ATS 2021 Welcome

The SPECTRA study: A Phase 2a single-arm, open-label, multicenter exploratory study to assess the effects of sotatercept for the treatment of pulmonary arterial hypertension (PAH)

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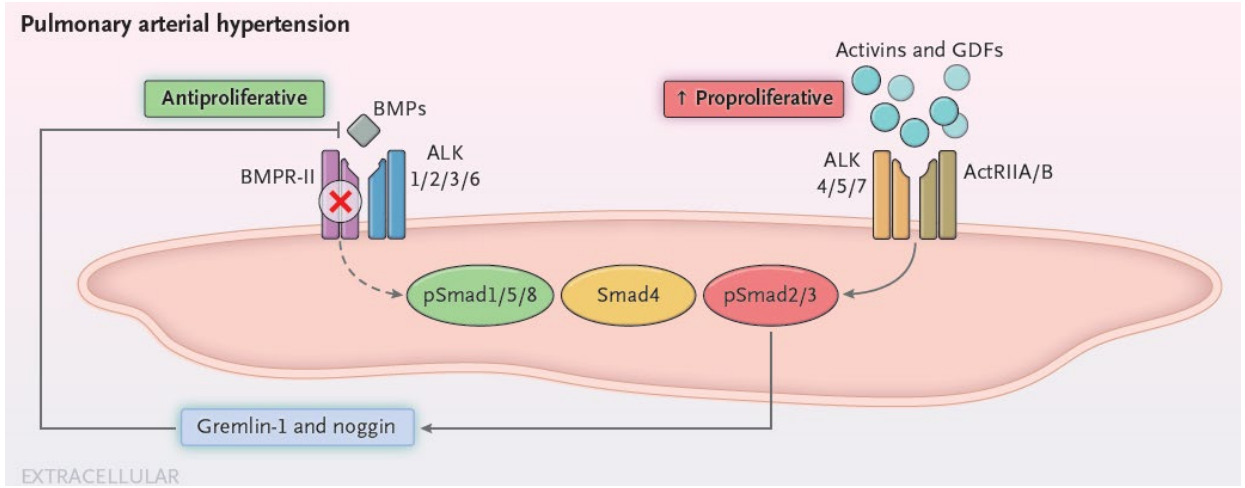
Disclosure to learners

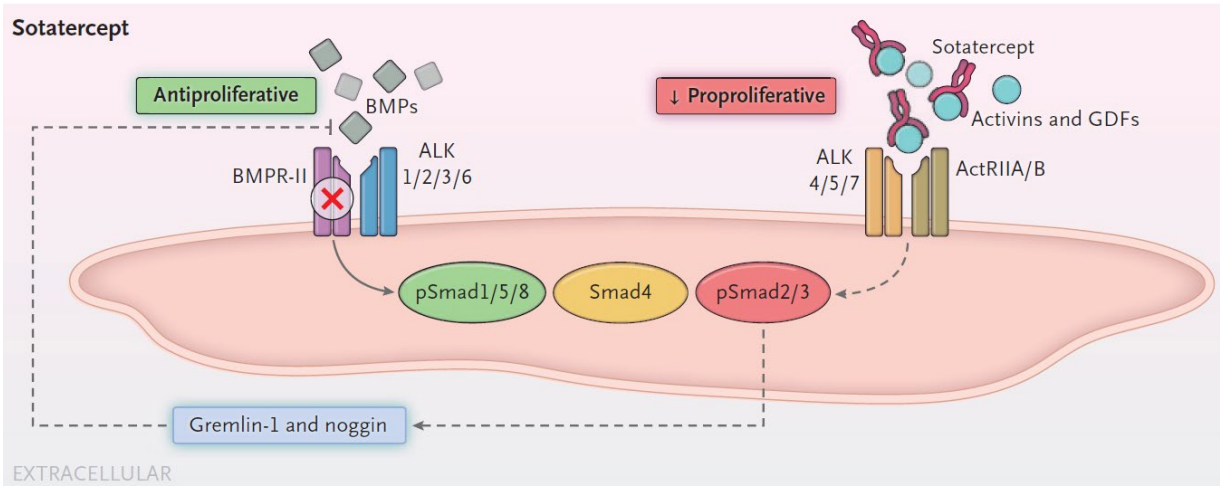
Financial relationships with relevant companies within the past 24 months:

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

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]

