Study Protocol Number:	**APD811-007**
Study Title:	An Open-label Extension Study of APD811-003 in Patients with Pulmonary Arterial Hypertension
Study Phase:	2
Product Name:	Ralinepag (APD811)
IND Number:	109021
Indication:	Pulmonary Arterial Hypertension
Investigators:	Multicenter
Sponsor:	United Therapeutics Corporation
Sponsor Contact:	United Therapeutics Corporation 55 T.W. Alexander Drive Research Triangle Park, NC 27709 USA

	Date
Original Protocol:	17 June 2014
Amendment 01:	15 August 2014
Amendment 02:	09 October 2017
Amendment 03:	04 Jun 2018
Amendment 04:	15 May 2019

LIST OF CONTACTS FOR THE STUDY

Contract Research Organizations	[redacted]
Study Sponsor	**United Therapeutics Corporation** 55 TW Alexander Dr Research Triangle Park, NC 27709 USA
SAE Reporting	**United Therapeutics Global Drug Safety** Global Fax [redacted] email: [redacted]
Clinical Laboratory	[redacted]
ECG	[redacted]

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "An Open-label Extension Study of APD811-003 in Patients with Pulmonary Arterial Hypertension" Amendment 4 dated 15 May 2019, and agree to abide by all provisions set forth therein.

I agree to comply with the International Council for Harmonisation Guideline for Good Clinical Practice and applicable Food and Drug Administration regulations/guidelines set forth in 21 Code of Federal Regulations Parts 50, 54, 56, and 312 and local regulations per country.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of United Therapeutics Corporation.

I also have read the current Investigator's Brochure for ralinepag and acknowledge that review of the information contained in the Investigator's Brochure is a requirement for Investigators before using ralinepag in a clinical study.

This protocol has been received for information only and must not be implemented before all necessary regulatory agency and ethics approval documents have been obtained.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

SYNOPSIS

Protocol Number:	APD811-007
Title:	An Open-label Extension Study of APD811-003 in Patients with Pulmonary Arterial Hypertension
Study Phase:	2
Name of Drug:	Ralinepag (APD811)
Indication:	Pulmonary Arterial Hypertension
Sponsor:	United Therapeutics Corporation
Sponsor Contact:	United Therapeutics Corporation 55 T.W. Alexander Drive Research Triangle Park, NC 27709 USA
Name of Principal Investigator:	Multicenter
Medical Monitor:	[redacted]
Dosage:	All subjects enrolled in extension Study APD811-007 will receive open-label treatment with ralinepag. The starting dose and titration schedule will be individually determined and in accordance with the starting dose and titration schedule optimized from Study APD811-003. Adjustments in the dose and titration schedule may be made according to subject tolerability. The Sponsor will provide adequate supplies of ralinepag immediate-release (IR) capsules presented in strengths of 10, 20, 30, 40, and 100 mcg per capsule or extended-release (XR) tablets in strengths of 50, 250, and 400 mcg (0.05, 0.25, and 0.4 mg) for oral administration.
Concurrent Control:	No concurrent control
Dosage Form; Route of Administration:	IR capsules, liquid filled; XR tablets, round; oral

Objectives:	**Primary:**
	To evaluate the long-term safety and tolerability of ralinepag in subjects with World Health Organization (WHO) Group 1 pulmonary arterial hypertension (PAH) who have completed Study APD811-003.
	Secondary:
	To evaluate the effect of ralinepag in subjects with WHO Group 1 PAH who completed Study APD811-003, as determined by the incidence of clinical worsening. Clinical worsening is defined as fulfillment of any 1 of the following criteria (as assessed by change from baseline in Study APD811-003):
	• Death, or onset of treatment-emergent adverse event (AE) with a fatal outcome occurring less than or equal to 14 days after study treatment discontinuation
	• Hospitalization for worsening PAH, heart-lung or lung transplant, or atrial septostomy
	• The subject requires the addition (or change in dose if applicable) of any of the following PAH-specific medications:
	  • Prostacyclin/prostacyclin analogue (intravenous [IV], subcutaneous [SC], oral, or inhaled)
	  • Phosphodiesterase type 5 inhibitor (PDE5-I)
	  • Soluble guanylate cyclase stimulator (sGC)
	  • Endothelin receptor antagonist
	• The combined occurrence of the events listed below:
	  • A decrease in 6-Minute Walk Distance (6MWD) by at least 20% from baseline, confirmed on two 6-Minute Walk Tests (6MWTs), on different days
	  • Increase (worsening) in WHO/New York Heart Association (NYHA) Functional Class (FC) from baseline
	  • 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 subject's condition (eg, worsening FC) is related to the underlying PAH or can be explained by an alternative cause (eg, transient infection, musculoskeletal disease, surgical or medical intervention other than pulmonary hypertension (PH) related, exacerbation of a

	concomitant lung disease, lacking compliance of medication intake). Only persistent clinical deteriorations caused by the underlying PAH and confirmed as per the above criteria, will be considered clinical worsening. In subjects with WHO Group 1 PAH who have completed Study APD811-003, to evaluate changes from Baseline for the following efficacy endpoints with ralinepag treatment • 6MWD • WHO/NYHA FC • Hemodynamics
Study Design:	This protocol describes an open-label extension study to determine the long-term safety and tolerability of ralinepag in subjects with WHO Group 1 PAH who have completed the Phase 2 study, APD811-003. Subjects must have completed Study APD811-003 and must meet eligibility criteria for Study APD811-007. Additionally, placebo-treated subjects who discontinue ralinepag treatment due to clinical worsening in Study APD811-003 will be permitted to enroll in Study APD811-007 upon approval of the medical monitor, provided that all End of Study procedures, including right heart catheterization (RHC), are performed per protocol. The Week 25 Visit in Study APD811-003 will serve as the Baseline Visit for Study APD811-007. If the Week 25 Visit for Study APD811-003 serves as the initial visit for Study APD811-007, subjects should be consented for Study APD811-007 prior to the final procedures being performed for Study APD811-003. All subjects enrolled in Study APD811-007 will receive open-label treatment with ralinepag. The starting dose and titration schedule will be individually determined and in accordance with the starting dose and titration schedule optimized from Study APD811-003. Adjustments in the dose and titration schedule may be made according to subject tolerability. After an individual subject completes Study APD811-003 and that subject's database is locked, subject unblinding will occur. Subjects on active treatment (ralinepag) will remain on current dose and have onsite clinical assessments performed every 3 months until the subject is discontinued from the study. Subjects in the placebo treatment group will undergo a Dose Titration Period until a stable, maximum tolerated dose (MTD) is reached (up to 9 weeks), followed by a Treatment Period after the MTD is determined, during which monthly onsite clinic

	assessments will be performed for the first 3 months and then every 3 months until the subject is discontinued from the study or the study is terminated. Discontinuation of the study may also occur at the Sponsor's decision to terminate the study. Dose reductions may be made at any time for safety reasons. Incremental dose increases will also be allowed during the Treatment Period at the discretion of the Investigator (as clinically indicated) and according to the stepwise titration scheme. Subjects will be assessed for clinical worsening during each clinic visit. If clinical worsening is confirmed, the Investigator may opt to either continue treatment with ralinepag at the current dose, increase the dose of ralinepag, interrupt treatment, or discontinue the subject at his/her discretion. In addition, all subjects will be contacted at the time of Study APD811-007 closure to assess vital (mortality) status. The vital status follow-up contact of subjects will depend on local regulations or specific agreement with the subject and Investigator. After the last subject enrolled in Study APD811-007 has completed approximately 6 months of the study, a cumulative all-subject data analysis will be performed for all subjects who entered the study. Subjects will continue to have visits to the clinic every 3 months indefinitely to collect data until marketing approval of ralinepag is granted or until the Sponsor discontinues the study. At the time of marketing approval or the Sponsor's decision to discontinue the study, all ongoing subjects will complete an End of Study Visit. A 28-day Follow-up Visit will be conducted to ensure appropriate subject safety. This visit may be conducted by telephone or in person based upon the Investigator's discretion. Subjects who remain on ralinepag at study termination and meet all eligibility criteria are eligible to roll into the open-label extension study (ROR-PH-303). <u>Concomitant Medications</u> Subjects are permitted oral disease-specific PAH therapy consisting of an ERA and/or a PDE5-I or sGC stimulator, but not all 3. The on-study addition/substitution of an ERA, PDE5-I, or sGC stimulator, if on a single such agent at Baseline, or dosage increase for such agents is permitted. In addition to ralinepag, subjects can be prescribed no more than 1 agent from the ERA class and 1 from the PDE5-I/sGC stimulator class at any 1 time. Substitution and dose adjustment within each of these classes is permitted. Subjects should be evaluated for the presence of clinical worsening if

	additional therapy or dose adjustments of current therapies are required. In addition, the following therapies, which may affect PAH, are permitted and doses may be adjusted as needed: • Vasodilators (including calcium channel blockers) • Digoxin • Spironolactone • L-Arginine supplementation Diuretics may be dosed as clinically indicated throughout the study. Subjects who require treatment with a prostacyclin/prostacyclin analogue (IV, SC, oral, or inhaled), except for acute vasodilator testing during cardiac catheterization, will be discontinued from the study.
Study Site:	Multiple centers in the United States, Europe, and Australia.
Subject Population:	Subjects with WHO Group 1 PAH who have completed Study APD811-003 as planned and who meet eligibility criteria for Study APD811-007. Additionally, placebo-treated subjects who discontinued study drug treatment due to clinical worsening in Study APD811-003 will be permitted to enroll in Study APD811-007, upon approval of the medical monitor, provided that all End of Study procedures, including RHC, are performed per protocol. All women, regardless of childbearing potential, must have a negative serum pregnancy test at Baseline. Males and females of childbearing potential must use adequate means of contraception and must agree not to participate in a conception process (ie, active attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization) during the study and for 1 month after the last dose of study drug.
Eligibility:	Key Inclusion Criteria: • Evidence of a personally signed and dated informed consent document • Is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures and is deemed an appropriate candidate for participation in a long-term extension study and administration of ralinepag

	• Fulfilled all eligibility criteria for Study APD811-003 and completed the study as planned • Subjects who discontinued for clinical worsening in Study APD811-003 and were assigned to placebo and completed all End of Study procedures, including RHC, may participate after their data from Study APD811-003 are cleaned and locked Key Exclusion Criteria: • Subjects who enrolled in Study APD811-003 and were withdrawn from study drug treatment due to any AE, serious adverse event (SAE), or clinical worsening if assigned to ralinepag, or subjects who did not complete Study APD811-003 for other reasons. • Female subjects who wish to become pregnant • Systolic blood pressure <90 mmHg at Baseline/Day 1 • 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 subject inappropriate for entry into this study.
Duration per Subject:	Treatment with ralinepag will be indefinite until either marketing approval of ralinepag is granted or the Sponsor discontinues the study. Subjects who remain on ralinepag at study termination and meet all eligibility criteria are eligible to roll into the open-label extension study (ROR-PH-303).
Subject Assignment:	All subjects will receive ralinepag
Sample Size:	Approximately 60 subjects
Primary Outcome Measures:	The primary endpoint for the study is long-term safety. The safety of ralinepag will be monitored throughout the study with safety endpoints being as follows: • Treatment-emergent AEs up to 28 days following discontinuation of the study drug. • Treatment-emergent SAEs up to 28 days following discontinuation of the study drug.

