ATS 2021 Welcome

PULSAR study open-label extension: Interim results from a Phase 2 study of the efficacy and safety of sotatercept when added to standard of care for the treatment of pulmonary arterial hypertension (PAH)

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Disclosure to learners

Financial relationships with relevant companies within the past 24 months:

Company name: Acceleron
Type of relationship: Research support/Consultant

Company name: Actelion/Johnson & Johnson
Type of relationship: Research support/Consultant

Company name: Altavant
Type of relationship: Research support

Company name: Arena/United Therapeutics/Lung LLC
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Company name: Reata
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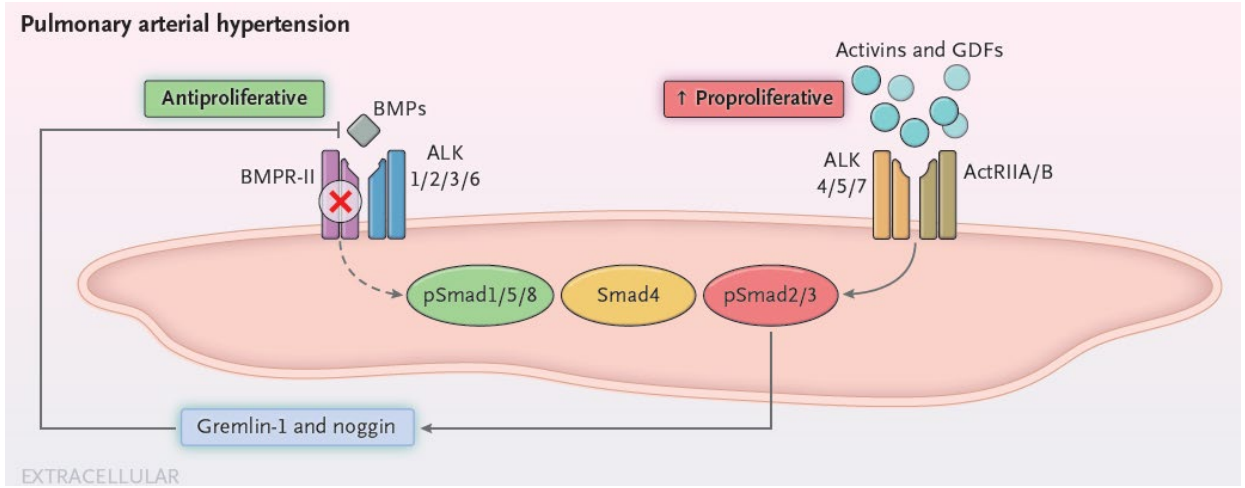
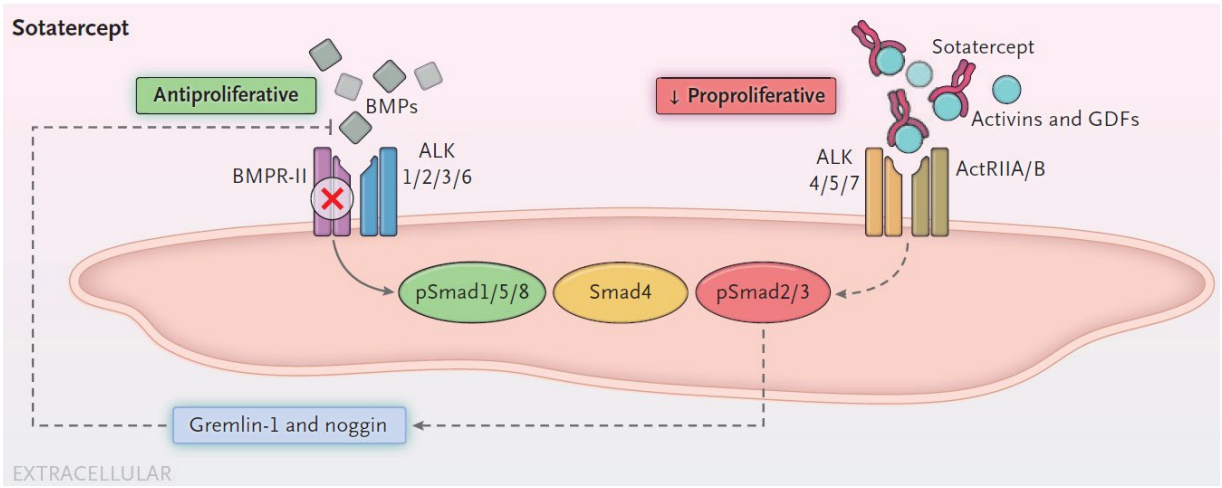
Company name: Respira
Type of relationship: Consultant