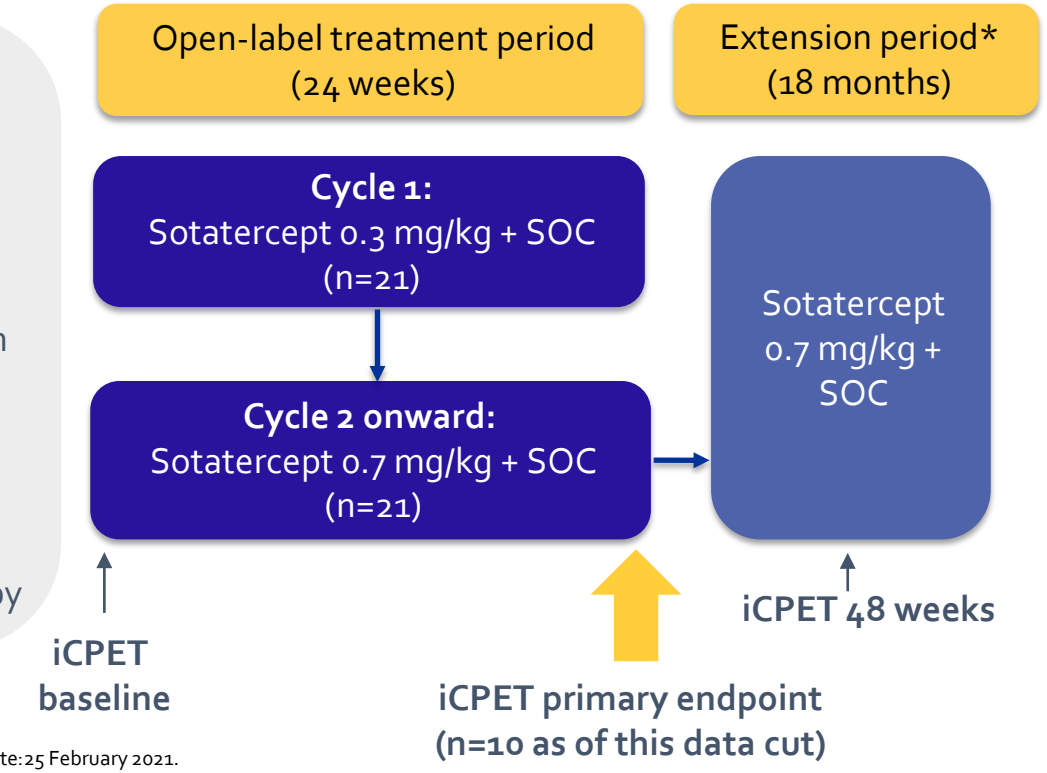
Sotatercept is an investigational product that is not approved for any use in any country.
ActRIIA/B: activin receptor type 2A/B; ALK: activin receptor-like kinase; BMP: bone morphogenetic protein; BMPR-II: bone morphogenetic protein receptor type 2; GDF: growth differentiation factor; PAH: pulmonary 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.

SPECTRA: Study design

- A Phase 2a single-arm, open-label, multicenter exploratory study to assess the effects of sotatercept for the treatment of PAH in 21 patients at four sites across the USA

Inclusion criteria

- WHO PH Group I (PAH)
- WHO Functional Class III
- Right heart catheterization with PVR ≥4 Wood units
- 6-minute walk distance (6MWD) 100–550 m
- Stable combination PAH therapy



Primary endpoint

- Change from baseline to week 24 in peak oxygen uptake (VO_2 max)

Select secondary endpoints

- Change from baseline to week 24 in exercise measures, including:
  - V_E/VCO_2 slope, Ca-vO_2, workload, mPAP, mRAP, PAWP, and cardiac output
- Change from baseline to week 24 in 6MWD

Enrollment closed on 31 January 2021. Interim analysis data cut-off date: 25 February 2021.
*Extension period followed by 8-week post-treatment follow-up.
6MWD: 6-minute walk distance; Ca-vO2: arteriovenous O2 content difference; iCPET: invasive cardiopulmonary exercise testing; mPAP: mean pulmonary arterial pressure; mRAP: mean right atrial pressure; PAH: pulmonary arterial hypertension; PAWP: pulmonary arterial wedge pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; SOC: standard of care; V_E/VCO_2: ventilatory efficiency; VO2: peak oxygen uptake; WHO: World Health Organization.

SPECTRA: Baseline characteristics

	Total patients enrolled n=21	Evaluable patients at week 24 n=10
Female, n (%)	17 (81)	6 (60)
Age, median (range), years	44 (21–70)	45 (25–66)
Time since diagnosis, median (range), years	4.9* (0.6–15.0)	3.2 (0.6–13.1)
PAH classification, n (%)		
Idiopathic	13 (62)	5 (50)
Heritable	1 (5)	1 (10)
Associated with connective-tissue disease	6 (29)	4 (40)
Missing	1 (5)	0 (0)
Standard-of-care PAH therapy, n (%)		
Prostacyclin infusion therapy	12 (57)	7 (70)
Double therapy	12 (57)	6 (60)
Triple therapy	9 (43)	4 (40)
6MWD, median (range), m	402 (254–525)	359 (254–506)

Interim analysis data cut-off date:25 February 2021.
*n=20; evaluable patients at week 24 defined as those with primary endpoint assessment at both baseline and week 24/early EOT before 24 weeks entered in the database.
6MWD: 6-minute walk distance; EOT: end of treatment; PAH: pulmonary arterial hypertension.