Efficacy Assessments:	Efficacy will be assessed via performance of the following procedures: • 6MWT • WHO/NYHA FC assessment • Assessment of clinical worsening • Vital status • RHC
Efficacy Endpoints:	Assessment of time to clinical worsening and change from baseline in Study APD811-003 of the following: • 6MWD • WHO/NYHA FC • Hemodynamics
Safety Assessments:	• Clinical laboratory tests (to include hematology, coagulation parameters, serum chemistry, and urinalysis) • Vital signs • Physical examinations • 12-lead electrocardiograms (ECGs) • AEs
Data Analyses:	Long-term safety and tolerability of ralinepag will be assessed by clinical and statistical review of all relevant safety parameters, including AEs, laboratory values, vital signs, and ECGs. All subjects who received at least 1 dose of ralinepag in this extension study will be included in the safety assessment. The time to clinical worsening will be summarized. Estimation and 95% confidence intervals for within-treatment change from baseline in 6MWD and WHO/NYHA FC assessment will also be performed. Baseline is defined as the Day 1 pre-dose measurement from Study APD811-003. A secondary analysis using a definition of Baseline as Day 1 of Study APD811-007 will also be performed.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

6MWD	6-Minute Walk distance
6MWT	6-Minute Walk Test
ADL	Activities of Daily Living
ADR	Adverse drug reaction
AE	Adverse event
AUC	Area under the curve
BP	Blood pressure
BID	Twice daily
BNP	Brain natriuretic peptide
C_{max}	Maximal drug concentration
CRF	Case Report Form
CRO	Contract Research Organization
EC_{50}	Median effective concentration
ECG	Electrocardiogram
ERA	Endothelin receptor antagonist
FC	Functional Class
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hCG	Human chorionic gonadotropin
hERG	Human Ether-a-go-go-related gene
IC50	Half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	Prostacyclin receptor
IR	Immediate-release
IRB	Institutional Review Board
IV	Intravenous(ly)
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NOAEL	No-observed-adverse-effect level
NT-proBNP	N-Terminal pro-brain natriuretic peptide
NYHA	New York Heart Association

PAH	Pulmonary arterial hypertension
PAP	Pulmonary artery pressure
PCWP	Pulmonary capillary wedge pressure
PDE5-I	Phosphodiesterase type 5 inhibitor
PGI_2	Prostaglandin I_2
PH	Pulmonary hypertension
PK	Pharmacokinetic(s)
PVR	Pulmonary vascular resistance
Q3	Every 3
QD	Once daily
QTcB	QT interval corrected for Bazett's formula
QTcF	QT interval corrected for Fridericia's formula
RHC	Right heart catheterization
RR	Respiratory rate
SAE	Serious adverse event
SC	Subcutaneous(ly)
sGC	Soluble guanylate cyclase
SOP	Standard Operating Procedure
SVR	Systemic vascular resistance
TEAE	Treatment-emergent adverse event
t_{max}	Time of maximum plasma concentration
WHO	World Health Organization
XR	Extended-release

1 INTRODUCTION

Ralinepag is an orally available potent and selective, nonprostanoid, 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, kidneys, and blood vessels. Activation of the IP receptor results in vasodilation and inhibits platelet aggregation.[1]

Ralinepag is being developed to treat World Health Organization (WHO) Group 1 pulmonary hypertension, designated as pulmonary arterial hypertension (PAH). Elevated pulmonary artery pressure (PAP) 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 (PVR) that leads to right ventricular failure and ultimately premature death. Prior to the development of effective therapies for PAH, the median survival of subjects with idiopathic PAH was approximately 2.8 years.[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 vascular 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 (PH).[4,5]

Studies indicate that subjects with PH have decreased levels of prostacyclin.[4,6] Epoprostenol, an intravenous (IV) 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.

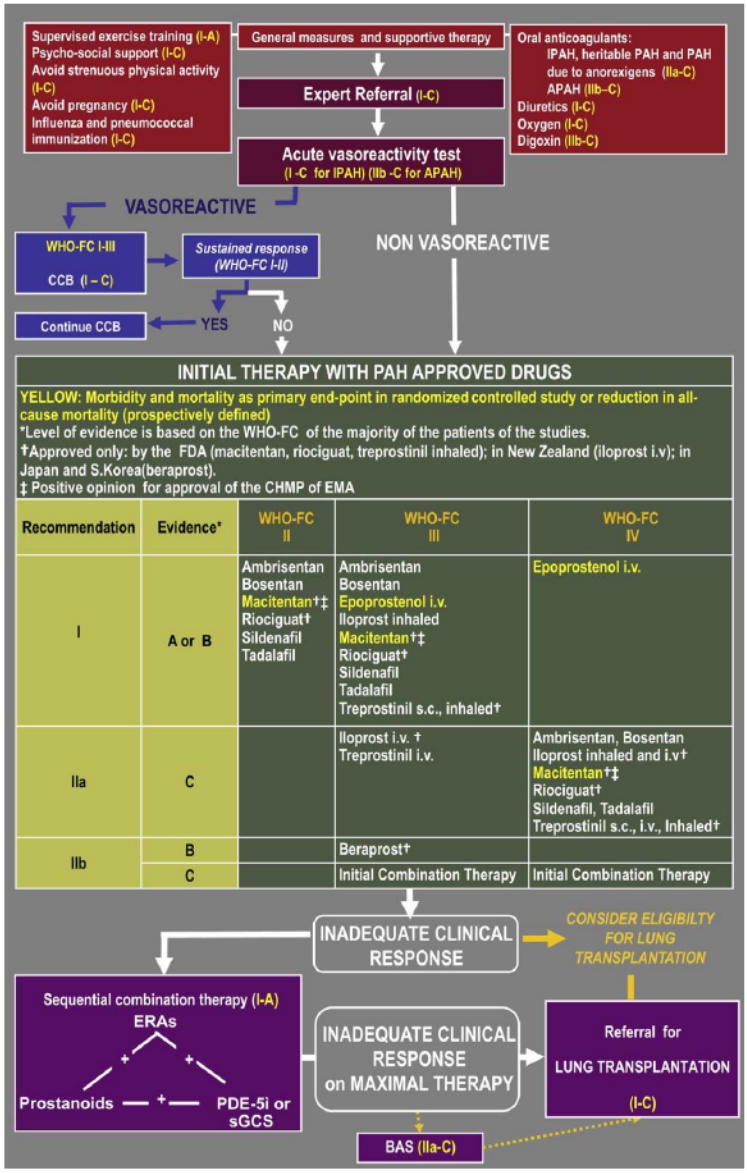
The clinical definition of PH requires confirmation by right heart catheterization (RHC) demonstrating a mean PAP >25 mmHg. The diagnosis of PAH requires a normal (≤15 mmHg) pulmonary capillary wedge pressure (PCWP) and an increase in PVR in addition to an elevated mean PAP. The latest clinical classification by the Sixth World Symposium on Pulmonary Hypertension divides PH into 5 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 subgroups in Group 1 PH 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 to 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 WHO (modification of the New York Heart Association [NYHA] classification for PH) Functional Class (FC) 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 nonresponders and are therefore candidates for treatment with an endothelin receptor antagonist (ERA), a phosphodiesterase type 5 inhibitor (PDE5-I) 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.

Due to availability of oral dosage forms, almost all patients initiate therapy with an ERA or a PDE5-I. The report from the Fifth World Symposium on Pulmonary Hypertension points out that the clinical role of aggressive early therapy with prostacyclin receptor agonists remains unknown since in randomized controlled studies, the available agents were evaluated primarily in subjects with more advanced disease. Multiple attempts at developing an IP receptor agonist for oral administration have been limited by molecules with unfavorable pharmacokinetic (PK) properties. Thus, there is a need for additional effective oral agents targeting the prostacyclin pathway.

Figure 1 Evidence-based Treatment Algorithm for PAH



Abbreviations: APAH, associated pulmonary arterial hypertension; BAS, balloon atrial septostomy; CCB, calcium channel blockers; ERA, endothelin receptor antagonist; FC, Functional Class; IPAH, idiopathic pulmonary arterial hypertension; IV, intravenous; PAH, pulmonary arterial hypertension; PDE5-I, phosphodiesterase type-5 inhibitor; SC, subcutaneous; sGC, soluble guanylate cyclase; WHO, World Health Organization

Source: Fifth 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% to 75% depending on PAH etiology and co-morbid conditions.[4,15] There is a significant need for alternative treatments for this disease. Ralinepag, an oral nonprostanoid IP receptor agonist, could be an effective and convenient treatment option.

Ralinepag 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 10 to 20 mcg, with adverse effects consistent with those reported for IP receptor agonists. The pathophysiology of PAH may be associated with changes in prostacyclin receptors within the pulmonary vascular circulation, and leads to differing responses than in healthy volunteers. This study is being undertaken to evaluate the long-term safety and tolerability of ralinepag in subjects with PAH who have completed the Phase 2 study, APD811-003, or subjects who were assigned to placebo and were discontinued for clinical worsening.

