A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Ralinepag to Evaluate Safety and Effects on Exercise Capacity Assessed by Cardiopulmonary Exercise Testing in Subjects with World Health Organization Group 1 Pulmonary Hypertension Who Recently Initiated Therapy

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Protocol ROR-PH-302

CONFIDENTIAL

UNITED THERAPEUTICS CORP.

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Amendment 2 Date:	29 November 2022

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INVESTIGATOR'S AGREEMENT

I have read the attached protocol amendment 2 entitled "A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Ralinepag to Evaluate Safety and Effects on Exercise Capacity Assessed by Cardiopulmonary Exercise Testing in Subjects with World Health Organization Group 1 Pulmonary Hypertension Who Recently Initiated Therapy," dated 29 November 2022, and agree to abide by all provisions set forth therein.

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

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 Corp.

I also have read the current Clinical Investigators' Brochure for ralinepag and acknowledge that review of the information contained in the Clinical Investigators' 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 Independent Ethics Committee/Institutional Review Board approval documents have been obtained.

Note that throughout this clinical study protocol, use of the word *should* means that something is suggested or recommended, but not required.

_____ _____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

PROTOCOL SYNOPSIS

Title	A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Ralinepag to Evaluate Safety and Effects on Exercise Capacity Assessed by Cardiopulmonary Exercise Testing in Subjects with World Health Organization Group 1 Pulmonary Hypertension Who Recently Initiated Therapy
Study Phase	3
Indication	Pulmonary arterial hypertension (PAH) (World Health Organization [WHO] Group 1 pulmonary hypertension)
Primary Objective	To evaluate the effects of ralinepag therapy on exercise capacity as assessed by change in peak oxygen consumption (VO_2) derived from cardiopulmonary exercise testing (CPET) after 28 weeks of treatment
Secondary Objectives	To evaluate the effects of ralinepag on: 1. N-terminal pro-brain natriuretic peptide 2. Minute ventilation (V_E)/carbon dioxide output (VCO_2) slope 3. WHO/New York Heart Association (NYHA) Functional Class (FC) 4. Health-related quality of life measured by the Short Form Health Survey 5. Time to first all-cause nonelective hospitalization 6. Safety and tolerability
Exploratory Objectives	To evaluate the effects of ralinepag treatment on: 1. Additional CPET parameters 2. Heart rate (HR) recovery following CPET 3. To assess changes in risk category for peak VO_2 (>15 [low risk], 11 to 15 [intermediate risk], and <11 mL/min/kg [high risk]) and V_E/VCO_2 slope (<36 [low risk], 36 to 44 [intermediate risk], and >44 [high risk]) 4. Change in Registry to Evaluate Early and Long-term PAH Disease Management risk score 5. Proteomics, metabolomics, transcriptomics, and genetics (optional)
Study Design	ROR-PH-302 is a 28-week, multicenter, randomized, double-blind, placebo-controlled study. Study visits will occur at Day 1 and every 4 weeks through Week 28, with weekly titration phone calls during the first 16 weeks. Approximately 193 subjects with WHO Group 1 pulmonary hypertension and on stable background therapy are planned to be enrolled. Subjects who meet entry criteria will be randomized 2:1 to receive ralinepag or placebo, in addition to their PAH-specific background therapy, as applicable. The primary endpoint is change from baseline in peak VO_2 (assessed by CPET) at Week 28. All subjects who complete the study on study drug through Week 28 will have the option to receive ralinepag in an open-label extension (OLE) study.

	Subjects will be stratified by WHO/NYHA FC (II vs III) and background PAH therapy (single vs dual). On Day 1, study drug (ralinepag or placebo, according to randomization) will be initiated at a dose of 50 mcg once daily for the first week of treatment, with the first dose taken in clinic. During each subsequent week, the dose of study drug will be increased, as tolerated, in 50-mcg increments to a maximum dose of 1400 mcg once daily or until the individual maximum tolerated dose is achieved. Between scheduled clinic visits for the first 16 weeks, subjects will be contacted at least once per week to titrate study drug dose (maintain dose or adjust up or down) according to the subject's clinical condition and Investigator's discretion, review study drug administration instructions, assess adverse events (AEs), and record concomitant medications. Background PAH therapies (regimen and doses) must remain stable throughout. After Week 16, subjects will be contacted as often as needed according to the subject's clinical condition and the Investigator's discretion to manage further dose titrations. The dose of study drug should not be titrated in the 7 days prior to Week 28 to ensure the dose is stable prior to the Week 28 efficacy assessments. Study procedures will be completed as described in Table 3-1. All subjects should remain on study drug for the duration of the 28-week Treatment Period. Subjects who prematurely discontinue study drug should complete the Study Drug Termination Visit assessments and return to the clinic for all subsequent scheduled study visits (off study drug) until they complete the study at the Week 28 Visit. All subjects who complete the study on study drug through Week 28 will have the option to enroll in an OLE study (ROR-PH-303) and receive treatment with ralinepag. Subjects who complete Week 28 on study drug and do not participate in ROR-PH-303, or discontinue study drug after Week 24 will attend a Follow-up Visit approximately 28 days after discontinuation of study drug. Subjects who discontinue study drug prior to Week 28, as well as those who complete Week 28 on study drug but choose not to participate in the OLE study, will be contacted every 6 months and at the end of the study to determine their survival status (unless consent is withdrawn). Subjects who prematurely discontinue study drug or withdraw from the ROR-PH-302 study for any reason will not be eligible to enter the OLE study.
Sample Size	It is assumed that change from baseline in peak VO_2 will be normally distributed with a standard deviation of 3 mL/min/kg and a baseline mean

	in the range 9 to 18 mL/min/kg. Assuming 2:1 randomization, 135 completed subjects are sufficient to achieve at least 90% power to detect a treatment effect of 1.8 mL/min/kg in favor of ralinepag (a clinically significant increase of ≥10% from baseline) by a 2-sample t-test using a 2-sided significance level of 0.05. Assuming 30% of subjects who are randomized will not have a valid end of study CPET assessment for any reason (eg, technical issues with the procedure, refusal or lack of effort by the subject) or will drop out before the Week 28 Visit, randomizing 193 subjects allows a final sample size of 135 completers with a valid end of study CPET assessment. A blinded review of the data to evaluate the assumption regarding the standard deviation of change from baseline in peak VO_2 is 3 mL/min/kg is planned when 50% and 75% of the planned subjects have completed the study. A revised sample size may then be calculated using suitably modified assumptions. The planned sample size will not be reduced as a result of the sample size re-estimation.
Summary of Subject Eligibility Criteria	Each subject must meet ALL the inclusion criteria and NONE of the exclusion criteria to be eligible for enrollment into the study. Key inclusion criteria are as follows: At least 18 years of age at the time of consent with a primary diagnosis of PAH and diagnostic right heart catheterization that is consistent with the diagnosis of PAH (mean pulmonary artery pressure >20 mmHg [at rest], pulmonary artery wedge pressure ≤15 mmHg, and a pulmonary vascular resistance >2 Wood units). Subjects must have WHO/NYHA FC II to III symptoms at baseline and must be on a stable dose of PAH-specific oral therapy, defined as no change in dose or regimen for at least 90 days prior to randomization. Allowable PAH-specific therapy includes an endothelin receptor antagonist and/or a phosphodiesterase type 5 inhibitor or a soluble guanylate cyclase stimulator. Screening 6-Minute Walk Distance must be ≥150 meters and subjects must have a peak VO_2 of ≥9 to <18 mL/min/kg during the Screening CPET, as assessed by the CPET core laboratory. In general, doses of allowed concomitant medications should be stable prior to entry. Key exclusion criteria are: Three or more risk factors for left ventricular disease/dysfunction, symptomatic coronary artery disease and/or myocardial infarction within past 6 months or current symptomatic aortic or mitral valve disease. Subjects are excluded if they have a forced expiratory volume in 1 second of <60% predicted or a total lung capacity <60% (predicted) and if they

	have evidence of thromboembolic disease. Subjects are not eligible if they require use of supplemental oxygen during CPET or if the respiratory exchange ratio is <1.0 at Screening CPET, have an acute non-cardiac disorder that may affect exercise performance or be aggravated by exercise, or if they have a corrected QT interval using Fridericia's formula >450 msec (males) or >470 msec (females). Those with severe chronic liver disease or confirmed active infection with hepatitis B virus or hepatitis C virus are excluded. At Screening, alanine aminotransferase or aspartate aminotransferase must not be ≥3 times the upper limit of normal and total bilirubin must not be ≥2 times the upper limit of normal. Subjects are excluded if they have an estimated glomerular filtration rate using the Modification of Diet in Renal Disease Study equation of <30 mL/min/1.73 m^2 or require dialysis. They cannot have used intravenous, subcutaneous, inhaled or oral prostacyclin pathway agents for PAH within 90 days of randomization and are not eligible if previous prostacyclin therapy was stopped for a safety or tolerability issue related to systemic prostacyclin adverse effects.
Drug Dosage and Formulation	The study drug (ie, ralinepag or matching placebo) will be supplied as 50, 250, and 400 mcg tablets for oral administration. The starting dose of study drug will be 50 mcg once daily for 1 week. Up-titration of study drug will occur in 50-mcg increments each week up to a dose of 1400 mcg once daily or until the individual maximum tolerated dose is achieved. The dose of study drug should not be titrated in the 7 days prior to Week 28.
Control Group	Placebo
Route of Administration	Ralinepag and matching placebo will be administered orally.
Procedures	The Screening Visit(s) will occur over no more than 28 days prior to randomization. Once Screening procedures are complete and the Investigator determines that the subject is eligible, the site must submit the pre-Baseline review form for approval by the Sponsor before the subject is randomized into the study. Subjects will be required to attend clinic visits on Day 1 (Baseline) and at Weeks 4, 8, 12, 16, 20, 24, and 28. Between scheduled clinic visits during the first 16 weeks, subjects will be contacted at least once per week to titrate study drug dose (maintain dose or adjust up or down) according to the subject's clinical condition and the Investigator's discretion, review study drug administration instructions, assess AEs, and record concomitant medications. After Week 16, subjects will be contacted as often as needed according to the subject's clinical condition and the Investigator's discretion to manage further dose titrations. The dose of study drug should

	not be titrated in the 7 days prior to Week 28 to ensure the dose is stable prior to the Week 28 efficacy assessments. Efficacy Assessments: CPET from which the following will be attained: blood pressure (mmHg), HR (bpm), rating of subjective symptoms (eg, dyspnea, fatigue using the Modified Borg CR10 scores), VO_2 (L/min), VO_2 (mL/min/kg), VCO_2 (L/min), V_E (L/min), end-tidal carbon dioxide (mmHg), end-tidal oxygen tension (mmHg), and respiratory exchange ratio. Other efficacy assessments include N-terminal pro-brain natriuretic peptide, WHO/NYHA FC, and the time to first nonelective hospitalization. Quality of life will be assessed with the Short Form Health Survey. Safety and Tolerability Assessments: AEs, clinical laboratory tests, vital signs, physical examinations, 12-lead electrocardiograms (in triplicate), and pregnancy testing for women of childbearing potential. Pharmacokinetic (PK) Assessments: Plasma samples for PK assessments will be obtained at Day 1 (Baseline Visit) prior to the first dose of ralinepag, and at each subsequent clinic visit through the Week 28 Visit. Blood samples for PK assessments will be collected pre-dose or >12 hours post-dose at every visit. Collected plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, or to assess other actions of ralinepag with plasma constituents. Exploratory Assessments: To evaluate the effects of ralinepag treatment on additional CPET parameters including HR recovery following CPET and changes in risk category for peak VO_2 and V_E/VCO_2 slope. Optional Assessments: To assess proteomics, metabolomics, transcriptomics, and genetics. All CPET data will be transmitted to a central repository and will be analyzed and reviewed by the central reader on an ongoing basis.
Statistical Considerations	The primary endpoint, change from baseline to Week 28 in peak VO_2, will be tested at the 0.05 (2-sided) level of significance. To protect the overall Type 1 error rate, the secondary endpoints will be tested sequentially at a significance level of 0.05 (2-sided). Hence, a significant result for a given secondary endpoint will only be interpreted in a confirmatory manner if all previous endpoints have achieved statistical significance. The primary endpoint will be analyzed using analysis of covariance with a model that includes treatment and the stratification factors (WHO/NYHA

	FC and background PAH therapy) as factors and baseline peak VO_2 as a covariate. Least-squares means, standard error, and 95% confidence intervals for the treatment groups and the treatment effect will be presented together with the p-value.
Sponsor	United Therapeutics Corp. 55 T.W. Alexander Drive Research Triangle Park, NC 27709 USA

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LIST OF ABBREVIATIONS

6MWD	6-Minute Walk Distance
6MWT	6-Minute Walk Test
AE	Adverse event
BP	Blood pressure
cAMP	Cyclic adenosine monophosphate
CPET	Cardiopulmonary exercise testing
CRO	Contract Research Organization
DBP	Diastolic blood pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
ERA	Endothelin receptor antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
FC	Functional Class
FDA	Food and Drug Administration
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IP	Prostacyclin or prostaglandin I_2 receptor
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention-to-Treat
IV	Intravenous(ly)
LV-CO	Left ventricular cardiac output
mITT	Modified Intention-to-Treat
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OLE	Open-label extension
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary artery wedge pressure
PDE5-I	Phosphodiesterase type 5 inhibitor
PH	Pulmonary hypertension

PK	Pharmacokinetic(s)
PVR	Pulmonary vascular resistance
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Fridericia's formula
RER	Respiratory exchange ratio
RHC	Right heart catheterization
RV-CO	Right ventricular cardiac output
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SDT	Study drug termination
SF-36	Short Form Health Survey
sGC	Soluble guanylate cyclase
TEAE	Treatment-emergent adverse event
TLC	Total lung capacity
VCO_2	Carbon dioxide output
V_E	Minute ventilation
VO_2	Oxygen consumption
V/Q	Ventilation-perfusion
WHO	World Health Organization
XR	Extended-release

1 BACKGROUND AND RATIONALE

1.1 DEFINITION OF CLINICAL PROBLEM

Pulmonary arterial hypertension (PAH) is a rare, progressive disease characterized by elevated pulmonary vascular resistance (PVR) that leads to right ventricular failure and ultimately premature death. The median survival time of patients with idiopathic PAH is approximately 2.8 years without effective treatment (McLaughlin 2009). The clinical definition of PAH requires confirmation by right heart catheterization (RHC) demonstrating a resting pulmonary artery pressure mean >25 mmHg. The diagnosis of PAH also requires a normal (≤15 mmHg) pulmonary artery wedge pressure (PAWP) and a PVR ≥2 Wood units (Humbert 2022). The World Health Organization (WHO) classification of pulmonary hypertension (PH), which is currently used by the US Food and Drug Administration (FDA) as well as the European Medicines Agency, divides it into 5 categories based on similarities in clinical presentation and response to treatments. Group 1 (PAH) is further divided into subgroups reflecting associated conditions. The subgroups share similar clinical characteristics and virtually identical histopathology in the pulmonary arteriolar circulation.

