates, such as baseline function class and baseline PVR.

For the repeated measures analysis in the MITT population, no explicit imputations will be made. Missing data are assumed to be missing at random (that is, ignorable missingness), which means that the missingness of the data does not depend on the value that is missing after adjusting for the effect of the data that are observed.

For the time to first event of clinical worsening endpoint, the duration is defined as from randomization to first occurrence of clinical worsening, otherwise it will be censored at the last recorded date of clinical worsening event assessment or end of study, whichever is later. The cumulative event rates and graphic presentation will be estimated and produced using the Kaplan-Meier method. Non-parametric methods such as the log-rank test stratified by baseline WHO/NYHA functional class stratum will utilized to compare the survival curve by treatment group. A Cox proportional hazards model will be applied to compare the hazard rates between treatment groups. The model will include treatment, baseline PVR and WHO/NYHA stratum as factors. The hazard ratio (HR) between the treatment groups (APD811 /placebo) will be estimated. The 95% CIs around the estimated HR along with event rates per 100 person years will be presented. Analytical and graphical methods will be employed to verify the proportional hazard assumption. The proportional hazards assumption will be tested by including the factor treatment*log(time) in the model; nonsignificance ($p>0.05$) of this factor implies proportionality, i.e., constancy of treatment effect over time.

Other exploratory analyses may be performed to further assess treatment effects on efficacy measures, and relationships between during treatment measures. There will be no inferential testing for these analyses and only point estimate and corresponding confidence interval will be reported. Analyses related to baseline subgroup will be described in section 6.2. Followings are potential exploratory analyses.

- Relationships between study drug exposure (intensity and duration) and efficacy measures (PVR, 6MWD, WHO/NYHA FC, BNP/NT-proBNP, etc.)
- Correlations between Week 22 efficacy measures (PVR vs. 6MWD, PVR vs. WHO/NYHA FC, 6MWD vs. WHO/NYHA FC, BNP/NT-proBNP vs. PVR, BNP/NT-proBNP vs. 6MWD, etc.)
- Proportion of patients achieving ≥ 10% 6MWD increase from baseline at Week 22
- Proportion of patients achieving ≥ 440 meters 6MWD at Week 22
- Proportion of patients achieving clinical improvement at Week 22, such as ≥ 10% 6MWD increase from baseline and WHO/NYHA FC I or II
- Proportion of patients achieving normalized PVR (< 240 units) at Week 22
- Proportion of patients achieving ≥ 15% in PVR reduction from baseline at Week 22
- Analysis of REVEAL score shift at end of study in comparison with baseline

4.4 Pharmacokinetic Analysis

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. 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.

4.5 Definition of Compliance Measure

Compliance will be assessed using patient data recorded in the drug accountability form of the electronic case report forms (eCRFs). On each day, a patient should take his/her assigned treatment. The compliance rate for each patient will be computed as 100% × (the total dose received/ the total dose planned). Days on treatment is defined as the number of days from the date of first dose to the date of last dose. Compliance rates will be summarized for each treatment arm.

5 SAFETY ANALYSES

Safety and tolerability will be assessed by a review of all safety parameters including adverse experiences (AEs), laboratory safety parameters, vital signs, and ECG. Only summary tabulations (N, mean [or median], SD, mean [or median] change/percent change). The 95% CIs for between-group differences will be reported for special safety analysis. Adverse experiences will only be presented as summary tabulations.

5.1 Safety Population

The analyses for all safety outcomes (categorical or continuous measures) will use the safety population which consists of all randomized patients who received at least 1 dose of study drug; in addition, if a patient is found to have taken a study therapy for the entire duration of the study different from that to which he/she was randomized, then the patient is counted in the treatment group of the drug he/she actually received.

For analysis based on laboratory measurements, at least 1 laboratory test post-randomization is required for inclusion in the safety population. When assessing change from baseline, a baseline measurement is also required. Baseline for the safety analysis is defined as the last pre-randomization measurement. -

5.2 Dose, Duration, and Dose Modification

The number and percentage of patients will be summarized based on the final dose level (the last treatment dose). 0.2 mg b.i.d. or 0.3 mg b.i.d. is the achieved target dose in this study. The number and percentage of patients whose final dose reached the achieved target dose will be summarized as well. The duration of treatment for each patient will be assessed by calculating the number of days on drug from the date of the first dose to the date of the last dose. For each arm, the range (minimum and maximum) of values for days on drug and the mean number of days on drug will be calculated.