1.1.2 Summary of Nonclinical Data

[redacted]

[redacted]

[redacted]

[redacted]

1.1.3 Summary of Clinical Data

The starting dose of 100 mcg for the first-in-human Study APD811-001 was determined in accordance with Food and Drug Administration (FDA) Guidance for Industry, *Estimating the Maximum Safe Starting Dose in Clinical Trials for Therapeutics in Adult Healthy Volunteers* (2005), and was based on the monkey NOAEL of 100 mcg/kg/day, using a safety factor of 20, and assuming a 60-kg human subject.

In 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 30, 50, and 100 mcg were generally tolerated in healthy male and female subjects. The administration of a single dose of 200 mcg ralinepag 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 100 mcg. The adverse events (AEs) most commonly experienced included headache, vomiting, nausea, and jaw pain.

No consistent effects were seen on blood pressure (BP), but pulse rate appeared to increase more in ralinepag subjects than placebo subjects (delta ~10 bpm) at the 3 highest doses. Consequently, uncorrected QT interval decreased, but rate corrected QT interval for Fridericia's formula (QTcF) was increased from baseline at time of maximum plasma concentration (t_{max}) in nondose responsive fashion, by means and medians ranging from 3 to 9 msec at the 2 highest doses. An effect on QT interval is not supported by preclinical findings (human ether-à-go-go-related gene [hERG] concentration that inhibits 50% [IC50] >20 µM, and no effect on QTc in a primate cardiovascular study at 3 to 4 times the C_{max} achieved in the 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 (Study APD811-002). The safety and tolerability of 2 different dosing regimens was evaluated: a once-daily regimen in Cohorts 1 and 2 (run concurrently) began at an initial dose of 50 mcg and was escalated as tolerated to doses of 100, 200, 300, and 400 mcg at 5-day intervals, and a twice-daily regimen in Cohort 3 began at an initial dose of 10 mcg twice daily (BID) and was escalated as tolerated to doses of 20, 30, 40, 50, and 70 mcg BID at 5-day intervals. In Cohorts 1 and 2, a total of 30 subjects were dosed, with 20 subjects receiving ralinepag and 10 subjects receiving placebo. In Cohort 3, a total of 25 subjects were dosed, with 20 subjects receiving ralinepag and 5 subjects 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 100 mcg or higher with either QD or BID regimens. The specific AEs 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 receptor 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 subject during the first portion of the study after receiving 5 days of 50 mcg QD. Study drug was discontinued. The subject was admitted overnight to a hospital, treated with metoprolol and subcutaneous (SC) 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 subject 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 Nervous System Disorders, Gastrointestinal Disorders, and Musculoskeletal and Connective Tissue Disorders (Medical Dictionary for Regulatory Activities [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.

Ralinepag 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 ralinepag and are also consistent with observations for other IP receptor agonists.

Intensive electrocardiogram (ECG) monitoring was undertaken in this study to better understand possible effects of ralinepag on QT interval and to evaluate risk for QT effects. Ralinepag 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% confidence interval below 10 msec, the threshold of regulatory concern.

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

Study APD811-004 was conducted as an open-label, randomized, single-dose, 2-treatment, crossover study to assess the PK properties of ralinepag at a dose of 30 mcg in the fed and fasted states. The t_{max} in the fed state was delayed compared to the fasted state (from 1 to ~4 h), the C_{max} reduced (estimated geometric mean ratio ~0.6), and the AUC largely maintained (estimated geometric mean ratio ~0.8). These results support dosing of ralinepag with food.

Study APD811-003 was a randomized, double-blind, parallel-group, placebo-controlled, Phase 2 study of ralinepag in subjects with PAH. In this 61-subject study, the primary efficacy analysis demonstrated a statistically significant absolute change from Baseline in PVR compared to placebo. Ralinepag also demonstrated numerical improvement in 6-Minute Walk Distance (6MWD). Ralinepag improved median PVR by 163.9 $dyn.s.cm^{-5}$ from baseline compared to a 0.7 $dyn.s.cm^{-5}$ worsening from baseline in the placebo arm ($p=0.02$). Subjects treated with ralinepag had a 29.8% reduction in PVR compared to the placebo arm ($p=0.03$) and a 20.1% reduction in PVR compared to baseline. Additionally, AEs observed in the study were consistent with other prostacyclin treatments for the management of PAH, with headache, nausea, diarrhea, jaw pain, and flushing being the most commonly reported AEs. Additional information is be presented in the Investigator's Brochure.

In Study APD811-011, an extended-release (XR) tablet formulation of ralinepag was evaluated in a dose escalation paradigm over approximately 4 weeks (with daily dosing starting at 60 mcg and slowly up-titrating, depending upon individual subject tolerability, by

additional 60 mcg dose increments every 5 days up to 30 mcg) in healthy subjects in both the fasted and fed states.

The data from this study showed that ralinepag peak and total plasma exposure for the XR tablet were dose dependent (appearing only slightly higher than dose proportional) and did not appreciably vary when taken with or without food. Lastly, the XR tablet shows a higher plasma concentration at 24 h compared to the immediate-release (IR) capsule, indicating an improved plasma PK performance over the IR capsule with respect to once-daily dosing in terms of extending exposure and minimizing peak-to-trough fluctuation.

Overall, there were no deaths or SAEs, and all AEs were mild or moderate with the exception of 1 Grade 3 adverse drug reaction (ADR). In both the fasted and fed states, the majority of subjects experienced at least 1 AE, most of which were ADRs, and the number and percentage of AEs and ADRs were comparable. The majority of AEs were transient in nature and had resolved by the end of the study. The profile of AEs from both fasted and fed subjects were consistent with the reference safety information for ralinepag and other prostacyclin receptor agonists, with notable exceptions of the AEs of Grade 3 increased transaminases and Grade 1 ventricular extrasystoles.

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 (2013 Version), International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use Guidelines for Good Clinical Practice (GCP), 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 Independent Review Board (IRB)/Independent Ethics Committee (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 study subjects
- Changes increasing the risk to subjects and/or significantly affecting the conduct of the study
- All AEs that meet the definition of an SAE
- New information that may affect adversely the safety of the subjects or the conduct of the study

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 to eliminate hazards to the subjects.

2 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

To evaluate the long-term safety and tolerability of ralinepag in subjects with WHO Group 1 PAH who have completed Study APD811-003.

2.2 SECONDARY OBJECTIVES

- To evaluate the effect of ralinepag in subjects with WHO Group 1 PAH who completed Study APD811-003, as determined by the incidence of clinical worsening.
- To evaluate changes from baseline in the following efficacy endpoints:
  - 6MWD
  - WHO/NYHA FC
  - Hemodynamics

3 INVESTIGATIONAL PLAN

3.1 OVERALL STUDY DESIGN AND PLAN

This is a Phase 2, multicenter, open-label, extension study to determine the long-term safety and tolerability of ralinepag in subjects with WHO Group 1 PAH who have completed the Phase 2 study, APD811-003, or who were assigned to placebo and were discontinued for clinical worsening. Subjects must also meet eligibility criteria for participation in this long-term extension study. The Day 1 (Baseline) visit in Study APD811-007 will coincide with the Week 25 Visit in Study APD811-003. For this reason, subjects should be consented to Study

APD811-007 prior to the Week 25 procedures being performed for Study APD811-003. Baseline/Day 1 evaluations will include medical history update, assessment of disease state, and determination of eligibility for each potential subject.

All subjects enrolled in Study APD811-007 will receive open-label treatment with ralinepag. The starting dose and titration schedule will be individually determined in accordance with the starting dose and titration schedule optimized from Study APD811-003. Adjustments in the dose and titration schedule may be made according to subject tolerability. After the completion of Study APD811-003, ongoing safety review of subject data will be conducted by the Sponsor to monitor for drug safety.

After an individual subject completes Study APD811-003 and that subject's database is locked, subject unblinding will occur. Subjects who were on active treatment (ralinepag) in Study APD811-003 will remain on current dose and have onsite clinical assessments performed every 3 months until the subject is discontinued from the study (see Table 1).

Subjects in the placebo treatment group of Study APD811-003 will undergo a Dose Titration Period until a stable maximum tolerated dose (MTD) is reached (up to 9 weeks); this will be followed by a Treatment Period in which monthly onsite clinic assessments will be performed for the first 3 months and then every 3 months until the subject is discontinued from the study or the study is terminated (see Table 2).

Subjects will continue to have visits to the clinic every 3 months indefinitely to collect data as specified in Table 1 and Table 2 until marketing approval of ralinepag is granted or until the Sponsor discontinues the study.

During the conduct of the study, subjects will switch from the IR formulation of ralinepag (as studied in ADP811-003) to an XR formulation that will be used in Phase 3 studies.

For both IR and XR formulations, dose reductions may be made at any time for safety/tolerability reasons. Incremental dose increases will also be allowed during the Treatment Period (Table 1 and Table 2) at the discretion of the Investigator (as clinically indicated) and according to the stepwise titration scheme outlined in Table 4.

Subjects will be assessed for clinical worsening during each clinic visit. If clinical worsening is confirmed, the Investigator may opt to either continue treatment with ralinepag at the current dose, increase the dose of ralinepag, interrupt treatment, or discontinue the subject at his/her discretion. Addition/dose increases/substitutions of 1 drug within the ERA class and 1 within the PDE5-I/soluble guanylate cyclase (sGC) stimulator class are also permissible.

In addition, all subjects will be contacted at the time of Study APD811-007 closure to assess vital (mortality) status. The vital status follow-up contact of subjects will depend on local regulations or specific agreement with the subject and Investigator.

Upon termination of the study, subjects will complete an End of Study Visit. A 28-day Follow-up Visit will be conducted to ensure appropriate subject safety. This visit may be conducted by telephone or in person based upon the Investigator's discretion. Subjects who remain on ralinepag at study termination and meet all eligibility criteria are eligible to roll into the open-label extension study (ROR-PH-303).