The pathophysiology of PAH involves multiple interrelated mechanisms, with prostacyclin and thromboxane A_2 playing a major role in maintaining pulmonary vascular tone through their balanced activity (Humbert 2006, Simonneau 2012). Prostacyclin, released by endothelial cells, promotes vasodilation and inhibits platelet aggregation by binding to G-protein-coupled receptors on nearby smooth muscle cells and platelets. Prostacyclin also has antiproliferative effects on vascular smooth muscle. In direct opposition, thromboxane A_2 promotes vasoconstriction and platelet aggregation. An imbalance in this homeostasis towards vasoconstriction, in situ thrombosis, and obstructive remodeling of the small pulmonary arteries results in PH (Archer 2010).

Studies indicate that patients with PAH have decreased levels of prostacyclin (Christman 1992, Tuder 1999). The prostacyclin receptor, also termed the prostaglandin I_2 receptor (IP receptor), is a rhodopsin-like, transmembrane-spanning, G-protein–coupled receptor that is expressed on platelets and on the smooth muscle cells of several tissues, including lung, heart, aorta, liver, kidney, and blood vessels. Activation of the IP receptor results in increased cellular cyclic

adenosine monophosphate (cAMP) followed by vasodilation in arteries and inhibition of aggregation in platelets (Hata 2004).

Epoprostenol, an intravenous (IV) prostanoid that binds the IP receptor, was the first therapy to demonstrate improved survival compared to standard therapy, supporting the utility of the IP receptor as a target for PAH therapy (Galie 2016). Epoprostenol requires continuous infusion through a portable pump, is unstable at room temperature (although a more stable product is now available), and it is associated with central venous catheter-related infections and thrombosis. Subsequent forms of IP-receptor agonists have been developed to address some of the limitations of epoprostenol and have demonstrated efficacy through improved exercise capacity. Currently, prostacyclin analogues are available in several parenteral forms, including continuous IV infusion, continuous subcutaneous infusion, and intermittent inhaled therapy. A prostacyclin analogue and an IP-receptor agonist for oral administration have gained marketing approval. As with epoprostenol, these medications are prescribed for PAH patients with WHO/New York Heart Association (NYHA) Functional Class (FC) II to IV to delay disease progression and improve exercise capacity (Orenitram Prescribing Information) and to delay disease progression and reduce the risk of hospitalization (Uptravi Prescribing Information).

Despite a large number of treatments for PAH that are available, the functional limitation and survival of patients with PAH remains unsatisfactory. Ralinepag (also known as APD811) is an orally available, potent and selective, non-prostanoid, IP-receptor agonist being developed to treat WHO Group 1 PH. Ralinepag has a longer half-life than selexipag (and its active metabolite MRE-269) and based on in vitro studies, it is more potent and efficacious than selexipag at increasing cellular cAMP levels (Bruderer 2014, Kaufmann 2015, Preston 2017). Given its prolonged half-life allowing for convenience in dosing and potency at inducing cAMP production, resulting in vasodilation and inhibition of smooth muscle proliferation, ralinepag may be an attractive oral alternative to the currently available prostacyclin analogues and non-prostanoid IP-receptor agonists for the treatment of PAH.

1.2 RALINEPAG BACKGROUND

The safety and efficacy of immediate-release ralinepag were evaluated in subjects with symptomatic WHO Group 1 PH in a Phase 2, randomized, double-blind, placebo-controlled

clinical study (APD811-003) (Torres 2019). In this study, eligible subjects could have received concomitant, oral, disease-specific PAH therapy consisting of an endothelin receptor antagonist (ERA) and/or an agent acting on the nitric oxide pathway, a phosphodiesterase type 5 inhibitor (PDE5-I), or a soluble guanylate cyclase (sGC) stimulator, provided the dose had remained stable for at least 3 months prior to the start of Screening. A total of 61 subjects were randomized 2:1 to ralinepag or placebo. Study drug was initiated at a dose of 10 mcg twice daily and up-titrated over 9 weeks to a maximum dose of 300 mcg twice daily. Following 22 weeks of treatment, a statistically significant treatment effect was observed for the primary endpoint of change in PVR (geometric mean ratio of 0.742 expressed as -25.8% change relative to placebo; p=0.0220). Ralinepag reduced median PVR by 163.9 dyn.sec/cm^5 from a baseline of 705 dyn.sec/cm^5. A median increase of 0.7 dyn.sec/cm^5 was observed with placebo. The overall safety and tolerability of ralinepag in the APD811-003 study was consistent with the known profile of the prostacyclin therapy class. Adverse events (AEs) that occurred more frequently with ralinepag than placebo were similar to the on-target effects expected for prostacyclin therapies: headache (77.5% versus 28.6%), nausea (50.0% versus 23.8%), diarrhea (47.5% versus 14.3%), jaw pain (35.0% versus 14.3%), and flushing (32.5% versus 4.8%). Overall, treatment-emergent AEs (TEAEs) were predominantly mild to moderate in severity (62.3%) and considered to be related to study drug (78.7%). Fewer subjects treated with ralinepag versus placebo had serious AEs (SAEs; 10.0% versus 28.6%, respectively). Only 1 SAE (electrocardiogram [ECG] QT prolonged) in a ralinepag-treated subject (who had SAEs of bradycardia, cardiac arrest, and syncope during the Screening RHC prior to the first dose) was considered related to study drug.

Three Phase 1 studies (APD811-006, APD811-009, and APD811-011) have evaluated an extended-release (XR) dosage form of ralinepag. These studies indicated that the XR formulation exhibited an improved plasma pharmacokinetic (PK) profile over the immediate-release capsule with respect to once-daily dosing in terms of extending exposure and minimizing peak-to-trough fluctuation. The current study uses the XR tablets that were evaluated in studies APD811-009 and APD811-011.

For additional information, please see the ralinepag Investigator's Brochure (IB).

1.3 RATIONALE FOR DEVELOPMENT OF STUDY DRUG IN DISEASE/CONDITION

The purpose of this study is to evaluate the effects of ralinepag therapy on exercise capacity obtained during cardiopulmonary exercise testing (CPET) after 28 weeks of treatment.

A significant reduction in exercise capacity is a hallmark characteristic in patients with PAH; the magnitude of this reduction is most accurately captured by CPET. CPET combines ventilatory expired gas analysis (eg, measurement of oxygen consumption [VO_2], carbon dioxide output [VCO_2], and minute ventilation [V_E]) with traditional exercise testing procedures (ie, monitoring heart rate [HR], blood pressure [BP], and subjective symptomatology). A robust body of literature demonstrates that key measures from CPET provide prognostic and diagnostic value, as well as readily respond to therapeutic interventions in PAH (Arena 2010, Arena 2011, Guazzi 2012). Of the measures obtained from CPET, peak VO_2 is of central importance in PAH.

Peak VO_2 is a well-accepted measure of exercise capacity. Peak VO_2 is significantly and similarly reduced in many chronic disease populations (eg, PAH, heart failure, chronic obstructive pulmonary disease, interstitial lung disease) and is a primary CPET measure for assessing exercise capacity from the context of physical limitations in patients with these chronic diseases. While the pathophysiologic mechanism may differ, patients with these chronic diseases have comparable reductions in peak VO_2 that reflect disease severity. Specifically, patients diagnosed with PAH, heart failure, chronic obstructive pulmonary disease, or interstitial lung disease have strikingly similar peak VO_2 reductions from a mean and range perspective. As such, it is recommended that patients diagnosed with these conditions have their peak VO_2 response quantified according to the Weber Classification system (Guazzi 2012). The pathophysiologic mechanism in PAH is increased PVR resulting in a reduction in right ventricular cardiac output (RV-CO) and ultimately left ventricular cardiac output (LV-CO) (Arena 2010, Arena 2011). Peak VO_2 is primarily driven by LV-CO as defined by the Fick equation and, as such, is a measure of the degree of cardiopulmonary pathophysiology present (ie, lower LV-CO leads to lower peak VO_2) (Fletcher 2013). In this context, given the interdependence between upstream RV-CO and downstream LV-CO in PAH, peak VO_2 provides important insight into PAH pathophysiology (Naeije 2017). Moreover, if an intervention reduces PVR, thereby increasing RV-CO and subsequently LV-CO, an improvement in peak VO_2 is

expected. A recent European Respiratory Society (ERS) statement reported peak VO_2 significantly responds to pharmacologic interventions relevant to PAH, generally a 1.5 to 2 mL/min/kg increase (ie, 9% to 14%) (Puente-Maestu 2016).

The 2022 European Society of Cardiology (ESC)/ERS guidelines for the diagnosis and treatment of PH have incorporated a risk stratification based on peak VO_2 and the V_E/VCO_2 slope (Humbert 2022). The fact that these CPET measures have been incorporated into PH guidelines is an indication of the convincing body of evidence demonstrating the clinical relevance of CPET, particularly peak VO_2 and the V_E/VCO_2 slope, portending important information on diagnostic, prognostic, and therapeutic efficacy and further justifying use of CPET as a primary endpoint in randomized controlled studies in this patient population. From these recommendations, with respect to exercise capacity in the same way that a 6-Minute Walk Distance (6MWD) >440 meters is a target, a peak VO_2 >15 mL/min/kg is a primary treatment goal measured by CPET.

1.4 RISK/BENEFIT ANALYSIS

PAH is a rare, progressive disease characterized by elevated PVR that leads to right ventricular failure and ultimately premature death. One other selective IP-receptor agonist, selexipag, is available to treat PAH. Ralinepag has a longer half-life than selexipag (and its active metabolite MRE-269) and based on in vitro studies, it is more potent and efficacious than selexipag at increasing cellular cAMP levels (Bruderer 2014, Kaufmann 2015, Preston 2017). Given its prolonged half-life allowing for convenience in dosing and potency at inducing cAMP production, resulting in vasodilation and inhibition of smooth muscle proliferation, ralinepag may be an attractive oral alternative to the currently available prostacyclin analogues and non-prostanoid IP-receptor agonists for the treatment of PAH.

Data to date have demonstrated the efficacy and safety of ralinepag. In study ADP811-003, a Phase 2, randomized, double-blind, placebo-controlled clinical study (Torres 2019), there was a statistically significant reduction in PVR, and the overall safety and tolerability of ralinepag were consistent with the known profile of the prostacyclin therapy class. For additional information about the efficacy, safety, and tolerability of ralinepag, as well as all known risks, please see the ralinepag IB.

The primary objective of this study is to evaluate the effects of ralinepag on exercise capacity as assessed by change in peak VO_2 derived from CPET after 28 weeks of treatment. Secondary objectives are to evaluate the effects of ralinepag on N-terminal pro-brain natriuretic peptide (NT-proBNP), V_E/VCO_2 slope, WHO/NYHA FC, health-related quality of life, time to first all-cause nonelective hospitalization, and safety and tolerability. Such clinical assessments, as well as the evaluation of potential adverse effects of treatment, may be influenced by knowledge of treatment assignments by the Investigator and/or the subject. Therefore, to allow for optimal efficacy and safety assessment without the potential bias caused by knowledge of treatment assignment, this study is designed as a randomized, double-blind, placebo-controlled study.

Subject safety will be monitored on a regular basis (clinic visits every 4 weeks, with phone calls between clinic visits) throughout the study. In accordance with FDA, European, and national regulations, the Sponsor will notify the FDA, other competent authorities, and all participating Investigators of any AE that is considered possibly attributable to study drug and is both serious and unexpected. An independent Data Monitoring Committee (DMC) will be utilized to monitor the safety of subjects and to enhance the integrity and credibility of the study. As part of its role, the DMC will conduct reviews of accumulating safety data at specified intervals during the conduct of the study, according to the guidelines detailed in the DMC Charter. To date, no risks have emerged which would preclude the use of ralinepag in clinical studies of PAH.

1.5 CLINICAL HYPOTHESIS

The hypothesis of this study is that treatment with ralinepag added to approved PAH therapy as compared with placebo with approved PAH therapy will increase exercise capacity as assessed by change in peak VO_2 derived from CPET after 28 weeks of treatment.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the effects of ralinepag therapy on exercise capacity as assessed by change in peak VO_2 derived from CPET after 28 weeks of treatment.