Company name: Johnson & Johnson
Type of relationship: Holds common stock

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]



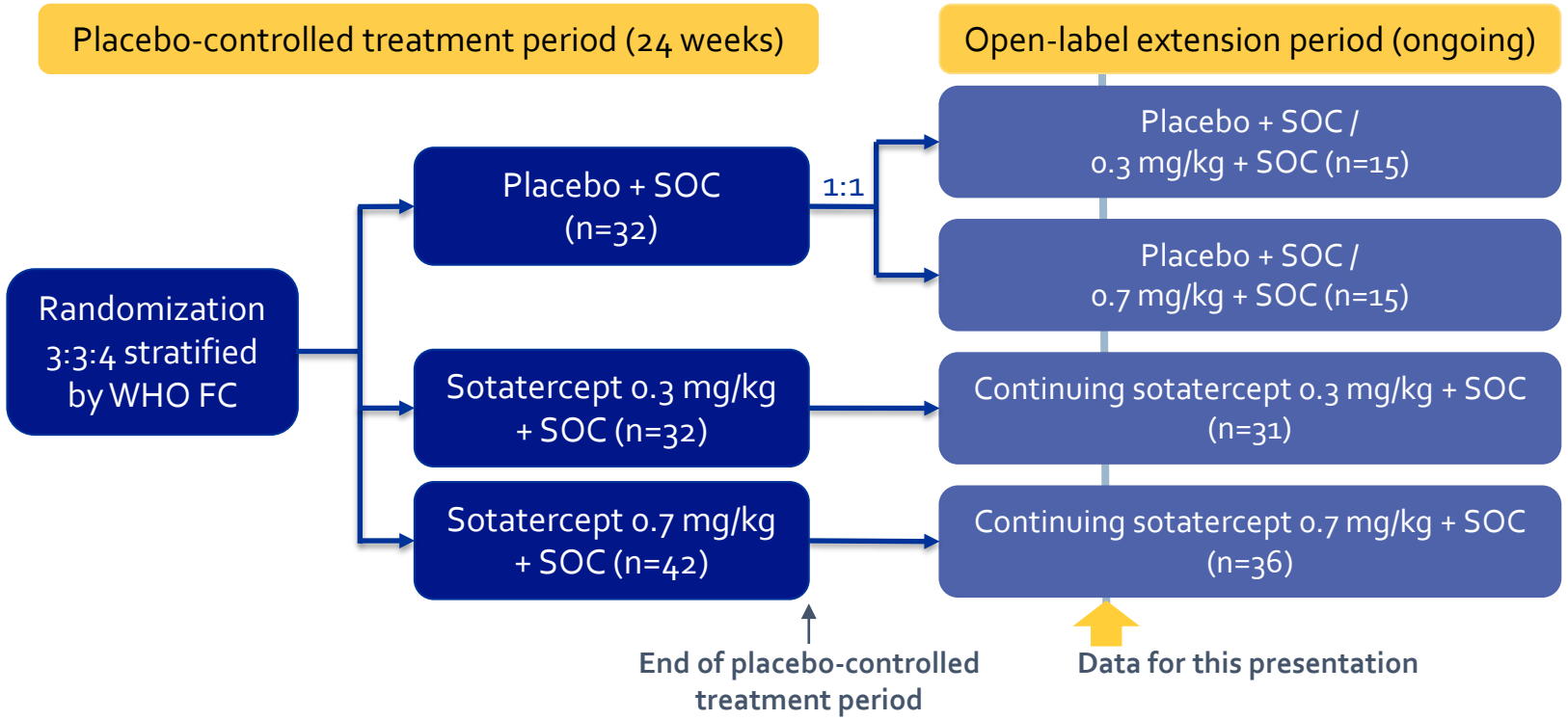


- Sotatercept is a first-in-class selective ligand trap proposed to rebalance pro- (ActRIIA-mediated) and anti- (BMPR-II-mediated) proliferative signaling, thereby having the potential to reverse the characteristic vascular remodeling that underlies PAH pathology[2–4]

