A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Ralinepag to Improve Treatment Outcomes in Subjects with Pulmonary Arterial Hypertension (ADVANCE Outcomes)

Richard Channick, MD[1]; Marc Humbert, MD, PhD[2]; CQ Deng, MD, PhD[3]; Miluska Escudero, BS[3]; Rob Grover, FRCA[3]; Derek Solum, PhD[3]; Vallerie McLaughlin, MD[4]

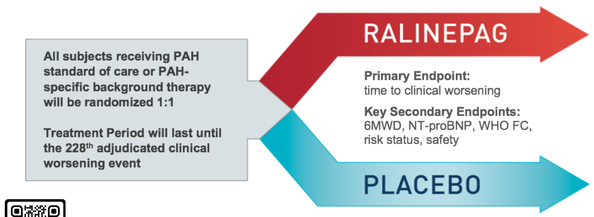
[1]UCLA School of Medicine, Los Angeles, CA, USA; [2]South Paris University, Clamart, France; [3]United Therapeutics Corporation, RTP, NC, USA;. [4]University of Michigan, Ann Arbor, MI, USA

INTRODUCTION

- There are 5 World Health Organization (WHO) categories of pulmonary hypertension (PH). Pulmonary arterial hypertension (PAH; WHO Group 1 PH) is a rare, progressive disease characterized by elevated pulmonary vascular resistance (PVR) that leads to right ventricular failure and premature death. Despite several available treatments for PAH, the functional limitation and survival of patients remains unsatisfactory. The median survival of patients with idiopathic PAH is approximately 2.8 years without effective treatment[1].
- Ralinepag is a novel, next-generation, once-daily, oral, potent, and selective prostacyclin (IP) receptor agonist in development to treat WHO Group 1 PH. Ralinepag demonstrates a longer half-life than selexipag and is more potent and efficacious than selexipag at increasing cellular cyclic adenosine monophosphate (cAMP) levels[2,3,4]. Given its prolonged half-life allowing for convenience in dosing and potency at inducing cAMP production, ralinepag may be an attractive oral alternative to the currently available prostacyclin analogues and non-prostanoid IP receptor agonists for the treatment of PAH.

STUDY OBJECTIVES

- The primary objective of the study is to assess the effect of ralinepag on time to first adjudicated clinical worsening event, a composite endpoint that includes death, hospitalization due to worsening of PAH, initiation of an inhaled/infused prostacyclin, disease progression, or unsatisfactory long-term response.
- Additional key assessments include changes from Baseline to Week 28 in plasma N-terminal pro-brain natriuretic peptide (NT-proBNP), 6-minute walk distance (6MWD), WHO/New York Heart Association (NYHA) Functional Class, and health-related quality of life measures. Subject safety will be evaluated throughout the study by capturing adverse events, hospitalizations, clinical laboratory, and electrocardiogram (ECG) parameters.
- Subjects who experience a clinical worsening event or are participating at the time of study closure will be eligible to enter an open-label extension study (ROR-PH-303 [NCT03683186]).



SCAN ME

METHODS

Study Design

- In this event-driven study, approximately 700 PAH subjects are randomly assigned (1:1) to receive ralinepag or placebo together with their standard of care/PAH-specific background oral therapy. Background oral PAH therapies (regimen and doses) must remain stable throughout the study.
- Dosing is individualized and titrated based on tolerability and clinical response.
- An independent Clinical Endpoint Committee (CEC) adjudicates all protocol-defined clinical worsening events in a blinded fashion throughout the study. The CEC is composed of clinicians who are not study investigators.
- The study includes a Screening Period of up to 28 days, a 16-week Titration Period, and an Optimal-dosing Period of variable duration, depending upon the occurrence of clinical worsening events and the overall duration of the study.
- Subjects return for study visits every 4 weeks during the Titration Period, and every 12 weeks thereafter.
- Efficacy and safety assessments will be performed at every visit until a total of 228 confirmed protocol-defined clinical worsening events have occurred.

RESULTS (Data presented through March 31, 2022)

- Enrollment is ongoing at approximately 200 sites in 33 countries following implementation of risk mitigation steps related to the COVID-19 pandemic (Figure 1).
- The data cut for this analysis includes 324 subjects randomized in approximately 30 different countries; 68% of participants have completed 28 weeks of treatment.
- Most subjects were female (79.9%) with a median age of 48.0 years, were receiving dual background therapy (82.4%), and were classified as Functional Class II (64.5%) (Table 1). Etiology presented in Figure 2.
- Subjects on study have averaged 357 days of ralinepag dosing (Table 2).
- Overall, 66 clinical worsening events have been reported at the time of the data cut. Of these, 46 subjects have elected to continue treatment in the open-label extension study (ADVANCE Extension) (Table 2).
- A total of 302 (93.2%) of subjects have experienced one or more adverse events (AEs) during the study and 12 (3.7%) subjects have experienced a serious AE. Overall, 7 (2.2%) subjects have died during the study. The most common AEs (>15% subjects) are headache, diarrhea, nausea, pain in jaw, myalgia, vomiting, and pain in extremity (Table 3).
- An independent Data Monitoring Committee reviewed safety data and recommended study continuation without modification.