2.2 SECONDARY OBJECTIVES

The secondary objectives of the study are to evaluate the effects of ralinepag on:

1. NT-proBNP
2. V_E/VCO_2 slope
3. WHO/NYHA FC
4. Health-related quality of life measured by the Short Form Health Survey (SF-36)
5. Time to first all-cause nonelective hospitalization
6. Safety and tolerability

2.3 EXPLORATORY OBJECTIVES

To evaluate the effects of ralinepag treatment on:

1. Additional CPET parameters
2. HR recovery following CPET
3. To assess changes in risk category for peak VO_2 (>15 [low risk], 11 to 15 [intermediate risk], and <11 mL/min/kg [high risk]) and V_E/VCO_2 slope (<36 [low risk], 36 to 44 [intermediate risk], and >44 [high risk])
4. Change in Registry to Evaluate Early and Long-term PAH Disease Management risk score
5. Proteomics, metabolomics, transcriptomics, and genetics (optional)

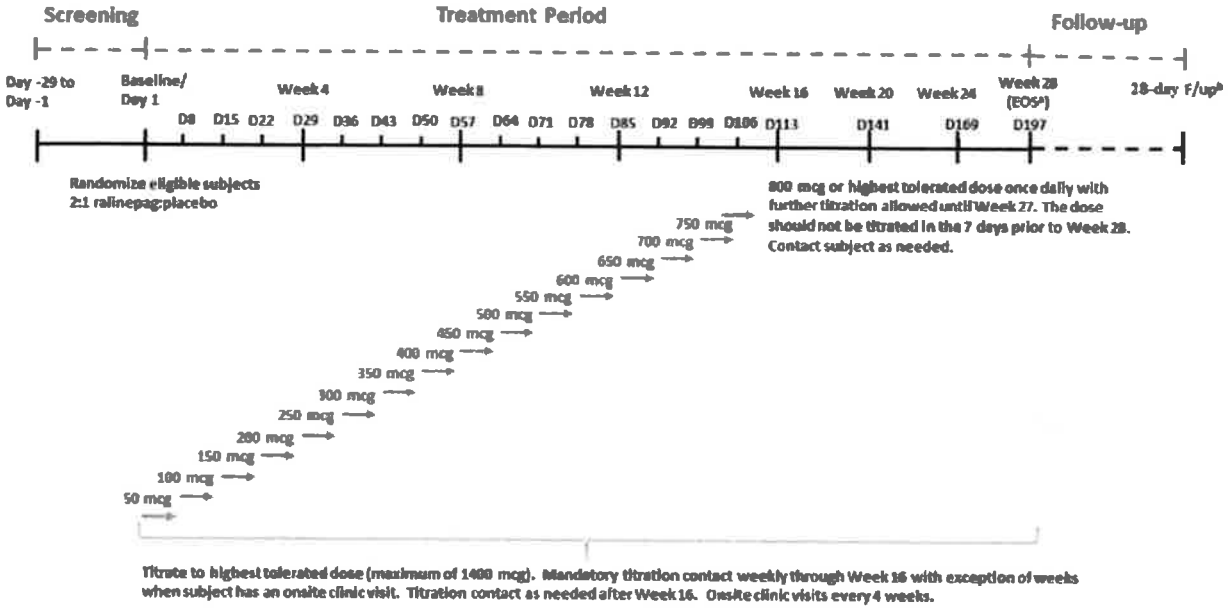
3 EXPERIMENTAL PLAN

3.1 STUDY DESIGN

ROR-PH-302 is a 28-week, multicenter, randomized, double-blind, placebo-controlled study (see Figure 3-1). Study visits will occur at Day 1 and every 4 weeks through Week 28, with weekly titration phone calls during the first 16 weeks. Approximately 193 subjects with WHO Group 1 PH and on stable background therapy are planned to be enrolled. Subjects who meet entry criteria will be randomly allocated (2:1 ratio) to receive ralinepag or placebo, in addition to their PAH-specific background therapy, as applicable. The primary endpoint is change from baseline in peak VO_2 (assessed by CPET) at Week 28. All subjects who complete the study on study drug through Week 28 will have the option to receive ralinepag in an open-label extension (OLE) study.

Subjects will be stratified by WHO/NYHA FC (II vs III) and background PAH therapy (single vs dual). The study will end when all enrolled subjects have completed their final study visit.

Figure 3-1 Study Schematic



a Enroll in ROR-PH-303 if eligible and consent
b Only for subjects who complete Week 28 on study drug and do not participate in ROR-PH-303, or discontinue study drug after Week 24.

3.1.1 Rationale for Study Design and Control Group

A significant reduction in exercise capacity and ability to carry out normal activities of daily living are hallmark characteristics in patients with PAH. A robust body of literature demonstrates key measures from CPET are capable of providing prognostic and diagnostic information and will respond to therapeutic interventions in PAH. In addition, the 2022 ESC/ERS guidelines for the diagnosis and treatment of PH have incorporated a risk stratification based on peak VO_2 and V_E/VCO_2 slope (Humbert 2022), demonstrating the relevance of CPET in the clinical evaluation of patients with PAH.

The primary objective of this study is to evaluate the effects of ralinepag on exercise capacity assessed by CPET after 28 weeks of treatment. Secondary objectives are to evaluate the effects of ralinepag on NT-proBNP, V_E/VCO_2 slope, WHO/NYHA FC, quality of life, time to first all-cause nonelective hospitalization, and safety and tolerability. Such clinical assessments, as well as the evaluation of potential adverse effects of treatment, may be influenced by knowledge of treatment assignments by the Investigator and/or the subject. Therefore, to allow for optimal efficacy and safety assessment without the potential bias caused by knowledge of treatment assignment, this study is designed as a randomized, double-blind, placebo-controlled study.

Subjects entering the study will have a diagnosis of symptomatic WHO Group 1 PH and will be treated with either 1 or 2 approved background PAH-specific therapies. Subjects who complete the study on study drug will have the option to enroll in an OLE study with ralinepag after Week 28; therefore, the placebo in this study is not anticipated to cause undue burden or risk to study subjects.

3.1.2 Screening and Enrollment

The Screening Visit(s) will begin no more than 28 days prior to randomization. The Screening procedures outlined in the Overall Schedule of Procedures and Visits (Table 3-1) must be performed during the screening window. The 6-Minute Walk Test (6MWT) must be performed at least 1 hour before the CPET. The site should allow enough time between Screening and the planned randomization to conduct all necessary procedures and obtain results from the central laboratory and central readers (eg, centrally read CPET data).

Once all Screening procedures are complete and the Investigator determines that the subject is eligible, the site must submit the pre-Baseline review form for approval by the Sponsor before the subject is randomized into the study.

Re-screening of subjects who do not meet entry criteria will be assessed on a case-by-case basis following discussion with the Sponsor. If a subject is re-screened, all applicable procedures, including re-signing the Informed Consent Form (ICF), must be repeated. Within the Screening Period, re-tests will be allowed following agreement with the Sponsor. In order to allow for flexibility, procedures may be completed over multiple days within the Screening Period.

3.1.3 Race and Ethnicity Data Collection

Race and ethnicity data will be collected in this study. This is important information to collect since, along with other demographic information like age and sex, these participant characteristics may influence responses to the study drug. In addition, this information is required to be collected by some regulatory agencies so that differences in responses to ralinepag can be investigated appropriately (FDA Guidance for Industry, *Collection of Race and Ethnicity Data in Clinical Trials*). Study data will be summarized by race and ethnicity to provide a more thorough examination of potential factors underlying the safety, tolerability, and efficacy of ralinepag.

3.1.4 Randomization and Treatment

If eligible, subjects will be required to attend clinic visits on Day 1 (Baseline) and at Weeks 4, 8, 12, 16, 20, 24, and 28. In order to allow for flexibility, baseline procedures may be completed over 72 hours. On subsequent visits, procedures may take place over multiple days, as long as they are completed within the allowable visit window (Table 3-1).

On Day 1, once eligibility has been verified and all other procedures have been completed, eligible subjects will be randomized to receive study drug (ralinepag or placebo). Study drug will be initiated at a dose of 50 mcg once daily for the first week of treatment. Subjects should take their first dose of medication in the clinic under supervision of site staff. During each subsequent week, the dose of study drug will be increased, as tolerated, in 50-mcg increments up to a dose of 1400 mcg once daily or until the individual maximum tolerated dose is achieved.

Between scheduled clinic visits for the first 16 weeks, subjects will be contacted at least once per week to titrate study drug dose (maintain dose or adjust up or down) according to the subject's clinical condition and the Investigator's discretion, review study drug administration instructions, assess AEs, and record concomitant medications. Background PAH therapies (regimen and doses) must remain stable throughout. After Week 16, subjects will be contacted as often as needed according to the subject's clinical condition and the Investigator's discretion to manage further dose titrations. The dose of study drug should not be titrated in the 7 days prior to Week 28 to ensure the dose is stable prior to the Week 28 efficacy assessments. See Table 3-1 for details and timing on the required assessments.

It is important to note that achieving the maximum dose that an individual subject can tolerate is thought to be directly related to achieving a therapeutic benefit. Every effort should be made to continually reassess whether the dose can be increased in order to ensure the dose is titrated to the individual maximum tolerated dose.

3.1.5 Study Completion

Subjects will return to clinic at Week 28 for Week 28 Visit assessments. All subjects who complete the study on study drug through Week 28 will have the option to enroll in an OLE study (ROR-PH-303) and receive treatment with ralinepag. The Week 28 Visit for ROR-PH-302 will serve as the Baseline Visit for participation in the OLE study. Subjects who complete Week 28 on study drug and do not participate in ROR-PH-303, or discontinue study drug after Week 24 will attend a Follow-up Visit approximately 28 days after discontinuation of study drug. Subjects may then receive any available PAH therapies, at the discretion of the treating physician.

Subjects who discontinue study drug prior to Week 28, as well as those who complete Week 28 on study drug but choose to not participate in the OLE study, will be contacted every 6 months and at the end of the study to determine their survival status (unless consent is withdrawn).

Subjects who prematurely discontinue study drug or withdraw from the ROR-PH-302 study for any reason will not be eligible to enter the OLE study.

3.1.6 Discontinuation of Study Drug

All subjects should remain on study drug for the duration of the 28-week Treatment Period. Subjects who wish to discontinue study drug will return to the clinic for the Study Drug Termination (SDT) Visit. If the SDT Visit occurs within 2 weeks of the next regularly scheduled study visit, the SDT Visit can take the place of the next scheduled study visit, unless the next scheduled visit is the Week 28 Visit. After completing the SDT Visit, the subject should return to the clinic for all subsequent scheduled study visits (off study drug) until they complete the study at the Week 28 Visit. Subjects who discontinue study drug prior to Week 28, as well as those who complete Week 28 on study drug but choose to not participate in the OLE study, will be contacted every 6 months and at the end of the study to determine their survival status (unless consent is withdrawn).

The procedures to be completed at the SDT Visit are outlined in Table 3-1.

Table 3-1 Overall Schedule of Procedures and Visits

Study Procedures	Treatment Period									SDT Visit[a]	28-day Follow-up Visit[b]
Study Visit/Week	Screening	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28		
Day Note: Study visits may take place over multiple days, as long as they are completed during the allowable window	-29 to -1	1 (to be completed within 72 hours)	29±5	57±5	85±5	113±5	141±5	169±5	197±5	Within 5 days of stopping study drug	28±5 days after SDT Visit or Week 28
On-site clinic visit	X	X	X	X	X	X	X	X	X	X	X
Informed consent	X										
Review eligibility criteria	X										
Demographics	X										
Medical, PAH, and social history, and substance use	X										
HIV, HBsAg, HCV (qPCR)	X										
Drug screen	X										
Serum pregnancy test	X										
Right heart catheterization if required	X										
Pulmonary function test if not performed within 1 year using a direct measurement of TLC	X										

Study Procedures	Treatment Period									SDT Visit[a]	28-day Follow-up Visit[b]
Study Visit/Week	**Screening**	**Baseline**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**		
Day **Note: Study visits may take place over multiple days, as long as they are completed during the allowable window**	**-29 to -1**	**1 (to be completed within 72 hours)**	**29±5**	**57±5**	**85±5**	**113±5**	**141±5**	**169±5**	**197±5**	**Within 5 days of stopping study drug**	**28±5 days after SDT Visit or Week 28**
V/Q lung scan if not available at the time of, or after, PAH diagnosis	X										
6MWT	X										
AE monitoring	←								→	X	X
Prior/concomitant medications	←								→	X	X
Weight (all visits); height (screening only)	X	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X							X	X	X
12-Lead ECG (triplicate, using same machine throughout study)	X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Chemistry, hematology	X	X	X	X	X	X	X	X	X	X	X
Coagulation (after Baseline, only applies to those on anti-coagulation therapy)	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	X				X			X	X	X

Study Procedures	Treatment Period									SDT Visit[a]	28-day Follow-up Visit[b]
Study Visit/Week	Screening	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28		
Day Note: Study visits may take place over multiple days, as long as they are completed during the allowable window	-29 to -1	1 (to be completed within 72 hours)	29±5	57±5	85±5	113±5	141±5	169±5	197±5	Within 5 days of stopping study drug	28±5 days after SDT Visit or Week 28
Proteomics, metabolomics, transcriptomics (optional)		X							X	X	
Pharmacogenetics (optional)		X									
Urine pregnancy test		X	X	X	X	X	X	X	X	X	X
PK plasma sample		X	X	X	X	X	X	X	X	X	
NT-proBNP (rest prior to sample and prior to performing CPET/6MWT)		X	X	X	X	X	X	X	X	X	
CPET	X								X	X	
WHO/NYHA FC assessment	X	X	X	X	X	X	X	X	X	X	X
SF-36		X				X			X	X	
Randomization		X									
First dose		X									
Study drug dispensation		X	X	X	X	X	X	X			
Study drug administration		X	X	X	X	X	X	X			

Study Procedures	**Treatment Period**									**SDT Visit[a]**	**28-day Follow-up Visit[b]**
Study Visit/Week	**Screening**	**Baseline**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**		
Day **Note: Study visits may take place over multiple days, as long as they are completed during the allowable window**	-29 to -1	1 (to be completed within 72 hours)	29±5	57±5	85±5	113±5	141±5	169±5	197±5	Within 5 days of stopping study drug	28±5 days after SDT Visit or Week 28
Study drug reconciliation			X	X	X	X	X	X	X	X	
Weekly telephone/email/text contact (on weeks without clinic visit)		←	—	—	—	→					
Telephone contact as needed							←	- - -	→		

Abbreviations: 6MWT, 6-Minute Walk Test; AE, adverse event; CPET, cardiopulmonary exercise testing; ECG, electrocardiogram; FC, Functional Class; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PK, pharmacokinetic(s); qPCR, quantitative polymerase chain reaction; SDT, study drug termination; SF-36, Short Form Health Survey; TLC, total lung capacity; V/Q, ventilation-perfusion; WHO, World Health Organization

a. Only for subjects who prematurely discontinue study drug. Subjects should complete all remaining study visits - see Section 8.1.

b. Only for subjects who complete Week 28 on study drug and do not participate in ROR-PH-303, or discontinue study drug after Week 24.