Concomitant Medications:
Subjects are permitted oral disease-specific PAH therapy consisting of an ERA and/or a PDE5-I or sGC stimulator, but not both. The on-study addition/substitution of an ERA, PDE5-I/sGC stimulator, if on a single such agent at Baseline, or dosage increase for such agents is permitted. In addition to ralinepag, subjects can be prescribed no more than 1 agent from the ERA class and 1 from the PDE5-I/sGC stimulator class at any 1 time. Substitution and dose adjustment within each of these classes is permitted. Subjects should be evaluated for the presence of clinical worsening if additional therapy or dose adjustments/substitutions of current therapies are required.

In addition, the following therapies, which may affect PAH, are permitted and may be adjusted in dose as needed:

- Vasodilators (including calcium channel blockers)
- Digoxin
- Spironolactone
- L-Arginine supplementation

Diuretics may be dosed as clinically indicated throughout the study.

Subjects who require treatment with a prostacyclin/prostacyclin analogue (IV, SC, oral, or inhaled), except for acute vasodilator testing during cardiac catheterization, will be discontinued from the study.

3.2 RATIONALE FOR STUDY DESIGN

This study is designed to evaluate the long-term safety and tolerability of ralinepag in subjects with PAH.

Inclusion of a placebo arm in Study APD811-003 and the requirement to maintain the blind in that study necessitates the re-titration of all subjects entering Study APD811-007. Thus, the dose titration scheme from Study APD811-003 will be employed in this study for subjects who were previously treated with placebo in Study APD811-003.

Optimal dosing of IP receptor agonists in PAH subjects requires dose titration on an individualized basis; furthermore, tolerability may improve with continued exposure.[15] It is anticipated that the starting dose of 10 mcg BID will be tolerated by most, if not all, subjects. Data from the previous Phase 1 dose titration study suggests that there are individual differences in tolerability of ralinepag in healthy volunteers, consistent with findings from other studies of prostacyclin receptor agonists in PAH subjects.

Table 1 Schedule of Procedures and Visits: Study APD811-003 Subjects Treated with Ralinepag Entering Study APD811-007

Evaluation[a]	Baseline[b] (APD811-003 Week 25 Visit)	Treatment Period		End of Study (EOS)	28-Day Follow-Up[c]
		Q3 Months	1 or 2 Years		
		±5 days	±3 months	±3 days	±3 days
Informed consent	X				
Medical history	X				
Physical exam	X			X	
ECG (12-lead)[d]	X	X		X	
Clinical laboratory tests[e]	X	X		X	
Pregnancy test[f]	X	X		X	
Vital signs[g]	X	X		X	
Study drug administration	X[h]	X			
6MWT	X	X		X	
BNP/NT-proBNP[k]	X	X			
Assessment of clinical worsening	X	X		X	X
WHO/NYHA FC assessment[i]	X	X		X	X
RHC[l]			X		
Dose escalation/de-escalation assessment		X[j]			
Adverse event monitoring	X	X		X	X
Concomitant medication monitoring	X	X		X	X

Abbreviations: 6MWT, 6-Minute Walk Test; BNP, brain natriuretic peptide; ECG, electrocardiogram; FC, Functional Class; hCG, human chorionic gonadotropin; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; Q3, every 3; QTcB, QT interval corrected for Bazett's formula; QTcF, QT interval corrected for Fridericia's formula; RHC, right heart catheterization; RR, respiration rate; WHO, World Health Organization

[a] Reference to pre-dose and post-dose activities in this schedule apply to the morning dose of study drug. Study drug should be taken with food.

[b] The Week 25 (Day 175) Visit from Study APD811-003 will serve as the Baseline/Day 1 Visit for Study APD811-007.

[c] This visit may be conducted by telephone or in person based upon the Investigator's discretion.

[d] Safety ECGs should be completed pre-dose. After the last subject enrolled in Study APD811-007 completes approximately 6 months of treatment and a cumulative all-subject data analysis is performed, as outlined in Section 9 (Planned Statistical Methods), ECGs will subsequently be conducted locally at the discretion of the

Investigator (as clinically indicated) during the Q3 monthly visits. The ECG will be performed at the End of Study Visit. Locally collected ECG values for RR, PR, QRS, QT, QTc, QTcB, and QTcF will be collected in the Sponsor's clinical database.

[e] Clinical laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Clinical laboratory tests will be completed pre-dose. After the last subject enrolled in Study APD811-007 completes approximately 6 months of treatment and a cumulative all-subject data analysis is performed, as outlined in Section 9, clinical laboratory tests will subsequently be conducted locally at the discretion of the Investigator (as clinically indicated) during the Q3 monthly visits. A complete clinical laboratory test will be conducted locally at the End of Study Visit. Locally collected laboratory values that are abnormal and clinically significant will be collected in the Sponsor's clinical database along with the reference ranges.

[f] Serum hCG pregnancy tests will be completed pre-dose at each visit during the Treatment Period. After the last subject enrolled in Study APD811-007 completes approximately 6 months of treatment and a cumulative all-subject data analysis is performed, as outlined in Section 9, pregnancy testing (either serum or urine) will subsequently be conducted locally during each Q3 monthly and the End of Study Visit. Locally collected positive values for hCG will be collected in the Sponsor's clinical database along with the reference range.

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

[h] Subjects treated with ralinepag in Study APD811-003 study will continue on current dose.

[i] WHO/NYHA Functional Class will be assessed pre-dose at all visits.

[j] An assessment for further dose escalation or de-escalation will be conducted during the Q3 months.

[k] After the last subject enrolled in Study APD811-007 completes approximately 6 months of treatment and a cumulative all-subject data analysis is performed, as outlined in Section 9 (Planned Statistical Methods), pro-BNP and NT-proBNP testing will subsequently be conducted locally at the discretion of the Investigator (as clinically indicated) during the Q3 monthly visits. Locally collected values will be entered into the Sponsor's clinical database along with the reference ranges.

[l] At 1 year (±3 months) after the subject enrolls into Study APD811-007, an RHC assessment will be conducted. If the subject has been in Study APD811-007 beyond 1 year (±3 months) at the time of regulatory/ethics approval of this amendment, an RHC assessment will be conducted at 2 years (±3 months) instead. If a subject has been enrolled in Study APD811-007 more than 2 years at the time of regulatory/ethics approval of Amendment #02, an RHC will be performed at the time of those approvals.

Table 2 Schedule of Procedures and Visits: Study APD811-003 Subjects treated with Placebo entering Study APD811-007

Evaluation[a]	Baseline[b] (APD811-003 Follow-up Visit)	Dose Titration Period									Treatment Period			End of Study (EOS)	28-Day Follow-Up[c]
		9-Week Period									M1-M3	Q3 Months	1 or 2 Years		
		1	2	3	4	5	6	7	8	9	±3 days	±5 days	±3 months	±3 days	±3 days
Informed consent	X														
Medical history	X														
Physical exam	X													X	
ECG (12-lead)[d]	X	X	X	X	X	X	X	X	X	X	X	X		X	
Clinical laboratory tests[e]	X		X			X				X	X	X		X	
Serum pregnancy test[f]	X					X					X	X		X	
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X		X	
Study drug administration		X	X	X	X	X	X	X	X	X	X	X			
6MWT[h]	X										X	X		X	
BNP/NT-proBNP[k]	X											X			
WHO/NYHA functional class assessment[i]	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Assessment for clinical worsening	X	X	X	X	X	X	X	X	X	X	X	X		X	X
RHC[l]													X		
Dose escalation/de-escalation assessment												X[j]			
Adverse event monitoring	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Concomitant medication monitoring	X	X	X	X	X	X	X	X	X	X	X	X		X	X

Abbreviations: 6MWT, 6-Minute Walk Test; BNP, brain natriuretic peptide; ECG, electrocardiogram; hCG, human chorionic gonadotropin; MTD, maximum tolerated dose; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; Q3, every 3; QTcB, QT interval corrected for Bazett's formula; QTcF, QT interval corrected for Fridericia's formula; RHC, right heart catheterization; RR, respiratory rate; WHO, World Health Organization

[a] Reference to pre-dose and post-dose activities in this schedule apply to the morning dose of study drug. Study drug should be taken with food.

[b] The Week 25 Visit from Study APD811-003 will serve as the Baseline/Day 1 Visit for Study APD811-007.

[c] This visit may be conducted by telephone or in person based upon the Investigator's discretion.

[d] Safety ECG measurements to be completed at Baseline and at Weeks 1 to 9, unless the subject reaches a stable MTD and the subject transitions into the Treatment Period; ECGs will be completed pre-dose and 2 hours post-dose. After the last subject enrolled in Study APD811-007 completes approximately 6 months of treatment and a cumulative all-subject data analysis is performed, as outlined in Section 9, ECGs will subsequently be conducted locally at the discretion of the Investigator (as clinically indicated) during the Q3 monthly visits. The ECG will be performed at the End of Study Visit. Locally collected ECG values for RR, PR, QRS, QT, QTc, QTcB, and QTcF will be collected in the Sponsor's clinical database.

[e] Clinical laboratory tests will include hematology, serum chemistry, coagulation, and urinalysis. Clinical laboratory tests will be completed pre-dose. After the last subject enrolled in Study APD811-007 completes approximately 6 months of treatment and a cumulative all-subject data analysis is performed, as outlined in Section 9, clinical laboratory tests will subsequently be conducted locally at the discretion of the Investigator (as clinically indicated) during the Q3 monthly visits. A complete clinical laboratory test will be conducted locally at the End of Study Visit. Locally collected laboratory values that are abnormal and clinically significant will be collected in the Sponsor's clinical database along with the reference ranges.

[f] Serum pregnancy test will be completed pre-dose at each visit during the Treatment Period. After the last subject enrolled in Study APD811-007 completes approximately 6 months of treatment and a cumulative all-subject data analysis is performed, as outlined in Section 9 (Planned Statistical Methods), pregnancy testing (either serum or urine) will subsequently be conducted locally during each Q3 monthly and the End of Study Visit. Locally collected positive values for hCG will be collected in the Sponsor's clinical database along with the reference range.