SPECTRA: Supine resting hemodynamics

- At rest, reductions were seen in mean change from baseline to week 24 in PVR and mPAP

	Supine resting		
	Baseline n=10	Week 24 n=10	Mean change at week 24 n=10
PVR, dynes-sec/cm^5	576.4 (139.2)	369.2 (121.1)	-207.3 (146.4)
mPAP, mmHg	43.4 (9.7)	30.6 (9.7)	-12.8 (7.1)
PAWP, mmHg	10.0 (4.0)	9.1 (4.8)	-0.9 (3.4)
Cardiac output, L/min	4.7 (0.7)	4.8 (1.4)	0.1 (1.4)

Interim analysis data cut-off date: 25 February 2021.
Data presented as mean (SD).
mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance.

SPECTRA: Peak exercise measures and 6-minute walk distance

- Improvements in mean change from baseline to week 24 were observed for peak oxygen uptake, ventilatory efficiency, total workload, and arteriovenous O_2 content difference
- Improvements were seen in mean change from baseline to week 24 in key peak exercise hemodynamics

	Peak exercise		
	Baseline n=10	Week 24 n=10	Mean change at week 24 n=10
VO_2 max, mL/min/kg	12.7 (3.5)	14.0 (4.4)	1.27 (2.6)
V_E/VCO_2 slope	50.7 (25.8)	41.2 (13.1)	-9.5 (15.7)
Ca-vO_2, mL/100 mL	9.7 (2.1)*	11.5 (3.2)*	1.4 (2.1)†
Workload, W	72.3 (34.0)	88.5 (37.6)	16.2 (13.0)
mPAP, mmHg	66.8 (14.3)	55.2 (14.1)	-11.6 (9.4)
mRAP, mmHg	10.9 (9.8)	4.7 (4.7)	-6.2 (8.4)
PAWP, mmHg	18.1 (23.2)^	10.7 (5.6)^	-9.7 (21.6)#
Cardiac output, L/min	9.7 (3.1)*	9.1 (2.2)	-0.5 (2.3)*

- In nine patients with available data, 6MWD improved by an average of 72.4 m (SD 87.7) from baseline to week 24

Interim analysis data cut-off date: 25 February 2021.
Data presented as mean (SD); *n=9, †n=8, ^n=7, #n=6.
6MWD: 6-minute walk distance; Ca-vO2: arteriovenous O2 content difference; mPAP: mean pulmonary arterial pressure; mRAP: mean right atrial pressure; O_2: oxygen; PAWP: pulmonary arterial wedge pressure; SD: standard deviation; VO2: oxygen consumption; V_E/VCO2: ventilatory efficiency.

SPECTRA: Safety

- As of the interim data cut, with a median follow up of 5.5 months (with up to 22 months), 16/21 (76%) patients reported treatment-emergent adverse events (TEAEs)
- Three serious TEAEs were reported (hematochezia, complication associated with central line, and fluid overload), but none were considered related to study drug and no dose interruption or reduction was required
- Sotatercept was generally well tolerated, consistent with the safety profile in other PAH studies

n (%)	n=21
TEAEs	16 (76)
Serious TEAEs	3 (14)
Serious related TEAEs	0 (0)
TEAEs of special interest*	0 (0)
TEAEs leading to treatment discontinuation	1 (5)^
TEAEs leading to death	0 (0)

Interim analysis data cut-off date:25 February 2021.
*TEAEs of special interest defined as any adverse event of fertility disorders with a focus on suppression of FSH, hepatic toxicity, cardiac events and embolic and thrombotic events, thrombocytopenia, leukopenia, and neutropenia.
^Patient discontinued due to worsening pain at Remodulin® site injection.
FSH: follicle-stimulating hormone; PAH: pulmonary arterial hypertension; TEAE: treatment emergent adverse event.

Conclusions

- In this preliminary analysis of patients in the ongoing SPECTRA study, encouraging results in hemodynamics , iCPET, and 6MWD were seen
- Safety findings were consistent with previous reports in PAH and in other patient populations
- These interim results further highlight the clinical efficacy of sotatercept and its potential as a new treatment option for patients with PAH
- The SPECTRA study is ongoing with further analyses planned; 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)

6MWD: 6-minute walk distance; iCPET: invasive cardiopulmonary exercise testing; 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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