Study Design of the Phase 3 ADVANCE Program Evaluating Time-to-Clinical Events and Exercise Capacity in Patients With Pulmonary Arterial Hypertension Treated With Ralinepag

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PHASE 3 PROGRAM INTRODUCTION

- Ralinepag is a novel, next-generation, oral, selective, potent prostacyclin (IP) receptor agonist in development for pulmonary arterial hypertension (PAH), with optimized pharmacokinetics (PK) and potent activity on pulmonary arteries, vascular smooth muscle cells, and platelets.
- The ralinepag clinical development program includes eight completed or ongoing studies. A total of 143 healthy volunteers and 55 subjects with PAH have been exposed to ralinepag (ralinepag immediate-release [IR] liquid-in-hard-gelatin capsule or extended-release [XR] capsules). All subjects received at least 1 dose of a ralinepag formulation at doses ranging from 10 to 600 mcg per day.
- The prolonged plasma PK profile of ralinepag XR tablet supports once daily dosing (Figure 1). The single-dose PK of selexipag is shown in Figure 2 for comparison.

Figure 1. Ralinepag XR Plasma Concentrations Over Time

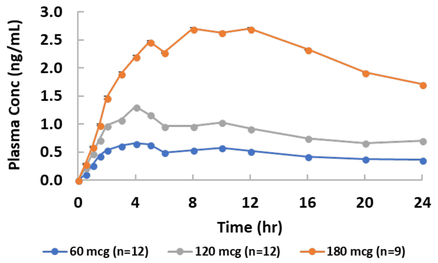
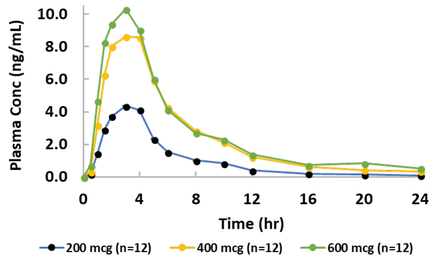


Figure 2. Selexipag Plasma Concentrations Over Time



- United Therapeutics is planning 3 placebo-controlled randomized studies and 1 open-label extension study with ralinepag.

A Study Evaluating the Efficacy and Safety of Ralinepag to Improve Treatment Outcomes in PAH Patients

ADVANCE™ outcomes

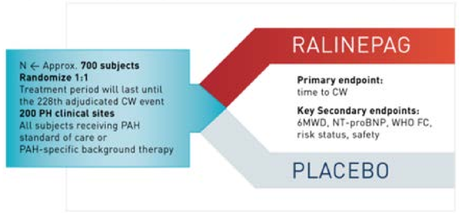
STUDY OBJECTIVE – ROR-PH-301

- The purpose of the ADVANCE Outcomes study is to evaluate the efficacy, safety, and tolerability of ralinepag when added to PAH standard of care or PAH-specific background therapy in subjects with World Health Organization (WHO) Group 1 pulmonary hypertension (PH).

STUDY DESIGN

- ADVANCE Outcomes (Figure 3) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study that includes a 16-week Titration Period (Figure 4).

Figure 3. Study Design for ADVANCE Outcomes Study

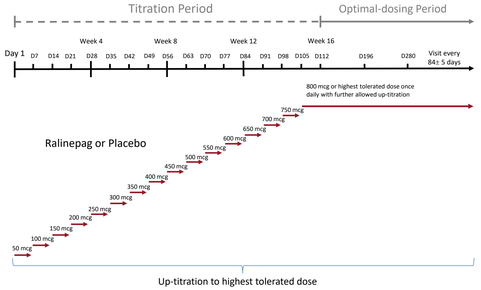


- The primary efficacy endpoint is the time to the first adjudicated clinical worsening (CW) event. Other secondary efficacy endpoints include change from Baseline to Week 28 in 6-Minute Walk Distance (6MWD), N-terminal probrain natriuretic peptide (NT-proBNP), and WHO/New York Heart Association functional class. Health-related quality of life measures will also be measured, as well as heart rate recovery time following completion of 6-Minute Walk Test.
- Subjects who experience a clinical worsening event or are on study drug at the conclusion of the study will be eligible to enter the open-label, extension study (ADVANCE Extension).