[g] Vital sign measurements (blood pressure, heart rate, respirations, body temperature, and pulse oximetry [SpO_2]), taken in supine position after 5 minutes of rest) will be taken at pre-dose on Day 1, and pre-dose on the first day of each dose increase. On the first day of each dose increase, blood pressure and heart rate will be taken approximately every hour for the first 4 hours after study drug administration. Vital signs will be measured prior to any blood draw that occurs at the same time point.

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

[i] WHO/NYHA Functional Class will be assessed pre-dose at all visits.

[j] An assessment for further dose escalation or de-escalation will be conducted during the Q3 months.

[k] After the last subject enrolled in Study APD811-007 completes approximately 6 months of treatment and a cumulative all-subject data analysis is performed, as outlined in Section 9, pro-BNP and NT-proBNP testing will subsequently be conducted locally at the discretion of the Investigator (as clinically indicated) during the Q3 monthly visits. Locally collected values will be entered into the Sponsor's clinical database along with the reference ranges.

[l] At 1 year (±3 months) after the subject enrolls into Study APD811-007, an RHC assessment will be conducted. If the subject has been in Study APD811-007 beyond 1 year (±3 months) at the time of regulatory/ethics approval of Amendment 2, an RHC assessment will be conducted at 2 years (±3 months) instead. If a subject has been enrolled in Study APD811-007 more than 2 years at the time of regulatory/ethics approval of Amendment 2, an RHC will be performed at the time of those approvals.

4 STUDY POPULATION SELECTION

4.1 STUDY POPULATION

The study population will include subjects with WHO Group 1 PAH who have completed Study APD811-003 or who were assigned to placebo and discontinued for clinical worsening and who are deemed appropriate candidates for participation in this long-term extension study.

All women, regardless of childbearing potential, must have a negative serum human chorionic gonadotropin (hCG) pregnancy test at each visit during the Treatment Period and at Week 5 of the Dose Titration Period, if applicable. Males and females of childbearing potential must use adequate means of contraception and must agree not to participate in a conception process (ie, active attempt to become pregnant or impregnation, sperm donation, in vitro fertilization) during the study and for 30 days after the last dose of study drug. Eligible subjects must meet all entry criteria prior to being randomized to receive study drug as outlined below. Any deviations from these criteria must be approved by the Sponsor prior to the subject being enrolled.

4.2 INCLUSION CRITERIA

Each subject must meet the following criteria to be enrolled into the study:

- Evidence of a personally signed and dated informed consent document
- Is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures and is deemed an appropriate candidate for participation in this long-term extension study
- Eligible female subjects will be:
  - Nonpregnant, evidenced by a negative serum hCG pregnancy test at Baseline
  - Nonlactating
  - 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 drug 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 drug.

- Eligible male subjects will either be:
  - Surgically sterile (ie, vasectomy) for at least 3 months prior to Screening
  - 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 drug administration
- Eligible male and female subjects must agree not to participate in a conception process (ie, active attempt to become pregnant or impregnation, sperm donation, in vitro fertilization) during the study and for 30 days after the last dose of study drug
- Fulfilled all eligibility criteria for Study APD811-003 and completed the study as planned
  - Subjects who were assigned to placebo in Study APD811-003 and experienced clinical worsening in that study may enroll in Study APD811-007 after he/she has completed all end of study procedures per protocol, including RHC, and have had their individual Study APD811-003 data locked.

4.3 EXCLUSION CRITERIA

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

- Subjects who enrolled in Study APD811-003 and were withdrawn from study drug treatment due to any AE or SAE, or subjects who did not complete Study APD811-003, with the exception made as above for placebo-treated subjects who experienced a clinical worsening event.
- Female subjects who wish to become pregnant
- Systolic BP <90 mmHg at Baseline
- 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 subject inappropriate for entry into this study.

5 STUDY TREATMENTS

5.1 TEST ARTICLE

The Sponsor will provide adequate supplies of ralinepag IR capsules. Ralinepag will be provided as 10, 20, 30, 40, and 100 mcg IR dose strengths, and later will be provided as 50, 250, and 400 mcg (0.05, 0.25, and 0.4 mg) XR tablet dose strengths.

5.2 TREATMENTS ADMINISTERED

The ralinepag IR formulation initially used in the study is a liquid-filled, size 4, hard-gelatin capsule containing ralinepag, polyoxyl 40 hydrogenated castor oil (Kolliphor® RH40) NF, butylated hydroxytoluene NF, and colloidal silicon dioxide NF. The ralinepag XR formulation tablet contains ralinepag, hydroxypropylmethyl cellulose (Methocel K4M Premium CF and Methocel K100 Premium LVCR), microcrystalline cellulose (Avicel PH102), mannitol (Pearlitol 100 SD), silicon dioxide, and magnesium stearate.

Ralinepag used for the capsules was manufactured under Current Good Manufacturing Practices compliance by the Sponsor (or designee). The APD811 capsules (IR) or tablets (XR) will be manufactured under Current Good Manufacturing Practices compliance by the Sponsor (or designee).

5.3 PACKAGING, LABELING AND STORAGE

For each IR formulation 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 2°C (36°F) to 8°C (46°F); the bottles should not be frozen.

XR tablets are packaged in PERLALUX® blisters (polyvinyl chloride [PVC]/polythylene/polyvinylidene chloride [PVDC], 250/30/90, and cover foil Alu 20 mcm) in a 1×8 configuration and carded in an 8×8 array, 64 tablets per card. The cards are stored at 15°C to 30°C (59°F to 86°F).

5.4 TEST ARTICLE ACCOUNTABILITY

The Investigator will maintain accurate records of the receipt of all study drug. In addition, accurate records will be kept regarding when and how much study drug is dispensed and used by each subject in the study. Reasons for deviation from the expected dispensing regimen must also be recorded. Study drug will be reconciled by the Sponsor's monitor or contracted designee. The Investigator agrees to provide sufficient access to study drug 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 drug will be reconciled by the Sponsor's monitor or contracted designee and then returned to either the Sponsor or a third-party contractor to be retained or destroyed according to applicable country regulations and investigative site SOPs. Prior to any action being taken with study drug after the study is completed, the Investigator will contact the Sponsor (or contracted CRO) for approval of such action.

5.6 DOSAGE AND ADMINISTRATION

Investigational product will be dispensed to the subjects under the supervision of the Investigator or his/her designee. Subjects should not crush, break, chew, or dissolve the capsules or tablets. Subjects should wash hands with soap and water after handling drug product.

Capsules or tablets should be taken with food.

5.6.1 Immediate-release Capsules

5.6.1.1 Dose Titration Period (Study APD811-003 Placebo-treated Subjects)

Subjects who were assigned to placebo treatment in Study APD811-003 will undergo a Dose Titration Period of up to 9 weeks. All subjects will be on active treatment (ralinepag) in the open-label study, APD811-007.

The dose titration scheme will be the same as conducted in Study APD811-003. Subsequent dose escalations will continue until the MTD is determined, with a possible maximum total daily dose of 600 mcg (300 mcg BID) if tolerated. Subjects will be observed for at least 4 hours after the initial dose of ralinepag, and at each subsequent dose escalation. AEs, BP, 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 subject may be monitored as an inpatient for the initial dose and/or subsequent increases in dose. The medical monitor should be notified in any instance that prolonged observation and/or inpatient monitoring is anticipated or required.

If a dose is not tolerated, the study drug should be decreased to the previous dose level. If the initial dose of 10 mcg BID is not tolerated, dosing may be decreased to 10 mcg QD.

If the initial dose is tolerated (10 mcg BID), then the dose will be increased in the following fashion at subsequent visits: 20, 30, 40, 60, 80, 100, 200, and 300 mcg BID. The dose may be escalated to a possible maximum total daily dose of 600 mcg (300 mcg BID) if tolerated.

Subjects may become symptomatic during the course of dose escalation, and adjustment up and/or down may be required to find the optimal dose for any given subject. Over the 9-week Dose Titration Period, there are opportunities to change the dose. 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/tolerability reasons at any time, but may not be increased without assessment in the clinic.

Table 3 indicates the dosing regimen during the Dose Titration Period.

Prolonged dosing may result in tolerance to some adverse effects, so that consideration should be made to attempt dose escalation if some time (eg, >7 days) has elapsed since the prior dose escalation attempt and the 9-week Dose Titration Period is not yet complete.

In order to simplify dose titration, the 10 mcg strength capsule will be used during the initial portion of the dose titration.

If a subject reaches the highest dose tolerated (stable dose) and no further dose escalations are planned, the Dose Titration Period will be considered completed.

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

Dose (mcg)		Supplied by		Total daily dose (mcg)
10	QD	1 × 10 mcg	QD	10
10	BID	1 × 10 mcg	BID	20
20	BID	2 × 10 mcg	BID	40
30	BID	3 × 10 mcg	BID	60
40	BID	4 × 10 mcg	BID	80
60	BID	3 × 20 mcg	BID	120
80	BID	4 × 20 mcg	BID	160
100	BID	5 × 20 mcg	BID	200
200	BID	2 × 100 mcg	BID	400
300	BID	3 × 100 mcg	BID	600

Abbreviations: BID, twice daily; QD, once daily

5.6.1.2 Treatment Period

Subjects who were on active treatment (ralinepag) in Study APD811-003 will remain on current dose and have onsite clinical assessments performed every 3 months until the subject is discontinued from the study (see Table 1). Subjects in the placebo treatment group of Study APD811-003 will undergo a Dose Titration Period until a stable MTD is reached (up to 9 weeks). At the conclusion of the Dose Titration Period and when a subject reaches the highest dose tolerated, the subject will transition directly into the Treatment Period with monthly assessments for the first 3 months and then every 3 months.

The optimal dose achieved for each subject at the end of the Dose Titration Period can be maintained throughout the Treatment Period; however, incremental dose increases will also be allowed during the Treatment Period at the discretion of the Investigator (as clinically indicated) and according to the stepwise titration scheme outlined in Table 4.

Table 4 indicates the possible IR dosing regimens to be used during the remainder of the Treatment Period according to each individual subject's optimally defined dose.