3.2 CLINICAL ASSESSMENTS

All assessments will be performed as outlined in Table 3-1 and should be conducted pre-dose (or >12 hours post-dose, for subjects who take study drug in the evening).

3.2.1 Efficacy Assessments

3.2.1.1 CPET

CPET assessments will be performed by cycle ergometry. A CPET assessment will be completed during Screening. The Screening CPET will serve as the baseline assessment for analysis. Sufficient time must be allocated to complete the CPET and get the CPET results back from the core laboratory prior to randomization. At the Screening Visit, if CPET and 6MWT are both performed on the same day, the 6MWT must be performed at least 1 hour prior to the CPET. Alternatively, CPET assessments and the 6MWT can be performed in any order if they are performed on separate days during Screening. The CPET should be completed at approximately the same time of day at each visit to minimize inter-day variability.

Briefly, each CPET will consist of:

1. Data collection will begin at rest on an upright cycle ergometer. The ECG performed by the local CPET laboratory during the CPET will be monitored continuously throughout for safety. BP and rating of perceived exertion (assessed with the Modified Borg CRT10 scale) will be recorded at rest (Heart Online 2014).
2. A ramp-incremental cycle ergometer protocol consisting of unloaded pedaling followed by increases in work rate by 10 Watts per minute in a ramp fashion until volitional intolerance or there is an indication to terminate the exercise test prematurely due to an abnormal physiologic response or subject request. The ECG will be monitored throughout the CPET, and BP and subjective symptoms (rating of perceived exertion by the Modified Borg CR10 scale) will be recorded every 2 minutes. Ventilatory expired gas analysis will be collected throughout the test. A peak respiratory exchange ratio (RER) during exercise of >1.0 is required for the test to be considered valid.
3. Data collection in recovery. If the test is not terminated prematurely, during the recovery, unloaded cycling will be continued for 3 minutes. HR and ECG will be monitored continuously throughout the recovery phase. BP will be recorded seated on the cycle every 2 minutes. Ventilatory expired gas analysis will be collected for 5 minutes during recovery.

Variables measured during each test will include:

- BP (mmHg)

- HR (bpm)
- Rating of subjective symptoms (ie. dyspnea, fatigue using the Modified Borg CR10 scores)
- VO_2 (L/min)
- VO_2 (mL/min/kg)
- VCO_2 (L/min)
- V_E (L/min)
- End-tidal carbon dioxide (mmHg)
- End-tidal oxygen tension (mmHg)
- RER

A detailed CPET procedure manual that contains instructions on how to set up and certify CPET equipment and perform CPET assessments during the study will be provided to sites.

Personnel from the CPET core laboratory will be available via phone or email for any questions or issues that may arise. CPET results from the CPET laboratory at each site will be transmitted to a central repository. The CPET core laboratory will download each subject's CPET file from the central repository for analysis. The CPET data required to determine eligibility will be returned to the site. The roles and responsibilities of the CPET core laboratory are defined in a separate charter. If the CPET core laboratory determines a test to be unreliable (eg, due to technical issues), CPET assessments may be repeated if possible. Only values obtained from the CPET core laboratory may be used to determine eligibility (for the exercise test-related relevant entry criteria).

Each site will be trained on the technical aspects of CPET as they relate to this study, and each site will conduct regular biological quality control during the course of the study. The site will recruit healthy volunteer(s) to serve as biological quality control test participants. Those healthy volunteer participants will give consent to serve in this capacity. Data collected from the biological quality control participants will only be used to ensure that the CPET system meets the specified accuracy criteria on a regular basis. These biological quality control tests, along with syringe linearity testing, will be completed in accordance with the CPET manual. The biological quality control data of the CPET equipment and procedures will not be entered into the electronic data capture (EDC) system. Details on the biological quality control procedures are described in the CPET manual.

3.2.1.2 NT-proBNP

Plasma samples for assessment of NT-proBNP will be collected as specified in Table 3-1. As NT-proBNP may be affected by recent exercise, subjects should be allowed to rest following arrival at the clinic, prior to obtaining this blood sample. NT-proBNP plasma samples must be obtained prior to CPET and the assessment of 6MWD when they are scheduled to be performed at the same visit. This sample should be collected with the subject in the same position at each visit (eg, sitting or semi-recumbent). Detailed instructions on sample collection, processing, and shipment will be provided in a separate manual.

3.2.1.3 WHO/NYHA FC

PAH severity will be classified according to a system originally developed for heart failure by the NYHA and then modified by the WHO for patients with PAH (Galie 2013). 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 (Section 15.1). The same Investigator or designee should complete the WHO/NYHA FC evaluation at the subject's first visit and for the duration of the study when possible.

3.2.1.4 SF-36

The SF-36 is an easily administered written survey that includes 36 questions to measure functional health and well-being from the subject's point of view (Ware 1992). The SF-36 consists of 8 health domains (vitality, physical functioning, bodily pain, general health perception, role physical, role emotional, social functioning, and mental health), as well as 2 summary measures (physical component summary and mental component summary). Detailed instructions on how to administer the SF-36 to subjects will be provided to sites. The SF-36 will only be measured in countries/regions where available in the local language and linguistically validated.

Additional details regarding components and scoring of the SF-36 will be provided in the Statistical Analysis Plan.

3.2.1.5 Nonelective Hospitalization

The time to first all-cause nonelective hospitalization during the study period will be assessed.

3.2.2 Safety and Tolerability Assessments

3.2.2.1 Medical and Social History

At Screening, relevant and clinically significant medical and social history will be collected during the subject interview. History of substance (drug/solvent) abuse will be reviewed. Concomitant medications, illnesses, and previous participation in other investigational drug studies will also be reviewed.

3.2.2.1.1 History of PAH

A complete history of PAH, including date of diagnosis based on RHC, associated illness and diseases, procedures, and medications will also be collected by chart review and subject interview.

3.2.2.2 Physical Examination

A full physical will be conducted at Screening, Baseline, Week 28 Visit, SDT Visit (if applicable), and the 28-day Follow-up Visit (if applicable) and will include the following assessments:

- General inspection
- Head/ears/eyes/nose/throat examination
- Neck
- Cardiac examination
- Auscultation of lungs
- Abdominal examination (liver, spleen, and lower abdomen)
- Neurological assessment
- Musculoskeletal assessment to include lower extremity edema evaluation

Any abnormalities found will be recorded in source documents and the electronic Case Report Form (eCRF) as either medical history (pre-existing conditions) or as AEs. At visits other than Screening, Baseline, Week 28, SDT (if applicable), and Week 28 Follow-up (if applicable), symptom-directed physical examinations will be conducted as needed.

3.2.2.3 Vital Signs

Vital signs measurements will include BP, HR, and respiratory rate. Vital signs should be measured prior to any blood draw that occurs at the same study visit.

At Screening, vital signs will be measured after a 5-minute rest while sitting, and BP will also be measured while supine (after a 5-minute rest) and after standing for 1 minute (orthostatic). At all other visits, vital signs will be measured after a 5-minute rest while sitting.

BP may be measured manually or by automated device.

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

3.2.2.4 12-Lead ECG

ECGs will be recorded in triplicate from a 12-lead ECG machine provided by the Sponsor (unless local regulations do not allow the collection via a third-party device). ECGs will be captured, recorded, and analyzed according to the ECG Procedure Manual.

Every attempt will be made to ensure that subject ECG readings are obtained using the same machine throughout the study.

ECGs will be recorded with subjects in the recumbent position and resting. Subjects will have been in this resting position for 5 minutes prior to ECG recording. ECGs should be performed prior to blood draws when both assessments are required at the same visit.

Intervals to be provided on the confirmed read by the core laboratory for each safety ECG are: RR, PR, QRS, QT, and QT interval corrected using Bazett's (QTcB) and Fridericia's (QTcF) formulae.

The Investigator will be responsible for the review and clinical interpretation of ECGs on site and determining if the ECG is normal, abnormal clinically insignificant, or abnormal clinically

significant. Findings will be documented in the source documents and in the eCRF. This information will be used in the ongoing safety review during the conduct of the study.

3.2.2.5 AEs

AEs will be recorded throughout the course of the study from the time that each subject signs the ICF until the time screen failure is documented, the subject has entered the OLE study, or until the Follow-up Visit assessments have been completed. Each subject will be questioned for AEs at each scheduled study visit. Subjects will also be instructed to report all AEs experienced at any time throughout the study.

The Investigator should determine if a clinically significant finding obtained during the Screening Period relates to a pre-existing medical condition (in which case it should be captured as medical history) or a condition that has developed (or worsened) since the subject signed the ICF (which must be recorded as an AE). Only AEs that occur (or worsen) after the first dose of study drug are reported in the Clinical Study Report as TEAEs.

All AEs must be followed until either resolution (or return to normal or baseline values), until they are judged by the Investigator to no longer be clinically significant, or for at least 4 weeks if the AE extends beyond the SDT Visit. All AEs meeting the criteria for serious must be monitored until resolution, death, or the subject is lost to follow up. AEs and SAEs should be reported beyond this period if per the Investigator, it is considered possibly or probably related to the study drug.

Section 9 provides the guidelines and definitions for recording AEs.

3.2.2.6 Clinical Laboratory Tests

All details regarding clinical laboratory sample collection, preparation, and shipment are included in the Laboratory Manual provided by the central laboratory.

In the event of abnormal clinical laboratory values, the Investigator will make a judgment whether or not the abnormality is clinically significant and must therefore be recorded as an AE.

3.2.2.6.1 Laboratory Parameters

Hematology, chemistry, coagulation, and urinalysis parameters that will be assessed using a central laboratory during the study are identified in Table 3-2 and should be performed as specified in Table 3-1. Subjects will be in a seated or supine position during blood collection.

Within the Screening Period, re-tests will be allowed following agreement with the Sponsor.

Table 3-2 List of Laboratory Tests

Hematology:	**Serum Chemistry:**
Hematocrit	Albumin
Hemoglobin	Alkaline phosphatase (ALP)
Mean corpuscular hemoglobin (MCH)	Alanine aminotransferase (ALT)
Mean corpuscular hemoglobin concentration (MCHC)	Aspartate aminotransferase (AST)
	Bicarbonate
Mean corpuscular volume (MCV)	Blood urea nitrogen (BUN)
Platelet count	Calcium
Red blood cell (RBC) count	Chloride
White blood cell (WBC) count with differential	Creatinine
Cluster of differentiation 4+ (if applicable)	Creatine kinase
	eGFR (calculated using the MDRD equation)
Urinalysis:	Glucose (random)
Appearance	Lactate dehydrogenase (LDH)
Bilirubin	Phosphorus
Color	Potassium
Glucose	Sodium
Ketones	Thyroid-stimulating hormone (TSH)
Microscopic examination of sediment	Thyroxine (T4) free
Nitrite	Total bilirubin
Occult blood	Triiodothyronine (T3) free
pH	Direct bilirubin
Protein	Total cholesterol
Specific gravity	Total protein
Urine drug screen	Triglycerides
Urobilinogen	Uric acid
HIV, HBsAg, and HCV (qPCR)	**N-terminal Pro-brain Natriuretic Peptide (NT-proBNP)**
Pregnancy Testing:	
Serum human chorionic gonadotropin (hCG)	
Urine hCG (only females of childbearing potential)	**Coagulation[a]:**
	Prothrombin time (PT)
	Activated partial thromboplastin time (PTT)
	International normalized ratio (INR)

a. All subjects have coagulation performed at Screening and Baseline. Subsequent evaluations are only performed on subjects taking any anti-coagulation medications.

3.2.2.6.2 Virology

Human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen, and hepatitis C virus (HCV) quantitative polymerase chain reaction assays will be performed at Screening only. Subjects with HIV-associated PAH may be included in the study as long as all entry criteria are met.

Subjects with confirmed active infection with hepatitis B virus or HCV at Screening are excluded.

NOTE: Subjects previously infected with HCV who have a negative viral load after receiving a course of curative treatment are allowed.

3.2.2.6.3 Urinalysis

Urinalysis parameters for clinical laboratory tests are presented in Table 3-2.

3.2.2.6.4 Drug Screening

A urine drug screen will be performed on all subjects at Screening.

Subjects who test positive for amphetamine, cocaine, methamphetamine, methylenedioxymethamphetamine, or phencyclidine in a urine drug screen performed at Screening, or who have a recent history (6 months) of alcohol or drug abuse, will not be eligible for study participation. Subjects will not be excluded due to a positive drug screen caused by prescribed medications.

3.2.2.6.5 Pregnancy Testing

A serum pregnancy test for human chorionic gonadotropin will be performed on female subjects of childbearing potential at Screening and urine pregnancy tests (human chorionic gonadotropin) will be performed on female subjects of childbearing potential at every scheduled visit during the study, beginning on Day 1 (Baseline Visit) and conclude 28 days after the last dose of study drug (Follow-up Visit), unless the subject entered the OLE study.