Sotatercept is an investigational product that is not approved for any use in any country.
ActRIIA/B: activin receptor type 2A/B; ALK: activin receptor-like kinase; BMP: bone morphogenetic protein; BMPR-II: bone morphogenetic protein receptor type 2; GDF: growth differentiation factor; PAH: pulmonary arterial hypertension; pSmad; phosphorylated Smad.
1. Lai YC *et al. Circ Res.* 2014; 115: 115–30; 2. Humbert M, *et al. N Engl J Med.* 2021; 384: 1204–15; 3. Cappellini MD, *et al. Haematologica.* 2019; 104: 477–84; 4. Yung L-M, *et al. Sci Transl Med.* 2020; 12: eaaz5660.

PULSAR: Study design

- A Phase 2, randomized, double-blind, placebo-controlled study to compare the safety and efficacy of sotatercept versus placebo when added to standard of care (SOC) for the treatment of PAH in 106 patients at 43 sites across eight countries



Primary endpoint

Change from baseline to week 24 in PVR

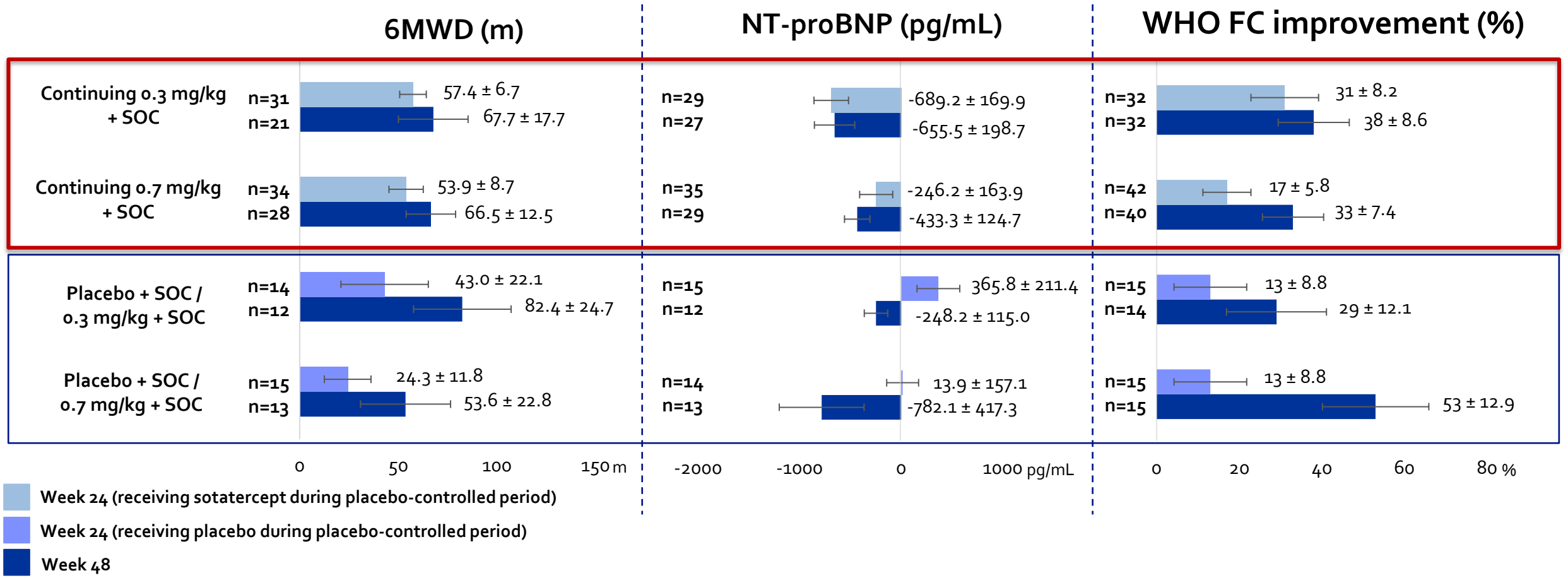
Select secondary endpoints

Change from baseline to week 24 in 6MWD, NT-proBNP, and WHO FC

6MWD: 6-minute walk distance; FC: functional class; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; SOC: standard of care; WHO: World Health Organization.