Additionally, the number and percentage of patient with at least one missed/interrupted dose and at least one dose reduction will be summarized separately. The missed/interrupted dose is defined as either Total Daily Dose is “0” or there is gap between the last date of previous treatment record and the first date of the next treatment record. The total days of the gap and the “0” daily dose will be considered as days of missed/interrupted dose of the patient. The number and percentage of patients with the different missed/interrupted dose and the different maximum dose before dose reduction will be summarized.

These summaries will be based on safety population, completers population and patients with early treatment discontinuation.

5.3 Adverse Events

Adverse events will be coded using the most current Medical Dictionary for Drug Regulatory Affairs (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 or placebo and will be recorded as medical history. All other AEs that occur or worsen after the first dose of study medication will be considered to be 'treatment-emergent'. Missing or incomplete start date of AE will be imputed as section 7.4.

Treatment-emergent AEs (TEAE) will be listed by patient and by treatment. They will be summarized per treatment and expressed in terms of maximum severity and relationship to study medication. The incidence of TEAEs classified according to system organ class will be summarized by treatment group. TEAEs will also be summarized by maximum intensity (assessed according to the Common Terminology Criteria for Adverse Events v4.03[2] definitions) and relatedness to study medication.

Summaries of the number (%) of patients in each treatment group with at least 1 TEAE, classified according to MedDRA system organ class and preferred term, will also be provided for:

- Drug-related TEAE
- Treatment-emergent AEs leading to permanent discontinuation of study medication (study medication discontinued or withdrawal from study).
- Serious adverse events (SAEs)
- Prevalence of selected treatment-emergent AEs over dose titration and treatment periods

Serious adverse events will be listed by patient and by treatment. If there are no SAEs at the end of the study, the tables or listings will state that there are no SAEs in the study.

5.4 Physical Examinations

Physical examination results (abnormalities only) at each study visit will be listed.

5.5 Concomitant Medication

Pre-treatment and concomitant medication administered during the study will be listed. Concomitant medications will be coded using the WHODRUG Dictionary. Medications initiated prior to start of treatment and maintained during the study, or taken during the course of the study will be considered as concomitant medications. Medications administrated prior to and not continuing on the study treatment will be considered as prior medications. Medications with partial or missing start date will be assumed to be concomitant medications, unless there is clear evidence (through comparison of partial dates or end date with the date of tipifarnib treatment) to suggest that the medications are not taken during study.

5.6 Vital Signs

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

measurements by treatment. Baseline value is defined as the Day 1 (randomization) measurement. If the Day 1 measurement is not available, the last non-missing pre-randomization measurement will be used as the baseline value.

5.7 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. Baseline value is defined as the Day 1 (randomization) measurement. If the Day 1 measurement is not available, the last non-missing pre-randomization measurement will be used as the baseline value. Standard units (SI) will be used to report results in listings and tables.

5.8 Safety ECGs

Individual safety 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. Summary statistics will also be provided for change from baseline in ECG values. Baseline value is defined as the Day 1 (randomization) measurement. If the Day 1 measurement is not available, the last non-missing pre-randomization measurement will be used as the baseline value.

6 OTHER ANALYSES

6.1 Interim Analyses

No interim analyses are planned for this study.

6.2 Subgroup Analyses

Subgroup analyses for the efficacy endpoints (PVR, 6MWD and other exploratory parameters) will be performed in order to explore whether the treatment effects are consistent across different subgroups. The baseline patient characteristics below are the subgroup factors to be explored.

- Sex (Male vs. Female)
- Age: < vs. ≥ median age, ≥ vs. < 65 years
- Race (White vs. Non-white)
- Baseline WHO/NYHA Functional Class (Class II vs. III or IV)
- Class of PAH therapy at baseline (ERA, PDE5, sGC)
    - With ERA vs. without ERA
    - With PDE5 vs. without PDE5
    - With sGC vs. without sGC
    - Monotherapy ERA
    - Monotherapy PDE5
    - Combination therapy: ERA + PDE5
- Etiology: IPAH vs Other Conditions
- Baseline 6MWD: <380m vs. ≥380m
- Baseline mean pulmonary arterial pressure (mmHg): < median vs.≥ median
- Baseline pulmonary vascular resistance: < median vs.≥ median
- Baseline pulmonary vascular resistance: ≤ 400 vs. > 400 units
- Baseline pulmonary vascular resistance index: < median vs.≥ median
- Baseline BNP/NT-proBNP: < median vs.≥ median
- Location: (North America vs. “Rest of World (Europe & Australia”)
- Time since PAH diagnosis: < median vs.≥ median