3.2.3 Exploratory Assessments

3.2.3.1 Heart Rate Recovery

HR recovery will be evaluated in conjunction with the CPET. HR recovery will be determined by measurement of the difference in HR at the completion of the exercise test and again 1 minute after completion of the exercise test. Sites will be provided with detailed instructions regarding assessment of HR recovery in the CPET manual.

3.2.4 Other Procedures Performed Only at Screening

3.2.4.1 6MWT

The 6MWT will be conducted according to the modified guidelines issued by the American Thoracic Society (ATS 2002). Technicians performing the test will be trained appropriately. The 6MWT should be conducted at least 1 hour before completing the CPET during Screening.

Details regarding the conduct of the 6MWT are described in Section 15.2.

3.2.4.2 RHC

RHC measurements may be obtained at Screening if a suitable historical RHC is not available. Subjects who have had an RHC performed at or within 3 years prior to Screening are not required to have a repeat Screening RHC. If more than 1 RHC was performed prior to Screening, the most recent RHC that includes parameters sufficient to evaluate inclusion/exclusion criteria must be used for this assessment.

3.2.4.3 Pulmonary Function Tests

Pulmonary function tests will be completed only if they are not performed within 1 year prior to Screening. Sites are required to use a direct measurement of total lung capacity (TLC) (eg, whole body plethysmography or gas dilution) for calculating the TLC % predicted.

3.2.4.4 Assessments to Exclude Chronic Pulmonary Thromboembolic Disease

3.2.4.4.1 Ventilation-perfusion Lung Scan

A ventilation-perfusion (V/Q) lung scan or other local standard-of-care diagnostic evaluation will be completed only if not available at the time of, or after, PAH diagnosis to rule out chronic thromboembolic PH.

3.2.4.4.2 Computed Tomography Angiogram

A computed tomography angiogram can be used in place of a V/Q lung scan if the subject does not have a history of venous thromboembolic disease.

3.2.4.4.3 Selective Pulmonary Angiogram

A selective pulmonary angiogram will be performed if a V/Q lung scan is unavailable and the subject has a history of venous thromboembolic disease. Selective pulmonary angiography will also be performed if the V/Q lung scan shows anything other than "normal" or "low-probability" of chronic thromboembolic disease.

3.2.5 Proteomics, Metabolomics, Transcriptomics, and Pharmacogenetic Analysis

For subjects who agree to participate in the optional proteomics, metabolomics, and transcriptomics analyses, blood samples will be collected at Baseline and the Week 28 Visit or the SDT Visit. For subjects who agree to participate in the optional genetic analysis, a blood sample will be collected at Baseline. Comparing treatment responses and treatment-related changes as they relate to these parameters may reveal important information with regard to 1) the pathophysiology and natural history of PAH, 2) treatment response and effect of treatment on proteomics, and 3) ralinepag mechanism of action. Participation is optional. Subjects can consent to participate in all, part, or none of these analyses, and subjects who do not wish to participate may still participate in the main clinical study.

Genetics will be evaluated to assess genetic variations that may impact the efficacy and mechanism of action of ralinepag. A blood sample for deoxyribonucleic acid isolation and whole genome sequencing will be collected from subjects who have consented to participate in the genetic analysis component of the study.

Transcriptomics will be performed by ribonucleic acid sequencing or comparable technology to assess the efficacy and mechanism of action of ralinepag. Blood samples for ribonucleic acid isolation will be collected from subjects who have consented to participate in the biomarker (transcriptomics) analysis component of the study.

Blood will be collected for exploratory proteomic and/or metabolomic analysis to assess the efficacy and mechanism of action of ralinepag.

Complete instructions regarding the processing, packaging, and shipping of samples will be provided in a separate Laboratory Manual. Samples for the proteomics, metabolomics, transcriptomics, and genetics analyses will be coded in a manner that allows them to be matched to a study site and/or a subject number, but will not carry personal identifiers that could be traced to a specific individual.

Samples for the proteomics, metabolomics, transcriptomics, and genetics analyses may be kept by the Sponsor for up to 10 years after the final subject has completed study participation. However, if it is determined that a sample is not needed, the samples may be destroyed earlier. In some cases, the samples may never be utilized; for example, if there are not an adequate number of samples to perform the analysis.

If a subject who has consented to participate in any part of the proteomics, metabolomics, transcriptomics, and/or pharmacogenetics analyses withdraws from the study for any reason other than "lost to follow-up," the subject will be given the following options regarding the analysis sample, if the sample has already been collected:

- The sample will be maintained per the subject's original consent.
- The subject's consent may be withdrawn and any remaining sample will be destroyed.

If a subject withdraws consent from any part of the proteomics, metabolomics, transcriptomics, and/or genetics analyses and/or requests sample destruction, the Investigator must document the request and inform the Sponsor. The Sponsor will only keep data that are collected or generated up to the point at which consent to use the sample is withdrawn by the subject. Withdrawal of consent from any part of the proteomics, metabolomics, transcriptomics, and/or genetics analyses does not affect consent to participate in any part of the analysis for which the subject has not withdrawn consent, nor does it affect consent to participate in the main clinical study.

3.2.6 Pharmacokinetics Assessments

Plasma samples for PK assessments will be obtained at Day 1 (Baseline) prior to the first dose of ralinepag, and at each subsequent clinic visit through the Week 28 Visit. Blood samples for PK assessments will be collected pre-dose or >12 hours post-dose at every visit. Collected plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method

validation purposes, stability assessments, metabolite assessments, or to assess other actions of ralinepag with plasma constituents.

3.3 NUMBER OF CENTERS

This study is multicenter with approximately 50 to 60 participating study centers.

3.4 NUMBER OF SUBJECTS

This study will randomize approximately 193 subjects, to have 135 completers with both a valid Screening and Week 28 CPET assessment.

3.5 ESTIMATED STUDY DURATION

Total planned study duration is up to 36 weeks, including a Screening Period of up to 28 days in duration, a 28-week Treatment Period, and a 28-day Follow-up Period (for those who complete Week 28 on study drug and do not participate in ROR-PH-303, or discontinue study drug after Week 24). Subjects will receive treatment with study drug (ralinepag or placebo) for a total of up to 28 weeks.

4 SUBJECT ELIGIBILITY

4.1 INCLUSION CRITERIA

Each subject must meet ALL the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated ICF, indicating that the subject has been informed of all pertinent aspects of the study prior to initiation of any study-related procedures.
2. At least 18 years of age at the time of consent.
3. Primary diagnosis of PAH classified by 1 of the following subgroups:
   a. Idiopathic PAH
   b. Heritable PAH
   c. Drugs or toxins induced based on prior exposure to drugs, chemicals, or toxins, such as fenfluramine derivatives, other anorexigens, toxic rapeseed oil, or L-tryptophan
   d. PAH associated with:
      i. Connective tissue disease
      ii. HIV infection
      iii. Congenital systemic-pulmonary intracardiac shunt (must have undergone surgical correction or repair with a closure device at least 1 year prior to

Screening) and have no, or a clinically insignificant, shunt fraction (1.0 ≤pulmonary-systemic flow ratio ≤1.5)

4. Has had a diagnostic RHC performed at or within 3 years before Screening (or at Screening if one is not available) that is consistent with the diagnosis of PAH, meeting ALL the following criteria:
    a. Pulmonary artery pressure mean >20 mmHg (at rest)
    b. PAWP ≤15 mmHg (if PAWP cannot be reliably attained, then left ventricular end diastolic pressure ≤15 mmHg)
    c. PVR >2 Wood units or >160 dynes/sec/cm^5

    If more than 1 RHC was performed within 3 years of Screening, the most recent RHC that includes parameters sufficient to evaluate the above criteria must be used for this assessment.
5. Has WHO/NYHA FC II to III symptoms at Baseline.
6. Must be on a stable dose(s) of PAH-specific oral therapy, defined as no change in dose or regimen for at least 90 days prior to randomization. Allowable PAH-specific therapy is an ERA and/or a PDE5-I or a sGC stimulator. Subjects may be on a stable dose of either a PDE5-I or a sGC stimulator, not both.
    a. If the subject's disease-specific PAH therapy does not include a PDE5-I, the use of a PDE5-I for erectile dysfunction, up to 3 doses per week, is permitted. The subject should not have taken a dose within 48 hours of Baseline.
7. Has a 6MWD ≥150 meters at Screening.
8. Removed in Amendment 2.
9. Has a peak VO_2 of ≥9 to <18 mL/min/kg during the Screening CPET, as assessed by the CPET core laboratory.
10. If the subject is taking concomitant medications that may affect the clinical manifestations of PAH (ie, calcium channel blockers, digoxin, diuretics, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or L-arginine supplements), the subject must be on a stable dose for at least 30 days prior to randomization. The exception is the that the dose of diuretics must be stable for at least the 10 days prior to randomization.
11. Both male and female subjects agree to use a highly effective method of birth control throughout the entire study period from informed consent through to the Week 28 Visit/28-day Follow-up Visit, if the possibility of conception exists. Eligible male and female subjects must also agree not to participate in a conception process (ie, actively attempt to become pregnant or to impregnate, sperm donation, in vitro fertilization) during the study and for 30 days after the final dose of study drug. Eligible male subjects must agree not to participate in sperm donation for 90 days after the final dose of study drug.

    Women who are surgically sterile or postmenopausal (defined as 12 consecutive months with no menses without an alternative medical cause) are not considered to be of childbearing potential. If of childbearing potential, female partners of male study participants should agree to utilize medically acceptable methods of contraception for the duration of study participation.

    Highly effective birth control methods include the following:

- Oral, implantable, or injectable contraceptives (starting ≥60 days before dosing) in combination with a diaphragm with vaginal spermicide, cervical cap with vaginal spermicide, or male condom.
- Standard intrauterine device, intrauterine system, progesterone implant, or tubal sterilization.
- Post vasectomy with confirmatory negative semen analysis and male condom, partner using diaphragm with spermicide, cervical cap with spermicide, estrogen and progesterone oral contraceptives, estrogen and progesterone transdermal patch, vaginal ring, or progesterone injection.
- Complete sexual abstinence defined as refraining from heterosexual intercourse for the entire period of risk associated with study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

4.2 EXCLUSION CRITERIA

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

1. For subjects with known HIV-associated PAH, a cluster of differentiation 4 T-cell count <200/mm^3 at Screening.
2. Has 3 or more of the following left ventricular disease/dysfunction risk factors:
    a. Body mass index ≥30 kg/m^2
    b. History of systemic hypertension
    c. Diabetes mellitus (any type)
    d. Historical evidence of significant coronary artery disease established by any 1 of the following:
        i. Myocardial infarction, percutaneous coronary intervention, or angiographic evidence of coronary artery disease (>50% stenosis in at least 1 coronary artery)
        ii. Positive stress test for cardiac ischemia with imaging
        iii. Previous coronary artery bypass graft
        iv. Angina
    e. Recurrent or persistent atrial fibrillation
3. Removed in Amendment 1.
4. Symptomatic coronary artery disease and/or myocardial infarction within past 6 months.
5. Current symptomatic aortic or mitral valve disease.
6. Has evidence of more than mild lung disease on pulmonary function tests performed within 1 year prior to, or during, Screening. Subjects with any of the following criteria will be excluded (BOTH measurements must be performed):
    a. Forced expiratory volume in 1 second <60% predicted

b. TLC <60% predicted

Note: Values for study eligibility should be pre-bronchodilator values.

7. Has evidence of thromboembolic disease as determined by V/Q lung scan or local standard of care diagnostic evaluation at or after diagnosis of PAH.
8. Current diagnosis of ongoing and clinically significant sleep apnea as defined by the Investigator.
9. Requires use of supplemental oxygen during CPET.
10. RER <1.0 at Screening CPET as determined by the CPET core laboratory.
11. Acute non-cardiac disorder that may affect exercise performance or be aggravated by exercise (eg, infection, renal failure, thyrotoxicosis).
12. Male subjects with a QTcF >450 msec and female subjects with a QTcF >470 msec on ECG recorded at Screening and analyzed by the central ECG laboratory. Subjects with evidence of intraventricular conduction delay (defined as a QRS interval >110 msec) will be excluded if the QTcF is >500 msec for both males and females.
13. Severe chronic liver disease (ie, Child-Pugh Class C), portal hypertension, cirrhosis, or complications of cirrhosis/portal hypertension (eg, history of variceal hemorrhage, encephalopathy).
14. Confirmed active infection with hepatitis B virus or HCV.
15. Subjects with alanine aminotransferase or aspartate aminotransferase ≥3 times the upper limit of normal or total bilirubin ≥2 times the upper limit of normal at Screening.
16. Chronic renal insufficiency as defined by an estimated glomerular filtration rate using the Modification of Diet in Renal Disease Study equation of <30 mL/min/1.73 m^2 or requiring dialysis at Screening (Levey 1999).
17. Hemoglobin concentration <9 g/dL at Screening.
18. Subjects treated with an IV, SC, inhaled, or oral prostacyclin pathway agent (eg, epoprostenol, treprostinil, iloprost, beraprost, or selexipag) for PAH within 90 days of randomization (use in vasoreactive testing is permitted). Subject is not eligible if previous prostacyclin therapy was stopped for a safety or tolerability issue related to systemic prostacyclin adverse effects.
19. Combined with Exclusion Criterion #18.
20. Subject has pulmonary veno-occlusive disease.
21. Malignancy diagnosed and/or treated within 3 years of Screening, with the exception of localized non-metastatic basal cell or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix excised with curative intent.
22. Subject tests positive for amphetamine, cocaine, methamphetamine, methylenedioxymethamphetamine, or phencyclidine in urine drug screen performed at Screening, or has a recent history (6 months) of alcohol or drug abuse. Subjects will not be excluded due to a positive drug screen caused by prescribed medications.
23. Initiation or discontinuation of a cardio-pulmonary rehabilitation program based upon exercise within 90 days prior to Screening and/or planned during study participation.