1. Humbert M, *et al. N Engl J Med*. 2021; 384: 1204–15.

PULSAR: Change from baseline at week 24 and change from baseline at week 48



Interim extension analysis data cut-off date: 14 September 2020.
Data presented as mean ± SE change from baseline for 6MWD and NT-proBNP; percentage of patients ± SE who improved by ≥1 WHO FC; not all data for in-person assessments (6MWD, NT-proBNP) were available due to COVID-19 delays and missing visits.
Per the statistical methods for calculating WHO FC, missing data for reasons other than COVID-19 are recorded as non-responders and therefore the overall n is different for WHO FC.
6MWD: 6-minute walk distance; FC: functional class; NT-proBNP: N-terminal pro-brain natriuretic peptide; SE: standard error; SOC: standard of care; WHO: World Health Organization.

PULSAR: Overall safety experience including open-label extension

- As of the interim data cut, 103/106 (97%) patients reported treatment-emergent adverse events (TEAEs)
- Serious TEAEs occurred in 30/106 (28%) patients
- Overall, 9/106 (9%) patients had TEAEs that led to study discontinuation; 2/106 (2%) died (cardiac arrest, brain abscess) and deaths were not considered related to study drug by the investigators
- The safety profile of sotatercept was consistent with the placebo-controlled treatment period

TEAEs during the OLE period only, n (%)	Continuing 0.3 mg/kg + SOC (n=31)	Continuing 0.7 mg/kg + SOC (n=36)	Placebo + SOC / 0.3 mg/kg + SOC (n=15)	Placebo + SOC / 0.7 mg/kg + SOC (n=15)
TEAEs	29 (94)	33 (92)	13 (87)	15 (100)
TEAEs of special interest*	1 (3)	2 (6)	5 (33)	0 (0)
Serious TEAEs	8 (26)	4 (11)	4 (27)	2 (13)
Serious related TEAEs	1 (3)	0 (0)	1 (7)	0 (0)
TEAEs leading to treatment discontinuation	1 (3)	0 (0)	0 (0)	0 (0)
TEAEs leading to study discontinuation	1 (3)	1 (3)	0 (0)	0 (0)
TEAEs leading to death	0 (0)	1 (3)	0 (0)	0 (0)

Interim extension analysis data cut-off date: 14 September 2020.
*TEAEs of special interest defined as any adverse event of leukopenia, neutropenia, or thrombocytopenia.
OLE: open-label extension; SOC: standard of care; TEAE: treatment-emergent adverse event.

Conclusions

- In this first interim report from the open-label extension period of PULSAR, clinical efficacy was maintained or enhanced with sotatercept treatment across multiple study endpoints for up to 48 weeks
- Improvements observed in patients re-randomized from the placebo group to sotatercept treatment align with the initial results from the placebo-controlled treatment period
- Safety findings were consistent with previous reports in PAH and other patient populations
- Final data from the open-label extension period are forthcoming and sotatercept will be further evaluated in a Phase 3 program[1–3]
  - The randomized, double-blind, placebo-controlled STELLAR study is currently recruiting (NCT04576988) and the HYPERION study in newly diagnosed intermediate- and high-risk patients with PAH is now active (NCT04811092)

PAH: pulmonary arterial hypertension.

1. ClinicalTrials.gov. A study of sotatercept for the treatment of pulmonary arterial hypertension (STELLAR). https://clinicaltrials.gov/ct2/show/NCT04576988 [Accessed 24 March 2021]; 2. ClinicalTrials.gov. A long-term follow-up study of sotatercept for PAH treatment (SOTERIA). https://clinicaltrials.gov/ct2/show/NCT04796337 [Accessed 24 March 2021]; 3. ClinicalTrials.gov. Study of sotatercept in newly diagnosed intermediate- and high-risk PAH patients (HYPERION). https://clinicaltrials.gov/ct2/show/NCT04811092 [Accessed 24 March 2021].

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