RESULTS (CONTINUED)

Figure 1. Enrollment Map

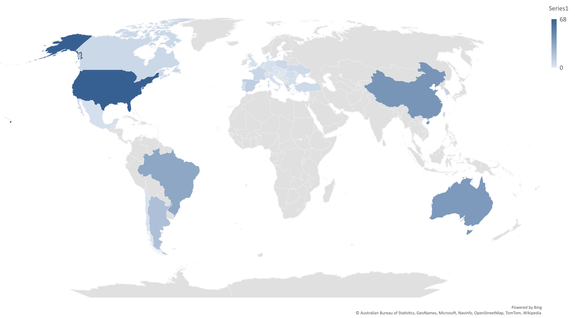


Table 1. Baseline Demographics*

Age at Study Entry (years), median (range)	48.0 (18, 83)
Female/Male	259/65
Time Since Diagnosis (years), mean (SD)	4.561 (5.716)
Ethnicity, n (%)	
Hispanic or Latino	70 (21.6%)
Not Hispanic or Latino	224 (69.1%)
Race, n (%)	
White	232 (71.6%)
Black	8 (2.5%)
Native Hawaiian/Pacific Islander	1 (0.3%)
Asian	70 (21.6%)
Multiple	2 (0.6%)
Other	6 (1.9%)
Not Reported	5 (1.5%)
Weight (kg), mean (SD)	70.59 (17.19)
Subjects Receiving Monotherapy, n (%)	44 (13.6%)
Subjects Receiving Dual Therapy, n (%)	267 (82.4%)
6MWD (m), mean (SD)	448.01 (106.18)
WHO Functional Class, n (%)	
I	0 (0%)
II	209 (64.5%)
III	115 (35.5%)
IV	0 (0%)
NT-proBNP (pg/mL), mean (SD)	789.9 (1575.1)
PVR (dynes/sec/cm^5), mean (SD)	744.3 (391.8)
mPAP (mmHg), mean (SD)	48.7 (14.1)
PCWP (mmHg), mean (SD)	9.4 (3.3)
Cardiac Output (L/min), mean (SD)	4.71 (1.40)
Percent Predicted TLC (%), mean (SD)	93.9 (14.0)
Percent Predicted FEV$_1$ (%), mean (SD)	84.6 (15.0)

Abbreviations: 6MWD, 6-minute walk distance; FEV1, forced expiratory volume in 1 sec; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; TLC, total lung capacity; WHO, World Health Organization

RESULTS (CONTINUED)

Figure 2. Etiology of PAH (n =324)

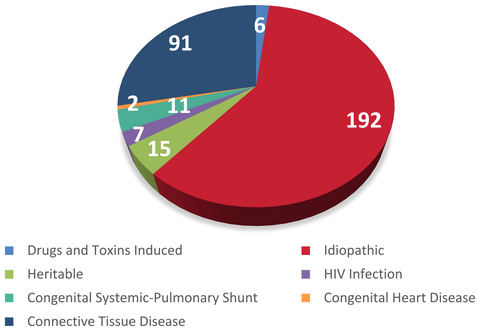


Table 2. Drug Exposure and Clinical Worsening Events*

Number of Days Dosed, mean (SD)	357.3 (257.9)
Dose (mcg) at End of Titration Period (Week 16), mean (SD)	544.2 (282.1)
Subjects with Clinical Worsening (All Events)	66
Subjects Transitioned to Open-Label Extension Study	46

Table 3. Treatment Emergent Adverse Events by Subject*

One or More Adverse Events, n (%)	302 (93.2%)
One or More Serious Adverse Events, n (%)	12 (3.7%)
Died During the Study, n (%)	7 (2.2%)

*** = Results for this ongoing placebo-controlledblinded study are presented for subjects overall.**

CONCLUSIONS

- ADVANCE Outcomes will assess whether ralinepag can improve function, delay disease progression, and prolong survival in subjects with PAH.

REFERENCES

1. McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol. 2009;53(17):1573-1619.
2. Bruderer S, Hurst N, Kaufmann P, et al. Multiple-dose up-titration study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of selexipag, an orally available selective prostacyclin receptor agonist, in healthy subjects. Pharmacology. 2014;94(3 4):148-156.
3. Kaufmann P, Okubo K, Bruderer S, et al. Pharmacokinetics and tolerability of the novel oral prostacyclin IP receptor agonist selexipag. Am J Cardiovasc Drugs. 2015;15(3):195-203.
4. Preston I, Morgan M, Raether B, et al. Safety and pharmacokinetics of ralinepag (APD811), a next-generation, selective prostacyclin receptor agonist, in healthy adult subjects. Poster presented at American Thoracic Society Conference; May 19-24, 2017; Washington, DC.

Presented at ATS 2022 International Conference | May 13-18, 2022 | San Francisco, CA | #6941
Disclosure: This study is sponsored by United Therapeutics Corporation.

United Therapeutics CORPORATION