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SPECTRA and Beyond: Signs of Disease Modification?

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Disclosures

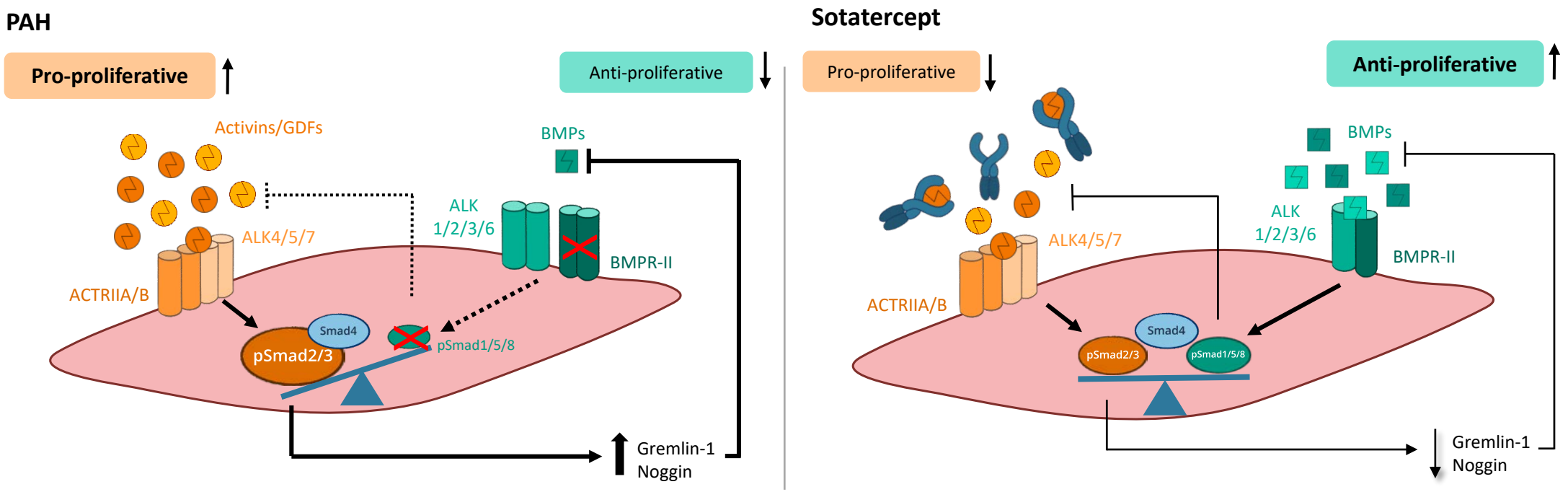
Financial relationships with relevant commercial interests for three years preceding this presentation:

- Acceleron Pharma

Sotatercept is an investigational product that is not approved for any use in any country

Sotatercept and the role of BMPR-II/TGF-β signaling

- Sotatercept is a novel, first-in-class fusion protein comprising the extracellular domain of human activin receptor type IIA linked to the Fc domain of human immunoglobulin G1
- Sotatercept is proposed to act by rebalancing signaling between pro- and anti-proliferative pathways, thereby reversing the characteristic vascular remodeling seen in PAH