Due to the fact that this study is 1:2 randomization ratio and sample size for placebo group is approximately 20, there will be no interferential comparison between treatment groups within a subgroup of subjects. Instead, summary statistics (N, mean or median, SD, 95% CI for change or percent change from baseline or N, frequencies, proportions, and 95% CI) will be provided for each of the subgroups by treatment group. Between treatment group difference and 95% CI will be reported for each subgroup for illustration purpose. Additional subgroup analyses and/or revision of above subgroup definition may be specified after database lock to accommodate available data as appropriate.

6.3 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 Section 4.3 Approaches to Efficacy Analyses preserves the overall Type 1 error rate for testing the primary hypotheses. Note that testing for secondary and exploratory endpoints will proceed only if the comparison for the change from baseline in PVR is significant.

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.

6.4 Safety Monitoring Committee

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 and/or time at each dose before escalation (escalation scheme), different dosage strengths, and even a higher final dose level than 0.3 mg bid. 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.

7 STATISTICAL TECHNICAL ISSUES

7.1 Planned Statistical Power and Sample Size

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.

7.2 Method of Assigning Study Participants to Treatment Groups

Patients who meet all the entry criteria and are eligible for the study will report to the investigator to be randomized on Day 1. 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. Sites will randomize approximately 60 patients for entry into the study using an Interactive Web Randomization System (IWRS) across the entire study, and is not constrained within a center. Randomization will be stratified by Baseline WHO/NYHA Functional Class (Class II vs. III or IV).

7.3 Blinding/Unblinding

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.

7.4 Handling of Missing Data and Sensitivity Analysis

For the ITT analysis of PVR missing week 22 assessments will be derived using the method of multiple imputation via the SAS/STAT procedure PROC MI and the fully conditional

specification (FCS) method to create 100 imputations resulting in 100 complete datasets. The 100 imputed datasets will then be analyzed using the methods described in Section 4.3.1, with the results of the analyses performed on the 100 datasets combined via PROC MIANALYZE. The imputation model will include the following variables: treatment, baseline PVR, baseline NYHA/WHO functional class category, baseline PAH therapy, baseline values for 6MWD, BNP, NT-proBNP, etiology, last on-treatment 6MWD and whether or not a patient experienced clinical worsening. It is anticipated that the imputation model will converge but should it not do so terms will be removed from the model to achieve convergence. The effects of any such model adjustment will be investigated.

To assess the impact of missing data and robustness of the results, the following sensitivity analyses will be performed for the primary, secondary and selected exploratory endpoints:

- Completers population analyses on primary and secondary efficacy endpoints will be performed without missing data imputation.

- Worst case imputation. For PVR, in all-treated patients, prior to ANCOVA analyses as detailed in Section 4.3.1 missing data at Week 22 due to any reason will be imputed by taking:

    - the worst percentage change from baseline in all patients regardless of treatment group.

    - the baseline observation carried forward.

- An additional 'tipping point analysis' *may* be performed for PVR, post-hoc, in the event that the primary analysis is statistically significant and at least 1 of the worst case imputation analyses yields a non-significant result.

For the proportion of patients who progress to clinical worsening, a sensitivity analysis to assess the impact of missing data will be performed wherein all patients who prematurely discontinue treatment for any reason will be considered to have had a clinical worsening event.

- Imputation of missing or incomplete AE start date

  - If year part of AE start date is missing, then the year of the first treatment date will be assigned.

  - If both month and day part of AE start date are missing, and the year part is the same as year of the first treatment date, then the first treatment date will be assigned;

  - If both month and day part of AE start date are missing, and year part is less than the year part of the first treatment date, then 'Dec31' will be assigned to the missing month and day part

- If both month and day part of AE start date are missing, and year part is greater than year part of the first treatment date, then 'Jan01' will be assigned to the missing month and day.

- If month part is present and day part is missing, and year and month are same as year and month of the first treatment date, then the first treatment date will be assigned;

- If month part is present and day part is missing, and year and month combination is before the year and month combination of the first treatment date, then the last day will be assigned;

- If month part is present and day part is missing, the year and month combination is after the year, month combination of the first treatment date, then '01' will be assigned to the missing day.