24. Prior participation in any study of ralinepag or participation in another interventional clinical study with medicinal products within 30 days prior to Screening. Concurrent participation in registry or observational studies is allowed, if the subject can fulfill all other entry criteria and comply with all study procedures.
25. Any reason that, in the opinion of the Investigator, precludes the subject from participating in the study (eg, any previous or intercurrent medical condition) that may increase the risk associated with study participation or that would confound study analysis (eg, right-to-left shunt detected during CPET) or impair study participation or cooperation.
26. Known hypersensitivity to ralinepag or any of the excipients.
27. Life expectancy <12 months based on the Investigator's opinion.
28. Women who are pregnant, lactating, or breast-feeding.

4.3 PRESCRIBED THERAPY

4.3.1 Prior and Concomitant Medications

All prescriptions and over-the-counter medications taken during the 30 days prior to Screening through the Week 28 Visit (or SDT Visit, if applicable) and 28-day Follow-up Visit (as applicable) will be documented with the indication, start date/time, and stop date/time, if known. Concomitant medications include any prescription, over-the-counter medications, natural products, and/or vitamins.

Attempts should be made to not change concomitant medications during the study, unless medically necessary or otherwise noted. All concomitant medications necessary for the health and well-being of a subject will be permitted.

Concomitant medications will be recorded on the subject's source documents and entered in the appropriate eCRF. Any changes to concomitant medications during the study will be recorded in the eCRF.

If the subject is taking concomitant medications that may affect the clinical manifestations of PAH (ie, calcium channel blockers, digoxin, diuretics, L-arginine supplements, beta blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers), the subject should remain on a stable dose of these medications throughout the study.

Subjects must be on a stable dose(s) of PAH-specific oral therapy, defined as no change in dose or regimen for at least 90 days prior to randomization and must remain on that dose/regimen

throughout the study. Allowable PAH-specific therapy is an ERA and/or a PDE5-I or a sGC stimulator. Subjects may be on a stable dose of either a PDE5-I or a sGC stimulator, not both.

If the subject's disease-specific PAH therapy does not include a PDE5-I, the use of a PDE5-I for erectile dysfunction (up to 3 doses per week) is permitted. The subject should not take a dose within 48 hours of any baseline or study-related efficacy assessments.

Prohibited PAH-specific therapy includes prostacyclin (epoprostenol), prostacyclin analogs (treprostinil, beraprost, or iloprost), or currently available IP-receptor agonists (use in vasoreactive testing is permitted).

Additional PAH-specific medications are not to be added at any time during the study, and the dose or regimen of a participants' PAH-specific background therapy should not be changed during the study. Short-term rescue therapy with a parenteral or inhaled prostacyclin will be permitted if a subject develops an acute intercurrent illness that requires temporary escalation of PAH-specific therapy while participating in the study.

4.3.2 Physical Activity

Initiation or discontinuation of a cardio-pulmonary rehabilitation program based upon exercise within 90 days prior to Screening and/or planned during study participation is prohibited.

5 SUBJECT ENROLLMENT

5.1 TREATMENT ASSIGNMENT

Approximately 193 PAH subjects with WHO Group 1 PH are planned to be randomized to achieve 135 completed subjects with both a valid Screening and Week 28 CPET assessment. Subjects who meet entry criteria will be randomly allocated (2:1 ratio) to receive ralinepag or placebo, in addition to their PAH-specific background therapy, as applicable.

5.2 RANDOMIZATION

After the completion of all Screening procedures, all eligible subjects will be randomly assigned to either ralinepag or placebo in a 2:1 ratio.

Subject randomization will be stratified by WHO/NYHA FC (II vs III) and background therapy (single vs dual). After successful completion of all Screening procedures, eligible subjects will

be randomized into the study using a centralized randomization schedule through an Interactive Response Technology (IRT) system. During this process, the system will assign the subject a randomization number. An independent, unblinded statistician will generate the randomization code.

5.3 BLINDING

The Sponsor, subjects, and all personnel directly involved with the conduct of the study (eg, Investigators, site personnel, Monitors, and clinical study staff at the Sponsor or the Sponsor's designee, except the Sponsor's Clinical Study Materials representative) will be blinded to the identity of the study drug and all randomization assignments and will remain blinded until the study is completed, and the clinical database is locked.

As an exception, a representative from the bioanalytical lab who is responsible for analyzing PK samples during the study will be unblinded to treatment assignments. This representative will not be involved in the management of the study or have access to other subject data.

6 DRUGS AND DOSING (OR TREATMENT PROCEDURES)

6.1 DRUG DOSAGE, ADMINISTRATION, AND SCHEDULE

6.1.1 Dosage and Administration

Study drug is taken once daily, with or without food, and should be taken at approximately the same time each day. For subjects who take their study drug in the mornings, study drug should not be taken prior to the visit on study clinic visit days. Study subjects will take their daily dose of study drug after study assessments have been completed. Assessments on clinic days should be performed >12 hours post-dose.

Subjects should be instructed to be careful not to break, chew, or disrupt the integrity of the tablet as this will result in inappropriate delivery of the active ingredient. If the tablet is inadvertently damaged during administration, the subject should contact site personnel in order to be monitored for the onset of symptoms due to possible overdose. Any tablet damaged during handling by the subject should not be consumed or discarded by the subject.

Randomized subjects will receive a starting dose of 50 mcg study drug once daily beginning on Day 1 (Baseline Visit). The initial dose of study drug following randomization will be consumed

in clinic. Following 1 week of treatment at this initial dose, study drug will be up-titrated in 50-mcg increments each week to a dose of 1400 mcg once daily or until the highest tolerated dose is achieved.

Increases (with at least 7-day intervals) or decreases in the study drug dose (in 50-mcg increments) will be allowed at any time to manage tolerability or AEs and attain the highest tolerated dose of study drug.

6.1.1.1 Contact Between Scheduled Clinic Visits

Between scheduled clinic visits, for the first 16 weeks after randomization, subjects will be contacted at least once per week to titrate study drug dose (maintain dose or adjust up or down), review study drug administration instructions, assess AEs, and record concomitant medications. After Week 16, subjects should be contacted as often as necessary to manage further dose titrations. These telephone calls must be completed by the Investigator or an appropriately delegated designee at the site, and the decision to increase, decrease, or keep the dose of study drug the same will be the responsibility of the Investigator. The decision to up-titrate, down-titrate, or keep the dose of study drug the same should be based on the occurrence and severity of the typical pharmacologic effects of the IP-receptor agonist class of drugs that cannot be tolerated by the subject, despite the use of symptomatic therapies (as and when appropriate). Examples of these effects include, but are not limited to, headache, diarrhea, flu-like symptoms, jaw pain, muscle pain and spasm, joint pain, flushing, nausea, and vomiting. All dose adjustments will be noted in source documentation and captured in the eCRF.

Further increases in study drug dose (in increments of 50 mcg per week) will be permitted between Weeks 16 and 27, according to Investigator discretion. The dose of the study drug may be decreased at any time to manage tolerability or AEs.

6.1.2 Interruptions of Study Drug

The Investigator must interrupt or permanently discontinue study drug if it is determined that continued administration is not in the best interest of the subject.

Interruption of study drug may be due to an AE, diagnostic procedure, therapeutic procedure, or administrative reasons (eg, withdrawal of consent). The reason for interruption of study drug must be noted in source documentation and captured in the eCRF.

In the event of a single missed dose, the normal assigned dose can be resumed. If there is a dose interruption, the subject must contact the site when 2 or more doses are missed for the site staff to provide continued dosing guidelines, as described in Section 15.3. If 3 to 4 doses are missed, the study drug dose should be reduced by half upon restarting and up-titrated in weekly 50-mcg increments. Subjects will be re-titrated up to their highest tolerated dose. If a subject's dose cannot be reduced by half (ie, the resulting dose would not result in a 50-mcg dose increment), the closest available dose below the one-half dose should be used (Section 15.3).

If a subject has missed 5 or more consecutive doses, the subject will be required to restart study drug at 50 mcg. Following restarting at 50 mcg, up-titration will occur in weekly 50-mcg increments. Subjects will be re-titrated up to their highest tolerated dose.

Site staff should instruct the subject how to achieve the recommended dose with the subject's current medication card. In the event a new kit is required, the subject should return to the site within 7 days.

6.2 ACCESS TO BLINDED TREATMENT ASSIGNMENT

The Sponsor, subjects, and all personnel directly involved with the conduct of the study (eg, Investigators, site personnel, Monitors, and clinical study staff at the Sponsor or the Sponsor's designee) will be blinded to the identity of the study drug and all randomization assignments and will remain blinded until the study is completed, and the clinical database is locked.

Exceptions include the DMC, as well as a representative from the Clinical Study Materials group at the Sponsor. These representatives will not be involved in the management of the study or have access to other subject data.

A subject's randomization assignment may be unblinded only in emergency situations, when knowledge of the treatment assignment is considered absolutely necessary for medical management of the subject or for clinical decision making. In cases of absolute medical

necessity, the Investigator may unblind the subject using the IRT associated with the study. In these emergent cases, the decision to unblind the subject resides solely with the Investigator.

If circumstances allow, it is preferred that the Investigator discuss the need for unblinding with the Sponsor before unblinding of a subject's treatment assignment in the IRT system. When a subject's treatment assignment is unblinded, the unblinding Investigator must complete a comprehensive source note that includes the date, time, and the reason(s) the subject was unblinded. If the reason for unblinding was discussed with the Medical Monitor, the source note must contain a record of the discussion.

It is mandatory that all personnel who are involved in the unblinding and who have access to the unblinded treatment assignment information maintain the confidentiality of the information by not divulging the treatment assignment.

Subjects who are unblinded will not be allowed to continue in the study and will not be allowed to participate in the OLE study.

6.3 COMPLIANCE

Subjects will self-administer study drug on all days during the study except the initial dose following randomization. Subjects should be instructed not to self-titrate the dose of study drug without direction by the Investigator, or authorized designee. To confirm that the correct doses of study drug are taken, subjects must bring all used and unused packaged study drug to the clinic at each visit. The number of remaining doses/tablets will be counted to verify the number of study drug doses/tablets taken.

7 EXPERIMENTAL PROCEDURES

The assessments that are performed during Screening, at Baseline, during the Treatment Period, and at completion of the study (or at the SDT Visit) are outlined in Table 3-1. In order to allow flexibility, procedures may be completed over multiple days within the Screening Period.

8 STUDY TERMINATION

8.1 CRITERIA FOR SUBJECT WITHDRAWAL

Subjects will be informed that they are free to withdraw from the study at any time for any reason. Subjects are considered withdrawn if they state their intention (in writing, electronic communication, or verbally) to withdraw from further participation in all aspects of the study, die, or are lost to follow-up. Once the subject withdraws consent, no further data will be collected in the eCRF from that date forward.

The Investigator must remove a subject from treatment with the study drug if there is evidence of significant non-compliance, loss of contact, new medical conditions not allowing for continuation of the treatment (for example because of retroactive failure to fulfill inclusion or exclusion criteria), occurrence of AEs leading to substantial changes in the individual risk-benefit relation, or pregnancy. All subjects should remain in the study for long-term follow-up for survival status unless or until they withdraw consent.

Subjects are considered lost to follow-up if all reasonable attempts made by the Investigator, study nurse, study coordinator, or delegate to communicate with the subject fail. A minimum of 3 attempts must be made to contact the subject. Each attempt must be documented in the subject's records (ie, method of communication, times, and dates).

All subjects should remain on study drug for the duration of the 28-week Treatment Period. Subjects who wish to discontinue study drug will return to the clinic for an SDT Visit. If the SDT Visit occurs within 2 weeks of a regularly scheduled study visit, the SDT Visit can take the place of the next scheduled study visit, unless the next scheduled visit is the Week 28 Visit. After completing the SDT Visit, the subject should return to the clinic for all subsequent scheduled study visits (off study drug) until they complete the study at the Week 28 Visit. Subjects who discontinue study drug prior to Week 28, as well as those who complete the study on study drug as scheduled and choose not to participate in the OLE study, will be contacted every 6 months and at the end of the study to determine their survival status (unless consent is withdrawn).

8.2 CRITERIA FOR TERMINATING THE STUDY

The study will be terminated early if, in the opinion of the Sponsor, DMC, or Institutional Review Board (IRB)/Independent Ethics Committee (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. In the event of early termination of the study for safety reasons, the Sponsor will inform regulatory authorities without delay in accordance with local reporting requirements.

8.3 CRITERIA FOR DISCONTINUING A SITE

The study may also be terminated at a given center if:

- The Principal Investigator elects to discontinue the study
- The Sponsor elects to discontinue the study at the site
- US FDA, European, or national regulations are not observed
- The protocol is violated
- Changes in personnel or facilities adversely affect performance of the study, or if the CPET laboratory does not comply with quality control and/or training standards

9 ADVERSE EVENT REPORTING

9.1 DEFINITIONS

9.1.1 AEs

An AE is defined as any untoward medical occurrence in a study subject which does not necessarily have to have a causal relationship with treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the study medication, whether or not related to the product.

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 during the course of a clinical study
- Pre-existing conditions which worsen in severity or frequency or which have new signs/symptoms associated with them

9.1.2 SAEs

An SAE is any AE that:

- Results in death
- Is life-threatening (note that this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

An SAE may also be any other important medical event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such events include intensive treatment in an emergency room or at home for bronchospasm, blood dyscrasias, or convulsions that do not result in a formal hospitalization.

The following are not considered to be 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 ICF)

9.2 SEVERITY

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to 1 of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.

Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.

Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an

event, and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE (see Section 9.1.2), NOT when it is rated as severe.