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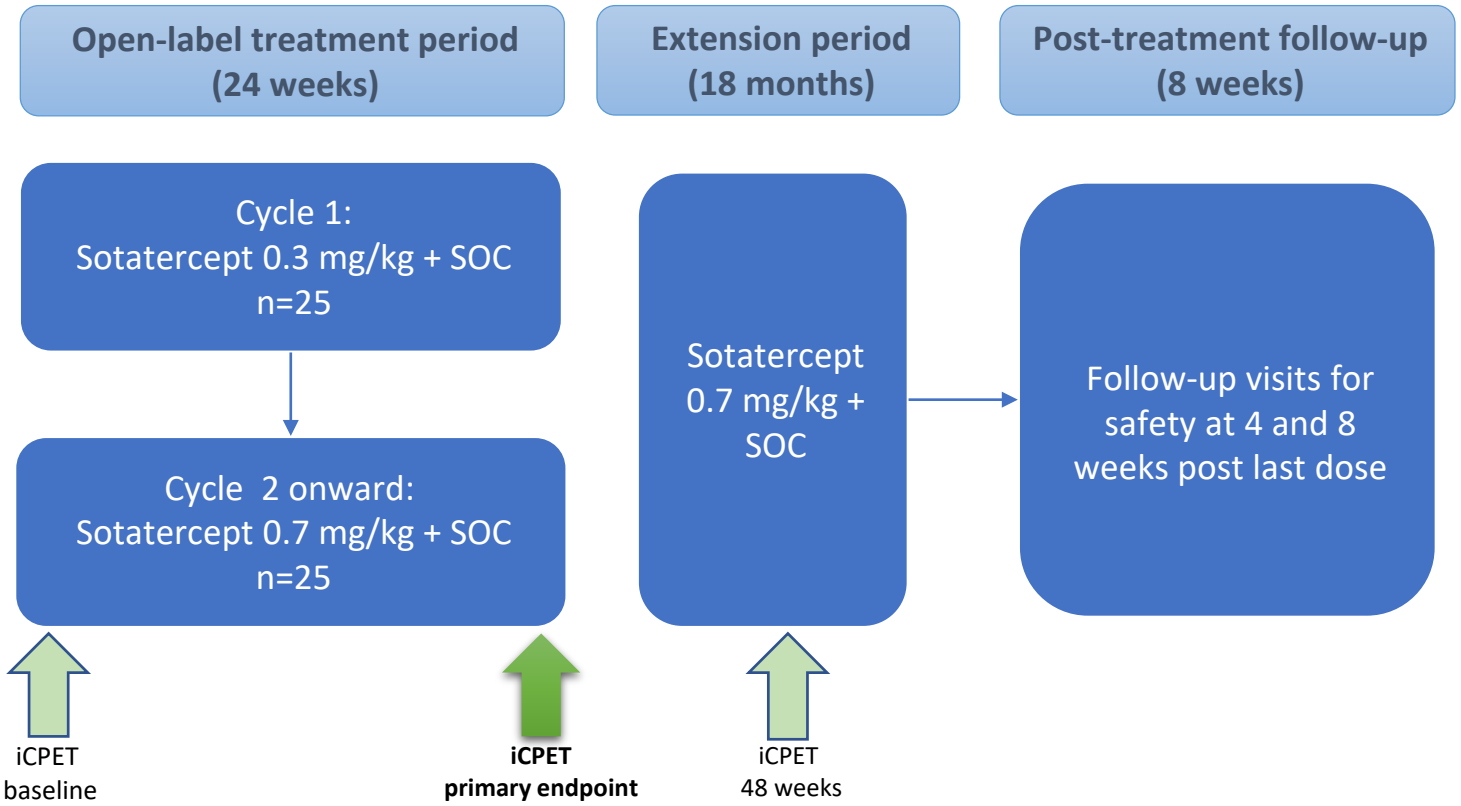
ACTRIIA: activin receptor type 2A; ALK: activin receptor-like kinase; BMP: bone morphogenetic protein; GDF: growth differentiation factor; PAH: pulmonary arterial hypertension; pSmad; phosphorylated Smad

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 up to 25 patients at 4 sites across the USA

- WHO PH Group I (PAH)
  - Idiopathic or heritable
  - Drug- or toxin-induced
  - CTD-associated
  - STP shunt-associated
- PAH WHO Functional Class III
- Right heart catheterization with PVR ≥ 4 Wood units
- 6-minute-walk distance 100 -550 m
- Hgb ≤ 16 g/dL
- Stable combination PAH therapy