After imputing: if the date of AE end a complete date, and the imputed ASTDT is later than the date of AE end, then reassign AE start date as AE end date.

8 DATA HANDLING CONVENTIONS

8.1 Baseline Definitions or Conventions

Baseline value is defined as the Day 1 (randomization) measurement. If the Day 1 measurement is not available, the last non-missing pre-randomization measurement will be used as the baseline value.

8.2 Time Points, and Day Ranges

Since it is not always possible for all study participants to come in for their clinic visits on the exact day specified in the protocol schedule, the "Week" of a patient's visit will be defined by the following relative day ranges. Tables 1 to 3 below give the mapping of relative day ranges to Week.

Table 1 Mapping for Endpoints measured at Day 1, Weeks 5, 10, 14, 18 and 22

Time Point	Target	Study Days
Baseline	**Day 1**	**≤ Day 1**
Week 5	Day 35	Days 2 ≤ to Days ≤ 52
Week 10	Day 70	Days 52 < to Days ≤ 84
Week 14	Day 98	Days 84 < to Days ≤ 112
Week 18	Day 126	Days 112 < to Days ≤ 140
Week 22	Day 154	> Days 140

Table 2 Mapping for Endpoints measured at Day 1, Weeks 10, and 22

Time Point	Target	Study Days
Baseline	**Day 1**	**≤ Day 1**
Week 10	Day 70	Days 2 ≤ to Days ≤ 112
Week 22	Day 154	> Days 112

Table 3 Mapping for Endpoints measured at Day 1 and Week 22

Time Point	Target	Study Days
Baseline	**Day 1**	**≤ Day 1**
Week 22	Day 154	> Days 2

If a patient has more than one assessment in a window, the assessment date closest to the target date will be selected. If a patient has 2 assessments that are equidistant from the target date, the later assessment will be selected.

8.3 Description of Data Handling Procedures Prior to Unblinding

All data will be screened, reviewed, and declared clean before data are unblinded according to Novella (Data Management CRO) guidelines and standard operating procedures. 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 Study. For patients who do not enter the extension study, study drug will be stopped after the treatment period at the Week 22, End of Study Visit and their individual patient database will not be locked, frozen or unblinded until the end of the study.

9 CHANGES FROM ANALYSIS PLANNED IN PROTOCOL

The protocol specified that the primary efficacy endpoint, PVR, should be analysed using the Modified Intent-to-Treat Population (MITT). This population consists of all patients randomized who received at least one study dose, have a baseline measurement, and have a post-randomization measurement. However, given that PVR is only measured once post-baseline, this amounts to a completers population and hence subjects who withdraw from the study produce missing data on the primary endpoint.

More recently this approach has been recognized as sub-optimal:

'Although it is possible to list conditions under which an analysis of complete cases provides a valid inference (essentially, conditional MCAR), this method is generally inappropriate for a regulatory setting. When missingness is in the outcome, the MAR assumption is generally weaker and can reduce bias from deviations from MCAR by making use of the information from incomplete data.

Furthermore, when missingness is appreciable, rejection of incomplete cases will involve a substantial waste of information and increase the potential for significant bias.'[3] (p. 55)

For this reason the changes from the analyses specified in the protocol are:

1. The primary analysis of PVR will be based upon the ITT population defined as consisting of all patients randomized who have a baseline PVR measurement.

2. Missing post-baseline PVR data will be imputed using the method of multiple imputation as outlined in Section 7.4 and detailed in Appendix 4.

3. The original planned analysis therefore becomes a sensitivity analysis in support of the new primary analysis.

The synopsis of protocol describes that ANCOVA model for primary analysis includes baseline PVR as a covariate, and treatment, baseline WHO/NYHA functional class and class of PAH

therapy at baseline as factors. The SAP clarifies that WHO/NYHA functional class at baseline (II vs, III or IV), and PAH therapy at baseline (With ERA vs. Without ERA) will be covariates in the models.

Other changes from protocol-specified analyses: the expansion of exploratory analyses specified in Section 4.3.3; addition of sensitivity analyses in dealing with missing data issues in Section 7.4; and clarifications of certain data handling details.

