PULSAR: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Sotatercept (ACE-011) When Added to Standard of Care for the Treatment of Pulmonary Arterial Hypertension (PAH)

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Background

- Pulmonary arterial hypertension (PAH) is characterized by abnormally high mean pulmonary arterial pressures and remodeling of the pulmonary vasculature culminating in progressive right ventricular dysfunction[1–4]
- Current disease-specific treatments for PAH include endothelin-receptor antagonists (ERAs), phosphodiesterase (PDE5) inhibitors, and prostanoids and are used with general supportive care agents (e.g., anticoagulants, diuretics, digoxin)
- Therapies that attenuate the development and progression of PAH are needed
- Mutations in bone morphogenetic protein receptor 2 (BMPR2) underlie many heritable cases of PAH[5,6]; however, the relevance of the BMPR2 pathway extends far beyond familial PAH[7]
- Disruptions in transforming growth-factor (TGF)-β and BMP signaling are associated with the development of PAH[8,9]

SOTATERCEPT

- Sotatercept (ACE-011) is a first-in-class human fusion protein consisting of the extracellular domain of the activin receptor IIA (ActRIIA) linked to the Fc domain of human IgG1
- Sotatercept works by binding specific TGF-β superfamily ligands such as activin A and B and growth differentiation factor (GDF) 11 to suppress TGF-β signaling and rebalance BMPR2 signaling[10-12]
- In preclinical rodent models of developing and established PAH, sotatercept has demonstrated preventive effects as well as improved outcomes related to pulmonary vascular remodeling and right heart failure[11,12]

Objective

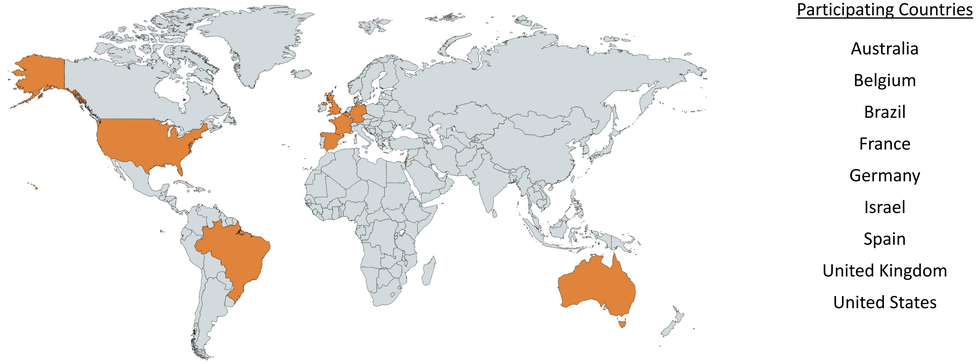
- To determine the efficacy and safety of sotatercept (ACE-011) plus standard of care (SOC)* versus placebo plus SOC in adults with PAH (World Health Organization [WHO] Group 1).

*SOC refers to approved PAH-specific medications and may have included mono- or combination therapy with an ERA, PDE5 inhibitor, soluble guanylate cyclase stimulator, and/or a prostacyclin analogue or receptor agonist.

STUDY POPULATION

One hundred participants with WHO Group 1 PAH (Functional Class II–III) at clinical sites in 9 countries **(Figure 1)**.

Study Design



Participating Countries

Australia
Belgium
Brazil
France
Germany
Israel
Spain
United Kingdom
United States