Table 4 Possible Dosing Regimen during the Treatment Period

Dose (mcg)		Supplied by		Total daily dose (mcg)
10	QD	1 × 0.01 mcg	QD	10
10	BID	1 × 0.01 mcg	BID	20
20	BID	1 × 0.02 mcg	BID	40
30	BID	1 × 0.03 mcg	BID	60
40	BID	1 × 0.04 mcg	BID	80
60	BID	2 × 0.03 mcg	BID	120
80	BID	2 × 0.04 mcg	BID	160
100	BID	1 × 0.1 mcg	BID	200
200	BID	2 × 0.1 mcg	BID	400
300	BID	3 × 0.1 mcg	BID	600

Abbreviations: BID, twice daily; QD, once daily

5.6.2 Extended-release Tablets

5.6.2.1 Formulation Switch and Dose Titration Period

During the study, all subjects will switch to an XR formulation of ralinepag that will be used in Phase 3 studies of ralinepag, per the guidance in Table 5. The switch to XR ralinepag should occur at a regularly scheduled visit, with dose titration to occur, as needed, in 50-mcg weekly increments. Weekly phone contact with the subject will be performed to guide XR dose titration to the highest tolerated dose.

Table 5 Dose Switching Guidance from Immediate-release to Extended-release Ralinepag

Current IR Dose (mcg; total daily)	Corresponding XR Dose (mcg)
<30	50 EOD
≥30 to <120	50
120	100
160	150
200	200
400	400
600	600

Abbreviations: EOD, every other day; IR, immediate-release; XR, extended-release

5.6.2.2 Treatment Period

After the dose switch and Dose Titration Period with the XR formulation, subjects will continue into the Treatment Period, in which subjects will have an assessment every 3 months. With the exception of the difference in ralinepag formulation, this Treatment Period will be identical to that which occurred with the IR formulation (Section 5.6.1.1, Section 7.2.3).

The optimal dose achieved for each period during the Formulation Switch and Dose Titration Period (Section 5.6.1.1) can be maintained; however, incremental dose changes (uptitration or down titration) will also be allowed during the Treatment Period at the discretion of the Investigator (as clinically indicated).

5.7 METHOD OF ASSIGNING SUBJECTS TO TREATMENT GROUPS

All subjects will receive ralinepag in this study. Subjects randomized to placebo during Study APD811-003 will begin a Dose Titration Period until a stable dose is reached. Subjects randomized to ralinepag during Study APD811-003 will start on the final dose achieved during that study. Subjects who remain on ralinepag at study termination and meet all eligibility criteria are eligible to roll into the open-label extension study (ROR-PH-303).

5.8 RANDOMIZATION AND BLINDING

Not applicable. This is an open-label study.

No re-randomization process is to take place for this study; subjects will retain the subject/randomization numbers assigned in Study APD811-003 as subject identifiers in this study.

6 STUDY PROCEDURES

Data resulting from procedures collected as part of the subject's standard of care may be collected in addition to the procedures outlined in this section. This will be outlined accordingly in the subject informed consent document and includes the collection of data resulting from performance of RHCs performed as standard of care.

6.1 INFORMED CONSENT

The Investigator will obtain and document the informed consent for each subject screened for this study. All subjects 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 subject's medical record should contain written documentation indicating that informed consent was obtained. The Informed Consent Form (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 ICH Guideline E6.

6.2 MEDICAL AND SOCIAL HISTORY

At Baseline, evaluations will include a medical and social history update, to include tobacco, alcohol, and caffeine use. Concomitant medications and concomitant nondrug treatments will also be recorded.

6.3 PHYSICAL EXAMINATION

Physical examinations will be conducted as per standard clinical practice and should include an assessment of each body system, height, and weight. Physical examinations should be performed in a manner that is reasonably consistent from visit to visit. The physical examination performed at the Week 25 Visit of Study APD811-003 will serve as the Baseline Visit for Study APD811-007.

6.4 VITAL SIGNS

Supine BP, heart rate, body temperature, respiratory rate (RR) and pulse oximetry will be measured after the subject 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 nondominant 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.
- The 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 and diastolic BP 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 systolic BP and diastolic BP should not be rounded.

6.5 ELECTROCARDIOGRAPHY

6.5.1 ECG Equipment

Safety ECGs will be recorded from an ECG machine (12-lead). Safety ECGs will be printed and reviewed on site by the Investigator or designee. Safety ECGs will be captured, recorded, and analyzed according to the Centralized ECG Procedure Manual for visits that require centralized ECG collection (see Table 1 and Table 2).

6.5.2 ECG Acquisition

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

- Subject initials (example: XYZ or X-Z)
- Subject number (enter the randomization number)
- Subject sex
- Subject date of birth (DDMMMYYYY)
- Study day and time

ECGs will be recorded with subjects in the recumbent position and resting. Subjects will have been in this resting position for 10 minutes prior to ECG recording, and the ECG will be 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. Subjects 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, QT interval corrected for Bazett's formula (QTcB), and QTcF.

Local: After the last subject enrolled in APD811-007 completes approximately 6 months of treatment and a cumulative all-subject data analysis is performed, as outlined in Section 9, ECGs will subsequently be conducted locally at the discretion of the Investigator (as clinically indicated) during the every 3 (Q3) monthly visits.

6.5.3 ECG Assessment

Baseline ECGs will be compared with the final ECG.

The Investigator will be responsible for the 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 Case Report Form (CRF). This information will be used in the ongoing safety review during the conduct of the study.

6.6 6-MINUTE WALK TEST

The 6-Minute Walk Test (6MWT) should be conducted according to the guidelines in Appendix 1, which have been adapted from the guidelines issued by the American Thoracic Society, *ATS Statement: Guidelines for the Six-minute Walk Test*.[16] 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 intra-day variability. The 6MWT performed at the Week 25 Visit of Study APD811-003 will serve as the Baseline assessment for Study APD811-007.

6.7 WHO/NYHA FUNCTIONAL CLASS ASSESSMENT

Subjects will be classified according to a system originally developed for heart failure by the NYHA and then modified by the WHO for subjects with PAH.[17] The severity of PAH will be graded according to the functional status of the subject and assessed at every visit. The grades range from FC I, where the subject's disease does not affect their day-to-day activities, to FC IV, where subjects are severely functionally impaired, even at rest (see Appendix 2).

6.8 RIGHT HEART CATHETERIZATION

At 1 year (±3 months) after the subject enrolls into APD811-007, an RHC assessment will be conducted. If the subject has been in the APD811-007 study beyond 1 year (±3 months) at the time of regulatory/ethics approval of Amendment 2, an RHC assessment will be conducted at 2 years (±3 months) instead. If a subject has been enrolled in APD811-007 for more than 2 years at the time of regulatory/ethics approval of Amendment 2, an RHC will be performed at the time of those approvals. It is recommended that every effort should be made to take the measurements approximately 4 hours after the last dose of study drug. An RHC should be performed when a subject terminates from the study early if an RHC has not been conducted within the previous year.

The following values will be obtained and recorded: PAP (systolic, diastolic, and mean), heart rate, right atrial pressure, PCWP right ventricular pressure and cardiac output, PVR, arterial and mixed venous oxygen saturation (if applicable). Systemic vascular resistance (SVR) will be estimated from BP measurements. Further specifications will be provided in a separate study manual.

6.9 ASSESSMENT OF CLINICAL WORSENING

The Investigator will evaluate the subject 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 fulfillment of any 1 of the following criteria (as assessed by change from baseline in Study APD811-003:

- Death, or onset of treatment-emergent AE (TEAE) with a fatal outcome occurring less than or equal to 14 days after study treatment discontinuation
- Hospitalization for worsening PAH, heart-lung or lung transplant, or atrial septostomy
- The subject requires the addition (or change in dose if applicable) of any of the following PAH specific medications:
  - Prostacyclin/prostacyclin analogue (IV, SC, oral, or inhaled)
  - PDE5-I or sGC
  - ERA
- The combined occurrence of the events listed below:
  - A decrease in 6MWD by at least 20% from baseline, confirmed on two 6MWTs on different days
  - Increase (worsening) in WHO/NYHA FC from baseline
  - 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 subject's condition (eg, worsening FC) is related to the underlying PH or can be explained by an alternative cause (eg, 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 PAH and confirmed as per the above criteria will be considered clinical worsening.

6.10 CLINICAL LABORATORY TESTS

All details regarding clinical laboratory sample collection, preparation, and shipment are included in the laboratory manual provided by the central laboratory for visits that require centralized lab collection (see Table 1 and Table 2).

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

After the last subject enrolled in APD811-007 completes approximately 6 months of treatment and a cumulative all-subject data analysis is performed, as outlined in Section 9, clinical laboratory tests will subsequently be conducted locally at the discretion of the Investigator (as clinically indicated) during the Q3 monthly visits. Locally collected laboratory values that are abnormal and clinically significant will be collected in Sponsor's clinical database along with the reference ranges.

6.10.1 Laboratory Parameters

Clinical laboratory tests will include the following:

Serum Chemistry	**Hematology**
Albumin (ALB)	Hematocrit (Hct)
Alkaline phosphatase (ALK-P)	Hemoglobin (Hb)
Alanine aminotransferase (ALT; SGPT)	Mean corpuscular hemoglobin (MCH)
Amylase	Mean corpuscular volume (MCV)
Aspartate aminotransferase (AST; SGOT)	Platelet count
Bicarbonate	Red blood cell count (RBC)
Blood urea nitrogen (BUN)	White blood cell count (WBC) with differential
Calcium (Ca)	
Chloride (Cl)	
Creatinine	**Coagulation**
Creatine kinase and MB subtype (if elevated)	Prothrombin time (PT)
Gamma-glutamyl transferase (GGT)	Activated partial thromboplastin time (PTT)
Glucose	International normalized ration (INR)
Lactate dehydrogenase (LDH)	
Lipase	**Additional tests**
Magnesium	Serum human chorionic gonadotropin (hCG) *
Phosphate	Brain natriuretic peptide (BNP)*
Potassium (K)	N-terminal pro-brain natriuretic peptide (NT-proBNP) levels*
Sodium (Na)	
Total bilirubin	
Total cholesterol	
Total protein	
Triglycerides	

* Tests performed at Week 25 Visit of Study APD811-003 will serve as baseline for Study APD811-007.