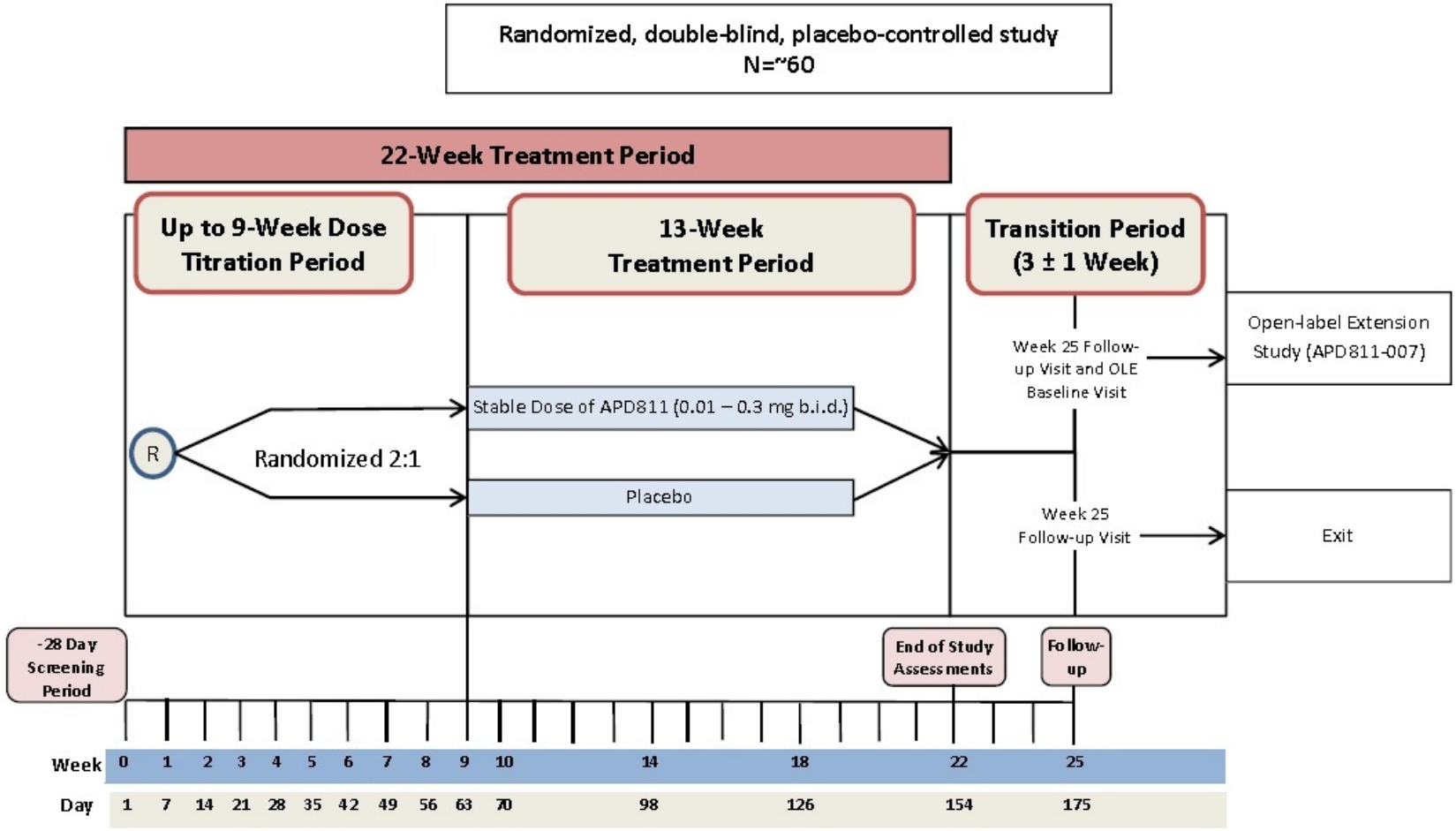
10 REFERENCES

1. APD811 Protocol 003: A Randomized, Double-blind, Parallel-group, Placebo-controlled Phase 2 Trial of APD811, an Oral IP Receptor Agonist, in Patients with Pulmonary Arterial Hypertension.

2. Common Terminology Criteria for Adverse Events v4.03 (CTCAE). Publish Date: June 14, 2010. Accessed October 2010. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

3. Council NR: The prevention and treatment of missing data in clinical trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. 2010, Washington DC: National Academies Press.

Appendix 1 Schematic of APD811-003 Study Design



Appendix 2 Schedule of Procedures and Visits:

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										
DNA Sample[l]		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**
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.

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]	
BNP/NT-proBNP[m]	X			X	X
Pharmacokinetic blood sample[n]	X	X	X	X	

[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.
[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.

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**
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	←	—	→		

[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.