Figure 1. Countries Participating in the PULSAR Clinical Trial

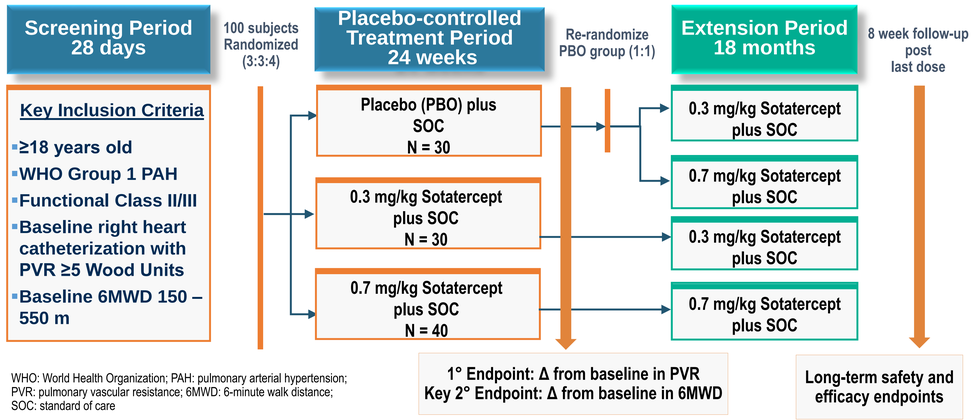


Figure 2. PULSAR Clinical Trial Design

TREATMENT PERIOD

This ongoing, Phase 2, randomized, double-blind, placebo-controlled, parallel-group study is comprised of 3 periods **(Fig. 2)**:

– Screening period (up to 28 days)
– Treatment period
  Placebo-controlled Treatment Period (24 weeks)
  Extension Period (18 months)
– Post-treatment Follow-up Period (8 weeks)

Subjects will be randomly allocated (3:3:4 ratio) to one of the 3 treatment groups:

Arm 1: Placebo subcutaneously (SC) every 21 days plus SOC
Arm 2: Sotatercept (0.3 mg/kg) SC every 21 days plus SOC
Arm 3: Sotatercept (0.7 mg/kg) SC every 21 days plus SOC

EXTENSION PERIOD

Participants who have not discontinued early from the Placebo-controlled Treatment Period can directly rollover into the 18-month Extension Period and be treated as follows **(Figure 2)**:

– Participants initially randomized to placebo will be re-randomized to receive sotatercept (0.3 mg/kg or 0.7 mg/kg) SC every 21 days plus SOC

– Participants initially randomized to sotatercept will continue on their current dose level, administered SC every 21 days, plus SOC

Study Endpoints

PRIMARY

- Change from baseline in pulmonary vascular resistance (PVR)

KEY SECONDARY

- Change from baseline in 6-minute walk distance

OTHER SECONDARY AND EXPLORATORY:

- Safety and tolerability of sotatercept based on adverse events and changes in clinical laboratory parameters
- Change from baseline in N-terminal prohormone of brain natriuretic peptide (NT-proBNP), TGF-β ligands, and other PAH-related biomarkers
- Change from baseline in echocardiographic parameters, including tricuspid annular plane systolic excursion (TAPSE)
- Clinical worsening (e.g., hospitalizations, change in WHO functional class)
- Change from baseline in quality of life
- Population pharmacokinetic parameters of sotatercept
- Correlation of clinical efficacy with BMPR2 expression and sex hormone metabolite levels

Study Status

- Enrollment began in June 2018 was completed June 2019
- Primary analysis results expected first quarter of 2020
- Study completion expected second half of 2021
- ClinicalTrials.gov Identifier: NCT03496207
- EudraCT Number: 2017-004738-27

References

1. Rubin LJ. N Engl J Med 1997;336:111-7.
2. Simonneau G, Galiè N, Rubin LJ, et al.. J Am Coll Cardiol 2004;43:5S-12S.
3. Schermuly RT, Ghofrani HA, Wilkins MR, et al.. Nat Rev Cardiol 2011;8:443-55.
4. Vonk-Noordegraaf A, Haddad F, Chin KM, et al. J Am Coll Cardiol 2013;62:D22-33.
5. Lane KB, Machado RD, Pauciulo MW, et al. Nat Genet 2000;26(1): 81-4.
6. Deng Z, Haghighi F, Helleby L, et al. Am J Respir Crit Care Med. 2000;161(3 Pt1): 1055-9
7. Atkinson C, Stewart S, Upton PD, et al. Circulation 2002 Apr 9; 105(14):1672-8.
8. Morrell NW. Proc Am Thorac Soc 2006;3:680-6.
9. Machado RD, Aldred MA, James V, et al. Hum Mutat 2006;27:121-32.
10. Yung LM, Yang P, Bocobo G, et al.. Am J Respir Crit Care Med 2018;197:A7399.
11. Yung LM, Pearsall RS, Bocobo G, et al.. Circulation. 2018;136:A18906.
12. Yung LM, Yang P, Bocobo G, et al.. Circulation. 2018;138:A17217.

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