6.10.2 Urinalysis

Urinalysis parameters for clinical laboratory tests include the following:

Appearance	Occult blood
Bilirubin	pH
Color	Protein
Glucose	Specific gravity
Ketones	Urobilinogen
Leukocyte esterase	

6.10.3 Sample Collection, Storage, and Shipping

Blood samples for hematology, coagulation parameters, serum chemistry, human immunodeficiency virus 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 and Table 2.

6.11 BNP/NT-PROBNP

As mean PAP increases, so does the brain natriuretic peptide (BNP)/N-terminal pro-brain natriuretic peptide (NT-proBNP) level as long as ventricular function is intact. In idiopathic PAH, the BNP/NT-proBNP level is related to functional impairment.

As BNP/NT-proBNP may be affected by recent exercise, subjects must be allowed to rest for a minimum period of **1 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 subject in the same position at all appropriate visits, eg, sitting or semi-recumbent. Detailed instructions about sample collection will be provided in a separate sample collection manual.

After the last subject enrolled in APD811-007 completes approximately 6 months of treatment and a cumulative all-subject data analysis is performed, as outlined in Section 9, pro-BNP and NT-proBNP testing will subsequently be conducted locally at the discretion of the Investigator (as clinically indicated) during the Q3 monthly visits. Locally collected values will be entered into the Sponsor's clinical database along with the reference ranges.

6.12 ADVERSE EVENTS ASSESSMENTS

AEs will be recorded and reported in accordance with ICH Guideline E6, *Good Clinical Practice: Consolidated Guidance* (1996). Definitions of AEs and SAEs will be the same as those presented in ICH Guideline E2A.

6.12.1 Adverse Event Reporting

Subjects will be instructed that they may report AEs at any time. All events reported following study drug administration will be recorded as TEAEs.

Monitoring of AEs will be continued up to 30 days after cessation of study drug 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 subject administered any dose of ralinepag 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 drug, whether or not related to the product.

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 subject 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

AEs 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 AE Form, including details of intensity, onset, duration, outcome, and relationship to the drug as determined by

the Investigator. Whenever possible, a constellation of signs and symptoms should be recorded as a unifying diagnosis (eg, 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 subjects after AEs will be documented.

6.12.2 Serious Adverse Events and Expedited Reporting of Adverse Events

SAEs will be captured from the Study APD811-007 Baseline Visit (Week 25 of Study APD811-003) to 30 days after the last dose of study drug and will be monitored until resolution or stabilization.

An 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 (see below)

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent 1 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 formal hospitalization.

The following are not considered SAEs despite requiring hospitalization:

- Pre-existing conditions that, in the opinion of the investigator, did not worsen or progress during study participation
- Routinely scheduled procedures or treatment (eg, routine RHC)
- Elective procedures that were scheduled prior to study participation (ie, signing of the informed consent document)

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 Report form must be submitted within 24 hours of notification to:

United Therapeutics Global Drug Safety
Global Fax: [redacted]
email: [redacted]

Other situations as defined in ICH Guideline E2A, *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (1994), 21 Code of Federal Regulations Section 312.32, and EU Volume 10 also qualify for expedited reporting. In the following situations, the process will be as detailed for SAEs above:

- SAEs which could be associated with the study procedures
- SAEs and AEs 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's Brochure

6.12.3 Pregnancy

If a study subject becomes pregnant during participation in this clinical study, site staff must notify the sponsor within 24 hours of learning of the pregnancy. Subjects who become pregnant during the study will be discontinued from ralinepag immediately. Although not considered an SAE or AE, pregnancies occurring during the period of ralinepag administration until 30 days after the last dose of ralinepag should be reported to the Sponsor and IRB/IEC in the same manner as an SAE, using a pregnancy notification form.

The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE. Pregnancies will be followed every trimester through the first well baby visit.

For female partners who become pregnant by male study subjects 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 subject.

6.12.4 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 Common Terminology Criteria for Adverse Events v. 4.03[20] 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.

* 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.

6.12.5 Assessment of Adverse Event Relationship to Study Drug

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 (eg, 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.

6.12.6 Assessment of Adverse Event Outcome

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

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

6.12.7 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

6.12.7.1 Action Taken for Study Drug

Any action taken with study drug will be defined according to ICH Guideline E2B, *Data Elements for Transmission of Individual Case Safety Reports* (1998) and documented in the CRF according to the following:

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

6.12.8 Collection of Extra Laboratory Samples/Investigations

In the event of a clinically important AE, a suitable sample may be collected for drug assay or for additional laboratory tests. The Investigator must ensure that the sample is properly

labeled and stored. The Investigator and others responsible for the care of the subjects 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.

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

The AEs present at the last study day (End of Study) that require follow up or a repeat laboratory test will be followed up initially for 30 days according to the Sponsor's. AEs that have not resolved or stabilized at 30 days after the last subject's last study dose will be reviewed 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.

6.13 CONCOMITANT MEDICATION ASSESSMENTS

All concomitant medications (over-the-counter and prescribed) taken by subjects will be recorded in the CRF with indication, start date/time, and stop date/time, if known.

Subjects are permitted oral disease-specific PAH therapy consisting of an ERA and/or a PDE5-I or sGC stimulator, but not all 3. The on-study addition/substitution of an ERA, PDE5-I or sGC stimulator, if on a single such agent at Baseline, or dosage increase for such agents is permitted. In addition to ralinepag, subjects can be prescribed no more than 1 agent from the ERA class and 1 from the PDE5-I/sGC stimulator class at any 1 time. Substitution and dose adjustment within each of these classes is permitted. Subjects should be evaluated for the presence of clinical worsening if additional therapy or dose adjustments of current therapies are required.

In addition, the following therapies, which may affect PAH, are permitted and may be adjusted in dose as needed:

- Vasodilators (including calcium channel blockers)
- Digoxin
- Spironolactone
- L-Arginine supplementation

Diuretics may be dosed as clinically indicated throughout the study.

Subjects who require treatment with a prostacyclin/prostacyclin analogue (IV, SC, oral, or inhaled), except for acute vasodilator testing during cardiac catheterization, will be discontinued from the study.

6.14 REMOVAL OF SUBJECTS FROM THE STUDY OR STUDY DRUG

Subjects will be allowed to remain on study drug until marketing approval of ralinepag is granted or until the Sponsor discontinues the study. 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 subjects is posed by the continuation of the study in light of review of the key safety data.

Subjects will be informed that they are free to withdraw from the study at any time for any reason should they so wish. The Investigator may remove a subject if, in his/her opinion, it is in the best interest of the subject. A subject 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
- Withdrawal of consent - any subject 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.

6.14.1 Handling of Withdrawals

Although a subject 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 subject's rights. If there is a medical reason for discontinuation, the subject will remain under the supervision of the study physician until in satisfactory health. Reasonable efforts will be made to contact a subject who fails to attend any follow-up appointments, in order to ensure that he/she is in satisfactory health.

If a subject is prematurely discontinued from this study, every attempt will be made to follow the End of Study Procedures described in Section 7.

In addition, all subjects will be contacted at the time of Study APD811-007 closure to assess vital (mortality) status. The vital status follow-up contact of subjects will depend on local regulations or specific agreement with the subject and Investigator.

6.15 ALLOWABLE VISIT AND PROCEDURE WINDOWS

A ±3-day window is allowed for study visits and procedures during the Dose Titration Period, Treatment Period, and End of Study and Follow-up Visits, with the exception of the Q3 Month Visits during the Treatment Period, which are allowed a ±5-day window.

7 STUDY ACTIVITIES

7.1 SCREENING VISIT

Given that this study serves as an extension to Study APD811-003, an independent Screening Visit is not required. In order for subjects to be eligible for this study, they must have completed Study APD811-003 as planned or have been assigned to placebo and discontinued for clinical worsening and fulfill the eligibility criteria outlined in Section 4.

Subjects who have an interest in participating in this study should be properly consented prior to completing the Week 25 Visit in Study APD811-003. This is to include a detailed oral presentation of the nature, purpose, risks, and requirements of the study in addition to receiving detailed written information. Each subject should have adequate opportunity to ask the appropriate person of the clinical staff (ie, Investigator or designee) presenting the study about any aspect of the study. Once the subject 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 subject will also sign the form to confirm consent has been obtained. Once signed, the Investigator will retain the original for the subject's study records and provide the subject with a signed copy. The Investigator will verify that informed consent has been obtained from each subject prior to admission into the study and prior to the subject undergoing any study-related procedures. If it is standard practice at the site to conduct a few general noninvasive study procedures (ie, medical/social history, collection of concomitant

medications, etc) before a subject can be considered for a specific study, the study center must have a written SOP detailing the procedure, and also ensure that each subject signs a general consent prior to undergoing the general procedures.

7.2 STUDY PROCEDURES

7.2.1 Baseline Study Procedures – All Subjects

Subjects 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 Baseline procedures and receive study drug and instructions. The study drug will be given in the morning at the study site during the Baseline Visit.

7.2.1.1 Pre-baseline Procedures

All Week 25 measurements from Study APD811-003 will serve as Baseline assessments for Study APD811-007.

Placebo-treated subjects who discontinued prematurely from Study APD811-003 due to clinical worsening are permitted to enroll in APD811-007 provided that all end of study procedures are performed per the ADP811-003 protocol. For these subjects, the time of the clinical worsening event that led to early termination in Study APD811-003 will serve as the Baseline time point for clinical worsening in APD811-007.

Any unresolved AE from Study APD811-003 will be carried forward and recorded.