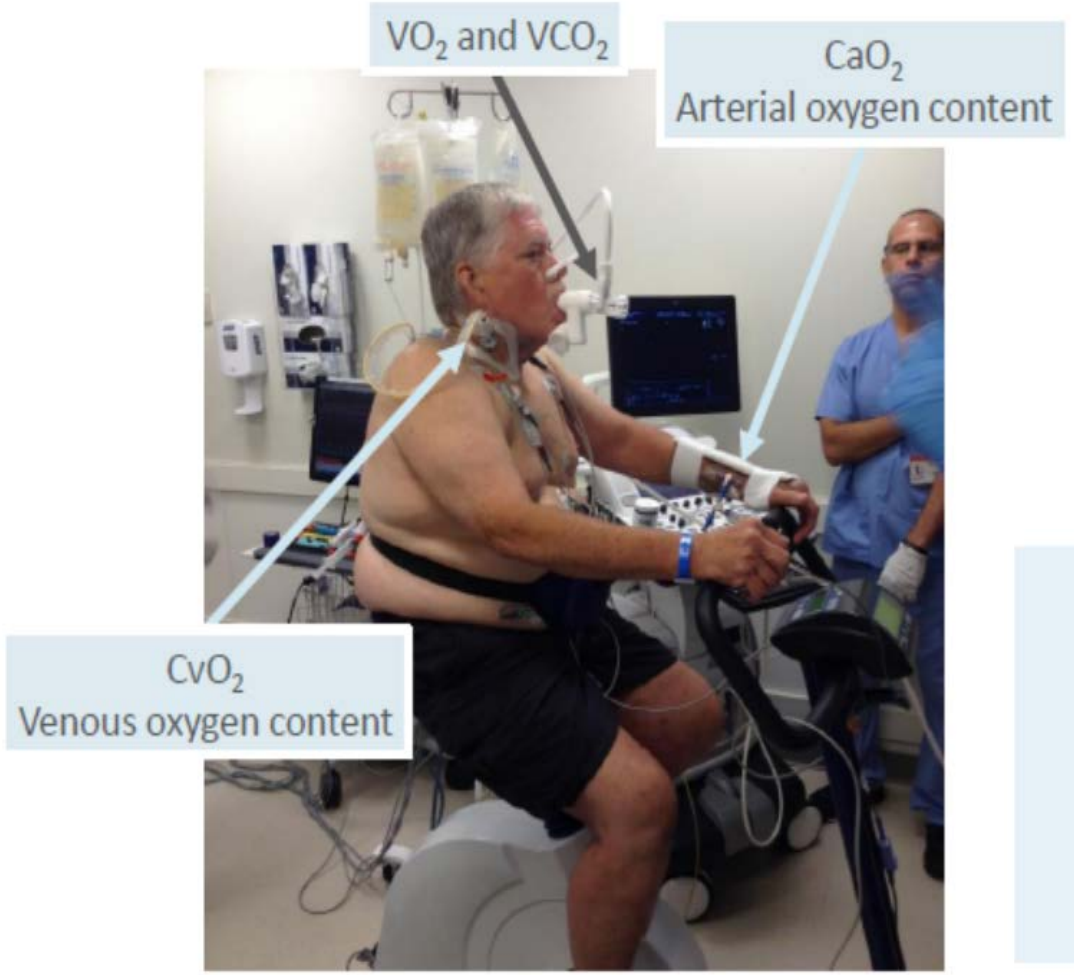
CTD: connective-tissue disease; Hgb: hemoglobin; iCPET: invasive cardiopulmonary exercise testing; PAH: pulmonary arterial hypertension; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; SOC: standard of care; WHO: World Health Organization

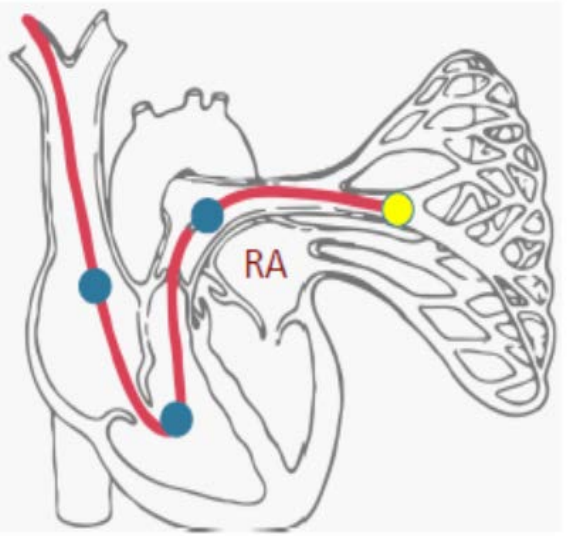
https://clinicaltrials.gov/ct2/show/NCT03738150 [Accessed 23 September 2020].