9.3 RELATIONSHIP

The Investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterized as not related, possibly related, or probably related.

Probably related: There is a reasonable causal relationship between the study drug and the SAE. The event responds to dechallenge. Rechallenge is not required.

Possibly related: There is a reasonable causal relationship between the study drug and the SAE. Dechallenge information is lacking or unclear.

Not related: There is not a temporal relationship to study drug administration (too early or late, or study drug not taken), or there is a reasonable causal relationship between another drug, or concurrent disease and the SAE.

All efforts should be made to classify the AE according to the above categories.

The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. The Investigator will also consult the IB and/or Prescribing Information for marketed products, in his/her assessment. For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. There may be situations in which an SAE occurred, and the Investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor. The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated

causality assessment. The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

9.4 DOCUMENTATION OF ADVERSE EVENTS

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

9.4.1 AEs

Subjects will be instructed that they may report AEs at any time. AEs will be regarded as "pre-treatment" if they occur between Screening and the time of administration of the first dose of study drug. AEs should be reported beyond this period if per the Investigator, they are considered possibly or probably related to the study drug. All events reported following study drug administration will be recorded as TEAEs.

Monitoring of nonserious AEs will be continued to 28 days after the last dose of study drug or until the 28-day Follow-up Visit, whichever is later. In the event that a nonserious 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.

AEs will be elicited as indicated in Table 3-1 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 Report Form, including details of severity, 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.

9.4.2 SAEs

All SAEs will be captured from the time of Screening to 28 days after the last dose of study drug or until the 28-day Follow-up Visit, whichever is later. SAEs should be reported beyond this

period if per the Investigator, they are considered possibly or probably related to the study drug. SAEs will be monitored until resolution, death, or the subject is lost to follow up.

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. SAEs should be entered in the EDC system. If the EDC system is not available for SAE entry, a paper SAE form should be utilized and emailed or faxed to United Therapeutics Corp. Global Product Safety and Pharmacovigilance in order to meet reporting timelines. The SAE should be entered in the EDC system as soon as the site is able to do so.

United Therapeutics Corp. Global Product Safety and Pharmacovigilance
Email: [redacted]
Global Fax: [redacted]

A follow-up SAE Report Form must be forwarded to Global Product Safety and Pharmacovigilance at United Therapeutics Corp. within 48 hours of the receipt of any new/updated information.

The Investigator must also promptly notify their IRB or IEC of the SAE, including any follow-up information, in accordance with applicable national regulations and guidelines set forth by the IRB or IEC. Other situations as defined in International Council for Harmonisation (ICH) Topic E2A, 21 Code of Federal Regulations Section 312.32, and EU Volume 10 also qualify for expedited reporting. In these situations, the process will be as detailed for SAEs above:

- SAEs that could be associated with the study procedures
- SAEs 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 ralinepag IB

9.4.3 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 study drug immediately. Although not considered an AE (serious or nonserious), pregnancies occurring during the period of study drug administration

until 30 days after the final dose of study drug must be reported to the Sponsor within 24 hours of awareness, using a paper Pregnancy Notification and Outcome Form. Pregnancies should also be reported to the IRB/IEC in accordance with applicable national regulations and guidelines set forth by the IRB or IEC.

The pregnancy must be followed up to determine the outcome (including premature termination) and status of mother and child using both the Pregnancy Notification and Outcome Form and the Infant Follow-up Form as required and permitted per local regulations. Pregnancy complications must be reported as an AE or SAE.

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.

9.4.4 Overdose

An overdose is defined as a known deliberate or accidental administration of study drug during the study, to or by a study subject, at a dose above that which is assigned to that individual subject according to the study protocol. During the study, any administration of study drug at a dose >200 mcg higher than the recommended daily dose for a given time frame according to the protocol (eg, an increase from 150 mcg once daily to 400 mcg once daily) will be considered an overdose.

All cases of overdose (with or without associated AEs) will be documented on an Exposure/ Study Drug Administration page of the eCRF, in order to capture this important safety information consistently in the database.

Cases of overdose without manifested signs or symptoms are not considered AEs. AEs associated with an overdose will be documented on AE eCRF(s).

SAEs associated with overdose should be reported according to the procedure outlined in Section 9.4.2.

In the event of a study drug overdose, the subject should be treated symptomatically, and the Investigator should contact the Medical Monitor or designee for further advice as and when necessary.

9.4.5 Management of Tolerability and AEs

Prostacyclin receptor agonist therapies are associated with multiple adverse effects, including headache, diarrhea, flu-like symptoms, jaw pain, muscle pain and spasm, joint pain, flushing, nausea, and vomiting. During up-titration, adverse effects may in some cases prevent a subject from reaching an efficacious dose. Informing subjects in advance about common adverse effects can help to prepare them for the up-titration process. Subjects can be reassured that adverse effects are more frequent when actively up-titrating and that once the appropriate dose has been reached, the adverse effects will likely improve. Compliance can be improved by explaining to subjects that adverse effects are often unavoidable to reach an appropriate dose, but they can usually be managed with supplemental medications. Investigators can also provide support by advising subjects that the dose can be decreased or up-titrated more slowly if adverse effects are not tolerated. This allows subjects to gain a sense of control during the up-titration process.

Adverse effects often impact quality of life in subjects with PAH and can lead to discontinuation. In order to maximize the benefit of prostacyclin pathway therapies, healthcare providers must identify, accurately assess, and appropriately manage prostacyclin adverse effects which otherwise may lead to discontinuation of therapy. Due to the adverse effect profile, prostacyclin pathway therapies are initiated at low doses and up-titrated slowly, as tolerated, until a maintenance dose is achieved. In general, and in the Phase 2 ralinepag study (APD811-003), adverse effects appear to be more common during the titration phase than in the maintenance phase. Subjects need to be educated to expect some adverse effects and that the incidence and severity of adverse effects will vary from subject to subject. Differentiating between adverse effects of prostacyclin pathway therapies and the signs and symptoms of PAH, such as worsening right heart failure, dyspnea, or syncope, is important.

Subjects should be counseled to contact the Investigator/site staff if side effects become too severe, so they can be managed with supplemental therapies before the need to limit dose increases and to avoid discontinuations. A number of steps can be taken to proactively manage

adverse effects. Providing subjects with a supply of analgesics, anti-emetics, and antidiarrheal agents to take home allows them to proactively manage or promptly manage adverse effects should they develop. Subjects may take these agents before dose increases, if headaches, nausea, or diarrhea have been problematic previously, or to avoid these adverse effects as doses of study drug increase. The up-titration process requires subjects to be well-informed, with clear explanations about what is involved and that adverse effects will likely abate over time. By providing support and managing their expectations, subjects can be empowered to be involved in their own self-care. Subject engagement and the benefits of involving subjects and their families and caregivers in decisions about their care is important. Subjects should be reassured that in most cases, adverse effects will lessen or abate over time, and the improvement in PAH symptoms will likely outweigh the difficulty faced with adverse effects during up-titration.

Practical considerations and steps to aid subjects taking study drug are as follows:

- Support for management of adverse effects
- Support and tools to aid compliance
- Medication reminders through alarms or apps on smartphones
- Ensure that the subject understands the basic function of the medication, the importance of regular dosing, and what to do if a dose is late or missed
- Nurses are in a key position to provide subject support and counseling
- Education on the up-titration process
- Subject associations/support groups
- Written materials and online information

9.5 REPORTING RESPONSIBILITIES OF THE INVESTIGATOR

All SAEs, regardless of expectedness or causality, must be reported to the Sponsor by recording it in the EDC, and if the EDC is not accessible for any reason, then via email or by fax immediately after becoming aware of the event, and no more than 24 hours of awareness (Section 9.4.2).

9.6 SAFETY REPORTS

In accordance with FDA, EU, and national regulations, the Sponsor will notify the FDA, other competent authorities, and all participating Investigators of any AE that is considered possibly attributable to study drug and is both serious and unexpected. The Investigator must report these

AEs to their IRB or IEC in accordance with applicable national regulations and guidelines set forth by the IRB or IEC.

10 STATISTICAL CONSIDERATIONS

10.1 DATA PROCESSING

The results of assessments will be transcribed into an eCRF for each subject who signs an ICF until study completion or study discontinuation for any reason. A representative from the Sponsor will verify eCRF data fields against source documentation. All data transmitted from the site will be reviewed and entered into a quality assured computerized database. Data clarifications will be generated, and the database will be edited as appropriate. The eCRF screens are to be reviewed by the Investigator for completeness and accuracy. The Investigator must electronically sign each subject's eCRF to signify his/her approval of the data. The Investigator will be required to re-sign an eCRF if changes are made to a subject's eCRF by the site after the Investigator initially signs the eCRF. The database will be final when all outstanding queries have been resolved and all data management quality assurance procedures are complete.

10.2 SAMPLE SIZE

It is assumed that change from baseline in peak VO_2 will be normally distributed with a standard deviation (SD) of 3 mL/min/kg and a baseline mean in the range of 9 to 18 mL/min/kg. Assuming a 2:1 randomization, 135 completed subjects are sufficient to achieve at least 90% power to detect a treatment effect of 1.8 mL/min/kg in favor of ralinepag (a clinically significant increase of ≥10% from baseline) by a 2-sample t-test using a 2-sided significance level of 0.05. Assuming 30% of subjects who are randomized will not have a valid end of study CPET assessment for any reason (eg, technical issues with the procedure, refusal or lack of effort by the subject) or will drop out before the Week 28 Visit, randomizing 193 subjects allows a final sample size of 135 completers with a valid end of study CPET assessment. The number of randomized subjects may be adjusted if the dropout rate is different than anticipated.

A blinded review of the data to evaluate the assumption regarding the SD of change from baseline in peak VO_2 is 3 mL/min/kg is planned when 50% and 75% of the planned subjects have completed the study. A revised sample size may then be calculated using suitably modified

assumptions. The planned sample size will not be reduced as a result of the sample size re-estimation.

10.3 ANALYSIS PLAN

Continuous variables will be summarized using the number of observations, mean, SD, median, minimum, and maximum. Categorical variables will be summarized using frequency counts and percentages. For time-to-event variables, the number of subjects at risk over time, as well as the cumulative percentage of subjects experiencing the event of interest, will be presented based on Kaplan-Meier methodology.

The following analysis populations are defined in this study:

- The Intention-to-Treat (ITT) Population will include all randomized subjects, irrespective of whether they received study drug.
- The modified ITT (mITT) Population will include all randomized subjects, irrespective of whether they received study drug who have valid post-baseline peak VO_2 measures through CPET.
- The Per-Protocol Population will include all subjects from the ITT Population without major protocol deviations that might affect the evaluation of the effect of the study drug on the primary endpoint. These violations will be pre-defined in the Statistical Analysis Plan and the Per-Protocol Population will be specified prior to unblinding.
- The PK Population will include all subjects in the ITT Population with at least 1 post-dose PK measurement.
- The Safety Population will include all randomized subjects who received study drug at least once.

All statistical tests will be performed at a significance level of 0.05 (2-sided).

10.3.1 Primary Efficacy Endpoint

The primary endpoint of the study is the change from baseline in peak VO_2 after 28 weeks of treatment with study drug. The primary endpoint will be analyzed using analysis of covariance on the mITT Population with a model that includes treatment and the stratification factors (baseline FC and background PAH therapy) as factors and baseline peak VO_2 as a covariate. Least-squares means, standard error, and 95% confidence intervals for the treatment groups and the treatment effect will be presented together with the p-value.

The primary analysis will be repeated on the ITT and Per-Protocol Populations. For the primary analysis on the ITT Population, missing peak VO_2 will be imputed using a multiple imputation approach. Also, the robustness of the result will be assessed using various sensitivity analyses (eg, baseline value carried forward, tipping point analysis).

10.3.2 Secondary Efficacy Endpoints

The following secondary endpoints will be analyzed in hierarchical order:

- Change from baseline at Week 28 in NT-proBNP: NT-proBNP with log transformation will be analyzed in the ITT Population using mixed-effect model repeated measures analysis with treatment, stratification factors, week, and treatment-by-week interaction as factors, and baseline NT-proBNP as a covariate.
- Change from baseline at Week 28 in V_E/VCO_2 slope: V_E/VCO_2 slope will be analyzed in the mITT Population and repeated in the ITT Population using analysis of covariance with a model that includes treatment and the stratification factors as factors and baseline V_E/VCO_2 slope as a covariate.
- Change in SF-36 scores from baseline to Week 28: the component and domain scores will be analyzed in the ITT Population using mixed-effect model repeated measures analysis with treatment, stratification factors, week, and treatment-by-week interaction as factors, and baseline component/domain score as a covariate.
- Time to first all-cause nonelective hospitalization in randomized subjects during the study period will be analyzed in the ITT Population using a Cox proportional hazard regression model that includes treatment and the stratification factors.

10.3.3 Additional Endpoints

Additional endpoints evaluated at Week 28 will include, but will not be limited to, the following:

- Changes from baseline to Week 28 in the following additional CPET parameters:
  - Proportion of subjects who achieve peak VO_2 >15 mL/min/kg
  - SBP response to exercise
  - Pulse oximetry response to exercise
  - End-tidal carbon dioxide response to exercise
  - HR recovery
- Improvement in risk category for peak VO_2 (>15 [low risk], 11 to 15 [intermediate risk], and <11 mL/min/kg [high risk]) and V_E/VCO_2 slope (<36 [low risk], 36 to 44 [intermediate risk], and >44 [high risk]) according to ESC/ERS Guidelines for the diagnosis and treatment of PH (Humbert 2022)
- Change in Registry to Evaluate Early and Long-term PAH Disease Management risk score

The efficacy measures at time points other than Week 28 will also be analyzed.

10.3.4 Safety Analyses

10.3.4.1 AEs

AEs will be coded using Medical Dictionary for Regulatory Activities version 21.0 or later.