KEY INCLUSION CRITERIA

- Male or female at least 18 years of age with primary diagnosis of symptomatic WHO Group 1 PH.
- Right heart catheterization (RHC) performed at or within 3 years of Screening that is consistent with the diagnosis of PAH, meeting all of the following criteria: 1) mean pulmonary arterial pressure (mPAP) ≥20 mmHg (at rest), 2) pulmonary capillary wedge pressure (PAWP) of ≤15 mmHg, and 3) pulmonary vascular resistance (PVR) ≥3.00 Wood units or ≥240 dynes/sec/cm^5.
- If on PAH-specific background therapy, subject is on stable therapy with either an endothelin receptor agonist (ERA) and/or a PDE5 inhibitor (PDE5-I) or a soluble guanylate cyclase (sGC) stimulator. Subjects may be naïve to PAH-specific treatment; however, subjects will still have access to locally available standard of care treatment in accordance with national guidelines.
- Has a 6MWD of ≥150 meters.

Figure 4. Dose Titration Scheme for ADVANCE Outcomes Study



A Study Evaluating the Long-term Efficacy and Safety of Ralinepag in Subjects with PAH via an Open-label Extension

ADVANCE™ extension

STUDY OBJECTIVE – ROR-PH-303

- The purpose of the ADVANCE Extension study is to evaluate the long-term safety and tolerability of ralinepag for subjects from ADVANCE Outcomes, ADVANCE Capacity, and ADVANCE Endurance.

ADVANCE™ capacity

A Study Evaluating the Efficacy and Safety of Ralinepag to Improve Exercise Capacity in PAH Patients

STUDY OBJECTIVE – ROR-PH-302

- The purpose of the ADVANCE Capacity study is to evaluate the effects of ralinepag therapy added to PAH therapy on exercise capacity derived from cardiopulmonary exercise testing (CPET).

STUDY DESIGN

- ADVANCE Capacity is a Phase 3, multicenter, randomized double-blind, placebo-controlled study that includes a 16-week Titration Period (Figure 5) and a 12-week Optimal-dosing Period. Approximately 135 PAH subjects to be enrolled to receive ralinepag or placebo, in addition to their standard of care/PAH-specific background therapy.
- The primary efficacy endpoint is the change from Baseline in peak VO_2 after 28 weeks of treatment.
- Extensive CPET training and rigorous CPET quality control throughout; all CPET assessments analyzed by a core lab.

ADVANCE™ endurance

A Study Evaluating the Efficacy and Safety of Ralinepag to Improve Exercise Endurance in PAH Patients

STUDY OBJECTIVE – ROR-PH-304

- The purpose of the ADVANCE Endurance study is to evaluate the effects of ralinepag added to PAH therapy on exercise endurance as assessed by 6MWD.

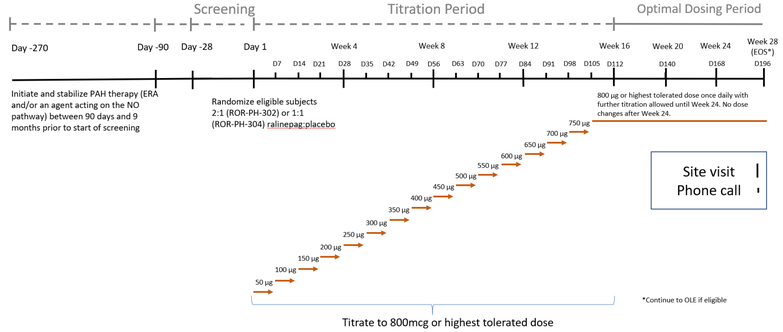
STUDY DESIGN

- ADVANCE Endurance is a Phase 3, multicenter, randomized double-blind, placebo controlled study that includes a 16-week Titration Period (Figure 5) and a 12-week Optimal-dosing Period. Approximately 300 PAH subjects to be enrolled to receive ralinepag or placebo, in addition to their standard of care or PAH-specific background therapy.
- The primary efficacy endpoint is the change from Baseline in 6MWD after 28 weeks of treatment.

KEY INCLUSION/EXCLUSION CRITERIA – ROR-PH-302 and ROR-PH-304

- Male or female subjects aged 18 to 70 years with WHO Group 1 PH; initiated PAH disease-specific therapy within 9 months of Screening, and on stable dose for at least 90 days prior to Screening.
- RHC performed at Screening consistent with PAH including the specific hemodynamic values listed for ROR-PH-301.
- **ROR-PH-302 only:** 6MWD of ≥150 meters at Screening, VE/VCO_2 output slope ≥38 during the Screening/Baseline CPET, and a peak VO_2 of ≥10 to <18 mL/kg/min.
- **ROR-PH-304 only:** 6MWD of ≥150 meters and <450 meters at Screening.

Figure 5. Dose Titration Scheme for ADVANCE Capacity and ADVANCE Endurance Studies



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