7.2.1.2 Baseline Procedures

- Medical history (partial history, to update findings from Study APD811-003)
- Physical exam[1]
- 12-lead ECG[1]
- Clinical laboratory tests (to include hematology, coagulation parameters, serum chemistry, and urinalysis)[1]
- Serum pregnancy test (women only)[1]
- Vital signs[1]
- 6MWT[1]
- BNP/NT-proBNP[1]
- Assessment of clinical worsening

- WHO/NYHA FC assessment[1]
- Record AEs[1]
- Record concomitant medications[1]

[1] Taken from Week 25 Visit in Study APD811-003

7.2.2 Study Procedures – for Immediate-release Dose Titration Period (Study APD811-003 Placebo Subjects)

Visits after Baseline should occur weekly for each escalation of study drug dose. There should be 1 study visit per week during the Dose Titration Period. Beyond the weekly visit, any additional visit during the Dose Titration Period will be documented as an 'unscheduled' visit.

If a subject reaches a stable MTD and no further dose escalations are planned, the Dose Titration Period will be considered completed and will be followed by monthly assessments for the first 3 months and then every 3 months until the subject is discontinued from the study, Sponsor termination of the study, or the last subject enrolled completes approximately 6 months of treatment with ralinepag.

7.2.2.1 Pre-dose Procedures for Dose Titration Period Visits (Study APD811-003 Placebo Subjects)

- Vital signs according to Table 2
- Safety ECG at Weeks 1 to 9 according to Table 2
- Assessment of clinical worsening
- WHO/NYHA FC assessment
- Clinical laboratory tests (to include hematology, coagulation parameters, serum chemistry, and urinalysis) at Weeks 2, 5, and 9
- Serum hCG pregnancy test (females only) at Week 5
- Record AEs
- Record concomitant medications

7.2.2.2 Post-dose Procedures for Dose Titration Period Visits (Study APD811-003 Placebo Subjects)

- Study drug administration
- Vital signs: every hour through the first 4 hours
- Safety ECG 2 hours post-dose at Weeks 1 to 9 according to Table 2
- Record AEs
- Record concomitant medications

7.2.3 Study Procedures for the Treatment Period – All Subjects (For Both Immediate-release and Extended-release Formulations)

7.2.3.1 Study Procedures M1-M3 (Study APD811-003: Placebo-treated Subjects) Q3 Months (Study APD811-003: Placebo- and Ralinepag-treated Subjects; Subjects who Switched to the XR Formulation)

- Safety ECG according to Section 6.5.2 and Table 1 and Table 2.
- Clinical laboratory tests (to include hematology, coagulation parameters, serum chemistry, and urinalysis) according to Section 6.10 and Table 1 and Table 2.
- Serum hCG pregnancy test (females only) according to Section 6.10 and Table 1 and Table 2
- Vital signs
- Study drug administration
- 6MWT
- BNP/NT-proBNP according to Section 6.10 and Table 1 and Table 2
- Assessment of clinical worsening
- WHO/NYHA FC assessment
- Dose escalation assessment according to according to Table 1 and Table 2
- Record AEs
- Record concomitant medications

7.2.3.2 Study Procedures - Year 1 or Year 2

- RHC – according to Table 1 and Table 2 (see study RHC manual)

7.2.3.3 Switch to XR Ralinepag and Dose Titration

At 1 of the regular quarterly visits, as outlined in Section 7.2.3.1, in addition to the regularly scheduled procedures, subjects will be given new dosing cards with an XR formulation of ralinepag. Dose-switching will occur as outlined in Table 5, and titration will occur as

described in Section 5.6.2.1 via weekly telephone calls until the next regularly scheduled quarterly visit, at which time the subject will resume procedures described in Section 7.2.3.1.

7.2.4 End of Study Visit – All Subjects

- Physical exam
- Safety ECG according to Section 6.5.2 and Table 1 and Table 2
- Clinical laboratory tests (to include hematology, coagulation parameters, serum chemistry, and urinalysis) according to Section 6.10 and Table 1 and Table 2
- Serum hCG pregnancy test (females only)
- Vital signs
- 6MWT
- Assessment of clinical worsening
- WHO/NYHA FC assessment
- Record AEs
- Record concomitant medications

7.2.5 28-day Follow-up – All Subjects

- WHO/NYHA FC assessment
- Assessment of clinical worsening
- Record AEs
- Record concomitant medications

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 transfer datasets to the Sponsor and biostatistician for analysis using secure electronic data transfer per the Sponsor's specifications.

8.2 DATA CODING

8.2.1 Adverse Events

AEs will be coded using the 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 drug, and action taken. Whenever possible, a constellation of signs and symptoms should be recorded as a unifying diagnosis (eg, 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). As there is no Screening Period in this study and subjects will enter the study on active treatment, all AEs that occur after the first dose of study drug will be considered 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 these 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 WHO Drug Dictionary.

9 PLANNED STATISTICAL METHODS

After the last subject enrolled in APD811-007 completes approximately 6 months of treatment, a cumulative all-subject data analysis will be performed.

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 Statistical Analysis Plan, which will be finalized before database lock. If, after the database has been locked, 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.

9.1 ANALYSIS POPULATIONS

Safety Population:

This population will include all subjects who received at least 1 dose of the study drug in this extension study.

Modified Intent-to-treat Population:

The analyses of all efficacy variables will use the Modified Intent-to-Treat Population. This population consists of all subjects randomized who received at least 1 dose of study drug in the extension study, have a baseline measurement, and have at least 1 measurement after entry into the extension study. The Last Observation Carried Forward approach will be used to impute missing values.

9.2 STATISTICAL METHODS

9.2.1 Safety Analysis

Safety is the primary analysis for this extension study. All subjects who receive study drug in the extension study will be evaluated for safety. Long-term safety and tolerability of ralinepag will be assessed by clinical and statistical review of all relevant safety parameters, including AEs, laboratory values, vital signs, and ECG findings.

9.2.1.1 Demographics and Baseline Characteristics

All baseline subject characteristics for demographic data (age, height, weight, race), medical history (abnormalities only), physical examination (abnormalities only), and concomitant medications at entry in Study APD811-003 and also at entry in this extension study will be listed for all subjects. Demographic data will be summarized and tabulated. Continuous variables will be summarized using number of observations, mean, standard deviation, median, minimum, and maximum. Frequencies and percentages will be reported for all categorical data.

9.2.1.2 Adverse Events

The AEs will be coded using the most current 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 drug, and action taken.

All AEs will be listed by subject and will be summarized and expressed in terms of maximum severity and relationship to study drug.

9.2.1.3 Physical Examinations

Physical examination results (abnormalities only) will be collected.

9.2.1.4 Vital Signs

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

9.2.1.5 Clinical Laboratory Values

Individual laboratory values will be listed by visit and summarized using descriptive statistics. Summary statistics will also be provided for change from Baseline in laboratory values. Shift tables from baseline to the last extension study 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 Investigator or Sponsor.

9.2.1.6 Safety ECGs

Individual ECG values will be listed by visit and summarized using descriptive statistics. Intervals to be provided for each ECG are RR, PR, QRS, QT, QTc, QTcB, and QTcF. 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 Investigator or Sponsor.

9.2.2 Statistical Analyses of Efficacy Measurements

Efficacy analyses are considered as secondary for this extension study. The time to clinical worsening will be summarized. Estimation and 95% confidence intervals for within-treatment change from baseline in 6MWD, WHO/NYHA FC assessment, and main hemodynamic parameters will also be performed. Baseline is defined as the Day 1 pre-dose measurements from Study APD811-003. A secondary analysis using a definition of Baseline as Day 1 of Study APD811-007 will also be performed.

10 REGULATORY REQUIREMENTS

10.1 PRE-STUDY DOCUMENTATION

The Sponsor must receive the following documentation prior to initiation of the study:

- Protocol signature page signed by the Investigator
- FDA form 1572 signed by the Investigator
- Curriculum vitae of the Investigator, updated within 2 years
- Current medical licenses for the Investigator
- 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 to the Sponsor at the following address:

United Therapeutics Corporation
55 T.W. Alexander Drive
Research Triangle Park, NC 27709, USA

10.2 INVESTIGATOR OBLIGATIONS

The Investigator is responsible for ensuring that all study site personnel and other study staff members adhere to all applicable FDA and/or applicable country regulations and guidelines regarding clinical studies, including guidelines for GCP (including the archiving of essential documents), both during and after study completion. The Investigator will be responsible for the subject's compliance to the study protocol. The Investigator 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 SUBJECT CONFIDENTIALITY

All information obtained during the conduct of the study with respect to the subjects' state of health will be regarded as confidential. This is detailed in the written information provided to the subject. 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 subject. The study data shall not be disclosed to a third party without the written consent of the Sponsor.

10.4 INFORMED CONSENT

According to ICH Guideline E6, *Good Clinical Practice: Consolidated Guidance* (1996), the Investigator will obtain and document informed consent for each subject screened for this study. All subjects 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 subject'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 ICH Guideline 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 Investigator 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 Investigator. The Investigator 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 Investigator 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 (ie, FDA or international regulatory authorities) at any time, and should consist of the following elements:

- Subject files, containing the completed CRFs, supporting source documentation from the medical records, 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 drug.

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 Investigator prior to the time of study initiation. The Sponsor and Investigator 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, 1 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 and/or applicable country regulations, and the maintenance of adequate and accurate clinical records. CRFs 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 subjects' complete medical records, laboratory data, and other source documentation as needed to monitor the study appropriately.

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Appendix 1 Guidelines for 6-Minute Walk Test

(Adapted from American Thoracic Society (ATS) Statement: Guidelines for the Six-Minute Walk Test. [ATS Statement 2002])

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 to 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 SpO_2 and until the end of the 6MWT (see below for SpO_2 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 heart rate of more than 120, a systolic BP of more than 180 mmHg, and a diastolic BP 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 SAEs. 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 AEs would occur if such subjects performed a 6MWT; they are, therefore, listed as relative contraindications.

Appendix 2 Functional Classification of Pulmonary Hypertension Modified After The New York Heart Association Functional Classification According to the WHO 1998

World Health Organization functional assessment classification	
Class I:	Subjects with pulmonary hypertension (PH) but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II:	Subjects with PH 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:	Subjects with PH resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV:	Subjects with PH with inability to carry out any physical activity without symptoms. These subjects manifest signs of right-heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Adapted from guidelines for the diagnosis and treatment of pulmonary hypertension[17]