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

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

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

10.3.5 Extent of Exposure

The duration of time on study and time on study treatment will be summarized for each treatment group using descriptive statistics. The number of subjects on treatment for certain time intervals will also be summarized. The total subject-years and total subject-years on study will also be included in this summary.

10.3.6 Clinical Laboratory Parameters

Laboratory parameters and their changes from baseline will be summarized by treatment group at each scheduled assessment time point using descriptive statistics.

10.3.7 Electrocardiograms

Individual ECG values will be listed by visit and summarized using descriptive statistics. The following intervals will be provided for each ECG: RR, PR, QRS, QT, QTcB, and QTcF. Post-baseline ECGs for each subject will be compared with the baseline ECG. Any clinically significant change from baseline may be recorded as an AE if deemed appropriate by the Investigator or Sponsor. Outlier analysis will be performed on all subjects with QTcF values >500 msec or change from baseline >60 msec.

10.3.8 Vital Signs

Descriptive statistics for vital signs (BP, HR, respiratory rate) and their changes from baseline will be presented by treatment group.

10.3.9 Physical Examination

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

10.3.10 PK Analyses

Plasma concentration data will be tabulated and plotted for each subject for whom concentrations are quantifiable.

10.4 INTERIM ANALYSIS

No formal interim analysis for efficacy is planned. A blinded sample size re-estimation may be conducted.

10.5 OTHER ANALYSES

Exploratory analyses may be conducted based on available study data.

10.6 TESTING STRATEGY

The primary endpoint, change from baseline to Week 28 in peak VO_2, will be tested at the 0.05 (2-sided) level of significance. To protect the overall Type 1 error rate, the secondary endpoints will be tested sequentially at a significance level of 0.05 (2-sided). Hence, a significant result for a given secondary endpoint will only be interpreted in a confirmatory manner if all previous endpoints have achieved statistical significance.

10.7 DATA LISTINGS AND SUMMARIES

All data gathered in this study will be presented in summary tables and listings in the Clinical Study Report.

10.8 DATA MONITORING COMMITTEE

An independent DMC will be utilized to monitor the safety of subjects and to enhance the integrity and credibility of the study. The roles and responsibilities of the DMC are described in detail in the DMC Charter.

The DMC will abide by the principles set forth in the FDA *Guidance for Clinical Trial Sponsors, Establishment and Operation of Clinical Trial Data Monitoring Committees*. As part of its role, the DMC will conduct reviews of accumulating safety data at specified intervals during the conduct of the study, according to the guidelines detailed in the DMC Charter. DMC recommendations to the study team will be communicated in a blinded fashion (ie, treatment assignment for individual subjects will not be shared). To ensure the scientific integrity of the study, members of the DMC will not be study Investigators or directly involved in the ongoing operational management of the study.

In addition to members of the DMC, an independent statistician responsible for interacting with the DMC will have access to unblinded study data. This statistician will not be directly involved in the conduct of the study.

11 PACKAGING AND FORMULATION

11.1 CONTENTS OF STUDY DRUG

Study drug will be packaged into blister strips placed into a single card. Each single card will consist of a total of 64 study drug tablets (a combination of 50, 250, and 400 mcg tablets). Four cards will be placed into a subject medication kit. The subject medication kit will include a tamper-evident seal and will be labeled in accordance with applicable country regulations. Dispensing, dosing, and titration instructions will be provided to the sites and subjects.

11.2 STORAGE AND HANDLING OF STUDY DRUG

Study drug will be shipped to the Investigator or designee (eg, study pharmacist) by a registered courier service. All study drug should be stored in a secure, limited-access area at 15°C to 30°C (59°F to 86°F) controlled room temperature. Allowable temperature storage excursions are provided in the Pharmacy Manual. The study drug must be stored and handled in accordance with the manufacturer's instructions. If storage conditions are not maintained per specified requirements, the Contract Research Organization (CRO), Investigator, and the Sponsor must be contacted.

The Investigator or pharmacist (or designee) will also keep accurate records of the quantities of study drug (ralinepag or placebo) dispensed, used, and returned by each subject. Reasons for

deviation from the expected dispensing regimen must also be recorded. The study Monitor will periodically check the supplies of study drug held by the Investigator to verify accountability of all study drug received and dispensed. At the conclusion of the study, all unused study drug and all containers will be handled in accordance with the Pharmacy Manual.

11.3 SUPPLY AND RETURN OF STUDY DRUG

At completion of the study, all study drug (ralinepag or placebo) will be reconciled by the Monitor or contracted designee and then returned at the direction of the Sponsor to either the Sponsor or a third-party contractor to be retained or destroyed according to applicable country regulations and investigative site Standard Operating Procedures. Prior to any action being taken with study drug during or after the study is completed, the Investigator will contact the Sponsor (or contracted CRO) for approval of such action.

Study drug may be destroyed on site provided the institution has written policies and/or procedures in place describing their process and maintains all documentation related to on-site destruction. Prior to proceeding with on-site destruction, the site should notify the Sponsor for review of their policies and/or procedures. For sites that perform on-site destruction of study drug, accountability by the Sponsor may not be performed prior to destruction.

11.4 STUDY DRUG ACCOUNTABILITY

The Investigator or Pharmacist (or designee) will maintain accurate records of the quantities of the study drug (ralinepag or placebo) dispensed, used, and returned by each subject. Reasons for deviation from the expected dispensing regimen must also be recorded. The study Monitor will periodically check the supplies of study drug held by the Investigator to verify accountability of all study drug received and dispensed.

12 REGULATORY AND ETHICAL OBLIGATION

12.1 US FDA OR APPLICABLE REGULATORY REQUIREMENTS

The study will be conducted in accordance with ICH, Good Clinical Practice guidelines, and all applicable national regulations. The Sponsor will obtain the required approval from each national regulatory authority to conduct the study. During the conduct of the study, an annual safety report will be compiled by the Sponsor for submission to those regulatory authorities and

IRBs/IECs that require it. Any additional national reporting requirements as specified by the applicable regulations, regulatory authorities, or IRB/IEC will also be fulfilled during the conduct of the study.

12.2 INFORMED CONSENT REQUIREMENTS

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 an ICF 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 the ICH of Technical Requirements for Pharmaceuticals for Human Use, *Guideline for Good Clinical Practice (E6).*

12.3 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD

Prior to study initiation at each site, the Investigator will obtain approval for the study from an appropriate IRB/IEC and provide the Sponsor with a copy of the approval letter. The IRB/IEC must also review and approve the study site's ICF and any other written information provided to the subject prior to enrollment, as well as any advertising materials used for subject recruitment. Copies of the ICF and advertising materials must be forwarded to the Sponsor for review before submission to the IRB/IEC prior to the start of the study.

If, during the study, it is necessary to amend either the protocol or the ICF, the Investigator is responsible for obtaining IRB/IEC approval of these amended documents prior to implementation. Copies of the IRB/IEC correspondence and approval letters must be sent to the Sponsor.

During the conduct of the study, an annual progress report will be compiled by the Sponsor for submission to those IRBs/IECs that require it.

A written summary of the study will be provided by the Investigator to the IRB/IEC following study completion or termination according to the IRB or IEC standard procedures. Additional updates will also be provided in accordance with the IRB/IEC's standard procedures.

12.4 PRESTUDY DOCUMENTATION REQUIREMENTS

Before commencing the clinical study, the following documents will be provided to the site: IB, protocol, ICF, Budget Agreement, and eCRF.

The site will be required to provide the following documents to United Therapeutics Corp. or designee prior to study start: Signature Page of the protocol, Form FDA 1572 or Statement of Investigator, Financial Disclosure Form, IRB/IEC Composition and Roster, IRB/IEC protocol, informed consent approval letters, and Curriculum Vitae of study staff listed on Form FDA 1572.

12.5 SUBJECT CONFIDENTIALITY

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

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

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

13 ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 PROTOCOL AMENDMENTS AND STUDY TERMINATION

Protocol amendments that could potentially adversely affect the safety of participating subjects or that alter the scope of the investigation, the scientific quality of the study, the experimental design, dosages, duration of therapy, assessment variables, the number of subjects treated, or

subject selection criteria may be made only after consultation between United Therapeutics Corp. or its designee and the Investigator.

All protocol amendments must be submitted to and approved by the appropriate regulatory authorities and IRB/IEC prior to implementation.

A report documenting study termination must also be submitted to and acknowledged by the appropriate IRB/IEC for each study site.

At the end of the study, where applicable, a final report will be provided to the local regulatory agencies.

13.2 STUDY DOCUMENTATION AND STORAGE

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

- Subject files containing the completed eCRFs (if applicable) and supporting source documentation, including medical records, laboratory data, and signed ICFs
- Regulatory files containing the protocol with all amendments and Investigator signature pages, copies of all other regulatory documentation, all correspondence between the site and the IRB/IEC and Sponsor, and drug accountability files, including a complete account of the receipt and disposition of 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 final shipment and delivery of study drug and the appropriate competent regulatory authorities are notified. The Sponsor will provide written notification when it is appropriate for the Investigator to discard the study-specific documents referenced above.

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

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

13.3 STUDY MONITORING AND DATA COLLECTION

In accordance with federal/national regulations, ICH, and Good Clinical Practice guidelines, Monitors for United Therapeutics Corp. or its designee will periodically contact the site and conduct on-site and/or remote visits. During these visits, the Monitor will at a minimum confirm ethical treatment of subjects, assess study progress, review data collected, conduct source document verification, verify drug accountability periodically, and identify any issues requiring resolution.

The Investigator agrees to allow the Monitor direct access to all relevant documents and to allocate his/her time and his/her staff to the Monitor to discuss any findings or any relevant issues.

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15 APPENDICES

15.1 WORLD HEALTH ORGANIZATION FUNCTIONAL CLASSIFICATION

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

15.2 PROCEDURES FOR THE 6-MINUTE WALK TEST

General Procedures

The 6-Minute Walk Test (6MWT) should be administered by the same tester at each study site throughout the study. The administration of the test and specifications of the testing area should be generally consistent with the American Thoracic Society guidelines and the usual practice of the study site. Before each 6MWT, the subject should rest (seated) for at least 10 minutes.

The area used for the 6MWT should be premeasured at approximately 30 meters in length (but no shorter than 15 meters [16 yards or 50 feet] in length) and approximately 2 to 3 meters in width. There must be no turns or significant curves to the 6MWT area. The length should be marked with gradations to ensure the accurate measurement of the distance walked. The area should be well ventilated. The tester may be at the starting end of the corridor or at the midpoint of the corridor with a stopwatch. Intermittent rest periods are allowed if the subject can no longer continue. If the subject needs to rest briefly, he/she may stand or sit and then begin again when he/she is sufficiently rested, but the clock will continue to run. At the end of 6 minutes, the tester will call "stop where you are" while simultaneously stopping the watch, and then measure the distance walked.

Instructions to the Subject

Subjects will be instructed that the preceding meal should be light. Subjects should be told to wear comfortable clothing and sneakers or comfortable walking shoes. The person administering the test will use the following **exact** dialogue with the subject:

"The purpose of this test is to find out how far you can walk in 6 minutes. You will start from this point and follow the hallway to the marker (eg, chair) at the end, turn around and walk back. When you arrive back at the starting point you will go back and forth again. You will go back and forth as many times as you can in the 6-minute period. You may stop and rest if you need to. Just remain where you are until you can go on again. However, the most important thing about the test is that you cover as much ground as you possibly can during the 6 minutes. I will tell you the time, and I will let you know when the 6 minutes are up. When I say STOP, please stand right where you are."

After these instructions are given to the subject, the person administering the test will then ask:

"Do you have any questions about the test?"

The person administering the test will then start the test by saying the following to the subject:

"Are you ready?"

"Start when I say 'GO.'"

The person administering the test will tell the subject the time at each minute by saying:

"You have 5 minutes to go."

"You have 4 minutes to go."

"You have 3 minutes to go."

"You have 2 minutes to go."

"You have 1 minute to go."

At 6 minutes, the person administering the test will tell the subject:

"Stop where you are."

No other instruction or encouragement will be given during the test. Eye contact with the subject should be avoided during the test.

15.3 STUDY DRUG DOSING INTERRUPTIONS AND RE-TITRATION SCHEDULE (SUGGESTED)

Dose at Time of Interruption (mcg)	Length of Interruption		
	1 to 2 Doses	3 to 4 Doses	≥5 Doses
	Suggested Initial Dose (mcg)		
50	50	50	50
100	100	50	50
150	150	50	50
200	200	100	50
250	250	100	50
300	300	150	50
350	350	150	50
400	400	200	50
450	450	200	50
500	500	250	50
550	550	250	50
600	600	300	50
650	650	300	50
700	700	350	50
750	750	350	50
800	800	400	50
850	850	400	50
900	900	450	50
950	950	450	50
1000	1000	500	50
1050	1050	500	50
1100	1100	550	50
1150	1150	550	50
1200	1200	600	50
1250	1250	600	50
1300	1300	650	50
1350	1350	650	50
1400	1400	700	50

15.4 CHILD-PUGH SCORE

Parameter	Points		
	1	2	3
Hepatic encephalopathy	None (absent)	Stage I to II (mild or suppressed with medication)	Stage III to IV (severe or refractory)
Ascites	None (absent)	Mild-moderate (suppressed with medication)	Moderate-severe (refractory)
Bilirubin (total) µmol/L (mg/dL)	<34 (<2)	34 to 50 (2-3)	>50 (>3)
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Prothrombin time (s)/INR	<4/(<1.7)	4-6/(1.71 to 2.20)	>6/(>2.20)

Abbreviations: INR, international normalized ratio

Class A (mild)=5 to 6 points

Class B (moderate)=7 to 9 points

Class C (severe)=10 to 15 points (subjects in this class are excluded from participation)