Appendix 3 Listing of Efficacy Parameters and Study Populations Analyzed

Efficacy Parameters	Response Analyzed	Study Populations Analyzed
Primary Endpoints		
PVR	Change from Baseline	ITT, CP
6MWD	Change from Baseline	MITT, CP
Secondary Endpoints		
Clinical Worsening	Proportion	MITT, CP
PVR	Percent Change from Baseline	ITT, , CP
Exploratory Endpoints		
BNP/NT-proBNP	Change from Baseline at Week 22	MITT, CP
WHO/NYHA functional class	Change in numeric scale from Baseline at Week 22	MITT, CP
WHO/NYHA functional class	Proportion of patients in categorical change of WHO/NYHA function class after 22 weeks of treatment.	MITT, CP
Hemodynamic parameters	Change from Baseline at Week 22	MITT
Longitudinal change from baseline in 6 MWD up to 22 weeks		MITT
Longitudinal change from baseline in WHO/NYHA functional class in numeric scale up to 22 weeks		MITT
Time to first event of clinical worsening		MITT

Appendix 4 Multiple Imputation Program Specification and Notes

```
/* imputation is sensitive to sort order of input dataset */
proc sort data=dataset;by group usubjid;run;

/* create 100 imputations noting that they are sensitive to the order of
variables specified in the var statement and the seed (which must be pre-
specified to avoid criticism of data-snooping */
/* note that it is convenient to make ALL vars numeric
   Current key:
        group is treatment: Placebo coded to 1
                            APD811 coded to 2
        erastrat is baseline therapy: 'Without ERA' coded to 0
                                      'With ERA' coded to 1
        fcstrat: is baseline functional class: 'CLASS II' coded to 1
                                           'CLASS III or CLASS IV' coded
to 2
        walkbase is baseline 6MWD
        probase is log-transformed baseline NT-ProBNP
        worse is clinical worsening event: Event=1; No Event=0
        etio is etiology: 'IPAH'=1; 'OTHER CONDITIONS'=2
        walklocf is 6MWD last observation carried forward
        pvrbase is baseline PVR
        bnpbase is log-transformed baseline BNP
        pvr_ch is PVR change from Baseline to W22 (the dependent variable
of primary interest
)

/* note that the fcs statement allows us to use the logistic model for
binary
   Variables and normal distribution for the others */
ods select none;
proc mi data=dataset nimpute=100 out=mi_fcs seed=141662;
class erastrat fcstrat worse group ;
var  group erastrat fcstrat walkbase probase worse etio walklocf pvrbase
bnpbase  pvr_ch;
fcs logistic(erastrat fcstrat worse group/link=logit) nbiter =100 ;
run;

/* analyse by imputation using the SAP specified model */
/* note that we are also testing the normality of each imputation */
proc sort data=mi_fcs;by _imputation_;run;
proc glm data=mi_fcs;
by _imputation_;
class group fcstraterastrat;
model pvr_ch=group pvrbase fcstrat erastrat /solution clparm;
estimate 'Active - Placebo' group -1 1;
lsmeans group/stderr cl;
ods output ParameterEstimates=mixed_fcs estimates=estimates
lsmeans=lsmeans;
output out = resid r=r;
run;quit;

/* combine results from 100 imputations also picking up variance
information*/
```

```
proc mianalyze data=estimates ;
          by parameter;
          modeleffects estimate;
          stderr stderr;
          ods output ParameterEstimates=est
varianceinfo=varianceinfo(drop=df parm);
          run;

 ods select all;
  proc print data=est; var parameter estimate stderr lclmean uclmean
tvalue probt;
  title 'Multiple Imputation Results';
 format estimate lclmean uclmean tvalue 8.2 stderr 8.3 probt 8.4;
run;
proc print data=varianceinfo label;
title 'Imputation Variance Information';
format betvar winvar totvar 8.3 rivar fracmiss releff 8.4;
run;
/* we want to know how many of the 100 imputations were significantly non-
normal */
   ods select none ;
   proc univariate data=resid normal ;
    var r;
   by _imputation_;
   ods output testsfornormality=normal_stats(keep=test pvalue);
   run;
   ods select all;
   data wilk;
     set normal_stats(where= (index(Test,'Wilk')));
    if pvalue lt 0.05 then result='Non-Normal';
    else result='Normal';
    run;
    proc freq data=wilk;
    tables result;
    title 'Frequency of Non-Normal Imputations';
    run;
```