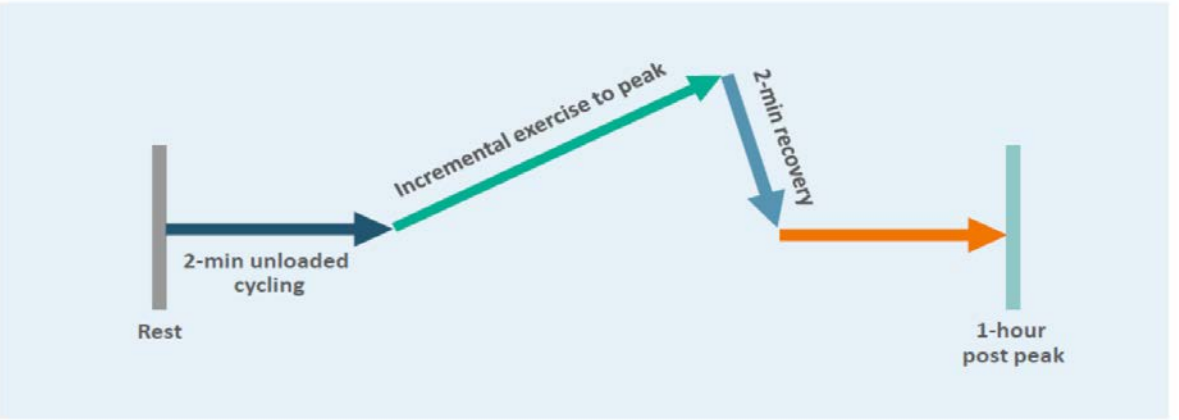
SPECTRA study: iCPET assessments

- Primary endpoint: Change from baseline in peak oxygen uptake (VO_2 max) at 24 weeks
- Secondary endpoints from iCPET measured as change from baseline at 24 weeks:
  - Ventilatory efficiency (VE/VCO_2 slope)
  - Cardiac index ($L/min/m^2$)
  - Mean pulmonary artery pressure, (mPAP, mmHg)
  - Arteriovenous O_2 content difference ($Ca\text{-}vO_2$)
  - VE/VCO_2 slope (ventilatory efficiency, “dead space” assessment)
  - VO_2 at AT (O_2 consumption at anaerobic threshold)

How do we perform iCPET?







iCPET: invasive cardiopulmonary exercise testing; RA: right atrium; VO_2: peak oxygen uptake

SPECTRA study: Baseline characteristics

	Total N=10
Female, n	6
Age, median (range), years	45 (25-66)
Time since diagnosis, median (range), years	3.2 (0.6-13.1)
PAH classification, n	
Idiopathic	5
Associated with connective-tissue disease	4
Heritable	1
Standard-of-care PAH therapy, n	
Parenteral prostacyclin	7
Double therapy	5
Triple therapy	5
Supine resting pulmonary vascular resistance, median (range), dyn·s/cm^5	564 (370-870)
6-minute walk distance, median (range), m	359 (254-506)

Data cut-off date 21 Sept 2020
PAH: pulmonary arterial hypertension

SPECTRA study results: Supine Resting Hemodynamics

	Baseline (n=10)	Week 24/EOS[#] (n=10)
Mean Pulmonary Arterial Pressure (mPAP), mmHg	43.4 ± 9.7	30.6 ± 9.7
Pulmonary Arterial Wedge Pressure (PAWP), mmHg	10.0 ± 4.0	9.1 ± 4.8
Cardiac Output (CO), L/min	4.7 ± 0.7	4.8 ± 1.4
Pulmonary Vascular Resistance (PVR), dyn·sec/cm^5	576 ± 139	369 ± 121

Data cut-off date 21 Sept 2020
Mean ± SD
[#]EOS: End of study visit, n=1, performed after 3 doses of study drug

SPECTRA Study: Safety

Treatment Emergent Adverse Events (TEAE) reported:

- 9/10 patients reported at least one TEAE
  - Arthralgia, dizziness, fluid overload, gingival bleeding, hematochezia, hemoglobin increased, infusion site pain, palpitations, pyrexia, upper respiratory tract infection, weight increased
- Two SAEs reported (fluid overload, resolved; hematochezia, resolved), both considered not related to study drug and no dose interruption or reduction required.
- One discontinuation due to AE (patient felt worsening pain at Remodulin® site injection)

Data cut-off date 21 Sept 2020
AE: adverse event; SAE: serious adverse event: TEAE: treatment-emergent adverse event

SPECTRA Study:

Case Report of First Patient (1/2)

- 25-year-old female, idiopathic PAH for 4.7 years, receiving tadalafil and ambrisentan for the treatment of PAH. At baseline, subject was classified as WHO FC III and 6MWD was 285.5 m.
- The subject's medical history includes gastroesophageal reflux disease, sleep disorder, depression, endometriosis, restless leg syndrome and dust allergy.

Resting supine hemodynamics	Baseline	Week 24	Week 48
mPAP, mmHg	39	13	11
mRAP, mmHg	8	2	2
PAWP, mmHg	8	4	3
CO, L/min	3.73	4.24	3.42
DPG, mmHg	20	3	5
PVR, dynes-sec/cm^5	665	170	187

- **At 24 weeks**, subject was classified as WHO FC I and 6MWD was 468.7 m (183.2 m increase from baseline).
- **At 48 weeks**, subject remained WHO FC I and 6MWD was 443.7 (158.2 m increase from baseline).

Data cut-off date 21 Sept 2020

6MWD: 6-minute-walk distance; CO: cardiac output; DPG: diastolic pressure gradient; FC: functional class; mPAP: mean pulmonary arterial pressure; mRAP: mean right arterial pressure; PAH: pulmonary arterial hypertension; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WHO: World Health Organization

SPECTRA Study

Case Report of First Patient (2/2) Peak Exercise Hemodynamics (iCPET)

	Baseline	Week 24	Week 48
Work, W	39	66	85
mPAP, mmHg	41	27	23
TPG, mmHg	37	25	22
PAWP, mmHg	4	2	1
CO, L/min	7.0	7.84	7.4
PVR, dynes-sec/cm^5	423	255	237
Pulmonary artery compliance, mL/mmHg	2.2	3.9	2.3
VO_2 max, mL/kg/min	10.7	17.7	20
VO_2 max, % predicted	33%	54%	62%
Ca-vO_2, mL/dL	9	10.4	15.3
V_E/VCO_2 slope	55	27	30

Data cut-off date 21 Sept 2020

Ca-vO_2: arteriovenous O_2 content difference; CO: cardiac output; iCPET: invasive cardiopulmonary exercise testing; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; TPG: transpulmonary pressure gradient; VO_2: oxygen consumption; V_E/VCO_2: ventilatory efficiency

Conclusions

- The ongoing SPECTRA study has shown substantial improvements in hemodynamics as well as exercise tolerance and capacity in the limited number of subjects studied to date.
- Sotatercept was generally well tolerated, consistent with the previously reported safety profile in PAH[1].
- Additional data on sotatercept will be presented during AHA 2020:
  - McLaughlin V, et al. “Sotatercept improves right ventricular – pulmonary arterial coupling and right ventricular function in the PULSAR study”, Dickinson W. Richards Memorial Lecture, *Cardiopulmonary Best Abstract Award,* presentation number 287
  - Joshi S, et al. “Sotatercept analog RAP-011 inhibits right ventricular remodeling and restores function in a mouse model of pressure overload”, poster number MP282

[1]Badesch, DB, et al. Sotatercept for the Treatment of Pulmonary Arterial Hypertension. Presentation at: ATS 2020 Virtual. American Thoracic Society International Conference; 24 June-10 November, 2020.

SPECTRA study: Acknowledgements

- We thank all the patients, their families, and all the SPECTRA study investigators who participated in the trial
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  - The study was sponsored by Acceleron Pharma, Cambridge, MA, USA
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