Sotatercept Phase 3 program design and rationale: A novel treatment for pulmonary arterial hypertension

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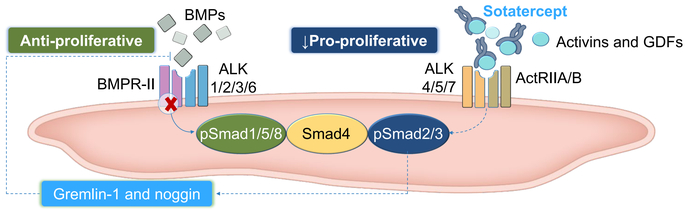
Introduction

Pulmonary arterial hypertension and sotatercept

- Pulmonary arterial hypertension (PAH) is characterized by pulmonary vascular remodeling, resulting in increased pulmonary artery pressure and progressive right ventricular dysfunction[1,2]
- Sotatercept acts as a reverse-remodeling agent proposed to rebalance the anti-proliferative (BMPR-II mediated) and pro-proliferative (ActRIIA-mediated) signaling (Figure 1)[2–6]
  - In pre-clinical models of PAH, sotatercept reversed pulmonary arterial wall and right ventricular remodeling[3]

Figure 1. Proposed mechanism of action of sotatercept



Sotatercept clinical development program in PAH

- The clinical efficacy and safety of sotatercept on top of background PAH therapy is being studied across an extensive clinical trial program[7–12]
  - The Phase 2 PULSAR and SPECTRA studies are currently ongoing[7,8]
  - In the placebo-controlled treatment period of the PULSAR study[2]:
    - Sotatercept improved pulmonary vascular resistance (PVR), 6-minute walk distance (6MWD), and NT-proBNP levels when added to background PAH therapy; mean pulmonary arterial pressure (mPAP) was also improved
    - Sotatercept was generally well tolerated with a safety profile consistent with that observed in other patient populations
  - Positive results from the Phase 2 studies have led to the initiation of a Phase 3 clinical development program comprised of four studies (STELLAR, HYPERION, ZENITH and SOTERIA) to further investigate the efficacy and safety of sotatercept on top of background therapy across the spectrum of PAH[9–12]

Sotatercept PAH Phase 3 clinical development program

- STELLAR, HYPERION and ZENITH are randomized, double-blind, placebo-controlled, Phase 3 studies evaluating the safety and efficacy of sotatercept on top of background PAH therapy in broad PAH populations (Table 1, Figure 2)[9–11]
- Participants transitioning from Phase 2 or 3 parent sotatercept clinical studies[7–11] will be further evaluated for long-term safety and tolerability in SOTERIA[12]

Sotatercept PAH Phase 3 clinical development program

Table 1. Overview of sotatercept PAH Phase 3 clinical development studies

	STELLAR	HYPERION	ZENITH
	NCT04576988	NCT04811092	NCT04896008
Study population	• N ≈ 284 • WHO FC II or III • Background PAH therapy (mono, double, or triple)	• N ≈ up to 662 • WHO FC II or III • Newly diagnosed as intermediate- or high-risk within 6 months of study screening (REVEAL Lite 2 risk score ≥6) • Background double or triple combination PAH therapy	• N ≈ up to 166 • WHO FC III or IV • High-risk (REVEAL Lite 2 risk score ≥10) • Background double or triple combination of PAH therapies
Primary endpoint	• Change from baseline in 6MWD at Week 24	• Time to clinical worsening (first confirmed morbidity event or death)	• Time to first event of all-cause death, lung transplant or PAH worsening relating to hospitalization
Select secondary endpoints	• Multicomponent improvement (Figure 3) • Change from baseline in PVR at Week 24 • Change from baseline in select PAH-SYMPACT® domain scores at Week 24 • Time to death or first occurrence of a clinical worsening event	• Multicomponent improvement (Figure 3) • Proportion of participants who achieve a low REVEAL Lite 2 risk score at Week 24 versus baseline • Proportion of participants who maintain or achieve a low- risk score using the simplified French Risk score calculator at Week 24 versus baseline	• Overall survival • Transplant-free survival • Proportion of participants who experience a mortality event • Change from baseline to Week 24 in REVEAL Lite 2 risk score

Figure 2. Study designs for (a) STELLAR, and (b) HYPERION and ZENITH

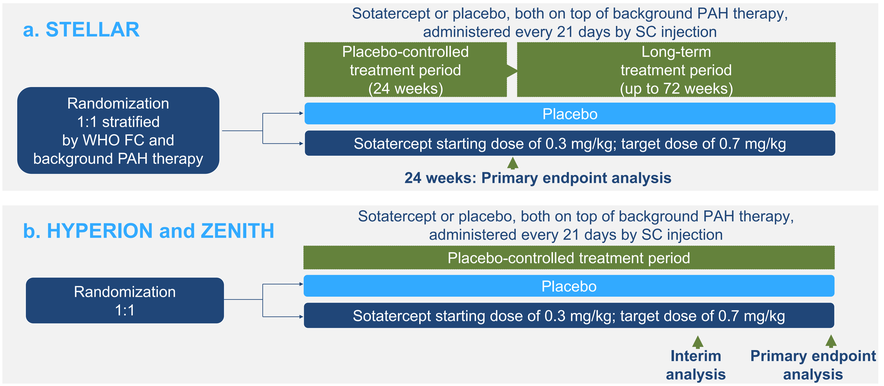
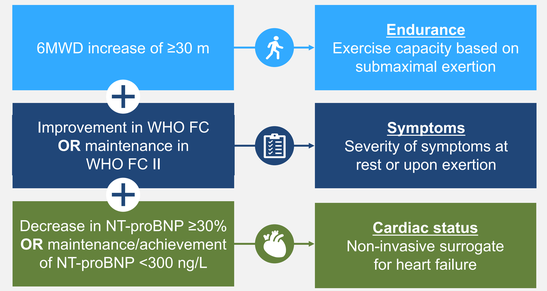


Figure 3. Multicomponent improvement



Key takeaways

- The STELLAR, HYPERION, ZENITH and SOTERIA studies are active
- The robust Phase 3 clinical program aims to further characterize the efficacy and safety of sotatercept across a broad spectrum of participants with PAH and establish its potential value in this patient population

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Sotatercept is an investigational drug that is not approved for any use in any country. The safety and efficacy of sotatercept have not been established.

Abbreviations: 6MWD: 6-minute walk distance; ActRIIA/B: activin receptor type 2A/B; ALK: activin receptor-like kinase; BMP: bone morphogenetic protein; BMPR-II: bone morphogenetic protein receptor type 2; FC: functional class; GDF: growth differentiation factor; mPAP: mean pulmonary arterial pressure; NT-proBNP: N-terminal pro–B-type natriuretic peptide; PAH: pulmonary arterial hypertension; PAH-SYMPACT®: Pulmonary Arterial Hypertension-symptoms and impact questionnaire; pSmad: phosphorylated Smad; PVR: pulmonary vascular resistance; REVEAL: Registry to Evaluate Early and Long-term PAH Disease Management; SC: subcutaneous; WHO: World Health Organization.

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