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Treatment response to sotatercept within 1 year of diagnosis of pulmonary arterial hypertension: subgroup analysis by cardiometabolic comorbidity burden

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Background: Sotatercept, a first-in-class activin-signalling inhibitor, has shown benefit and manageable safety in participants with pulmonary arterial hypertension (PAH), including participants <1 year from diagnosis in HYPERION (NCT04811092). Cardiometabolic comorbidities (CMCs) are frequent in PAH, yet their impact on response to sotatercept remains unclear.

Aims: Post-hoc analysis to assess HYPERION efficacy and safety outcomes by CMC burden.

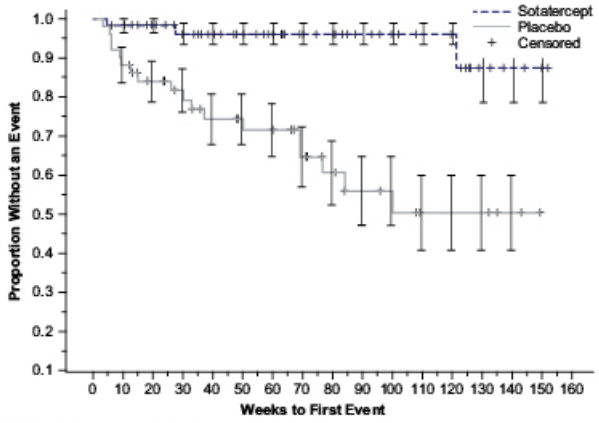
Methods: Participants with WHO FC II/III PAH at intermediate-to-high mortality risk (REVEAL Lite 2 risk ≥6 or COMPERA 2.0 risk ≥2) on background therapy were randomised to sotatercept or placebo every 3 weeks. Outcomes at the final database lock are by absence or presence of a CMC (diabetes, hypertension, coronary artery disease or BMI ≥30 kg/m2) at baseline.

Results: Participants with 0 (n=109) or ≥1 (n=211) CMC had a longer time to a first clinical worsening event with sotatercept vs placebo (hazard ratio [95% CI]): 0 CMC 0.13 (0.04–0.43; *P*<0.0001); ≥1 CMCs 0.29 (0.16–0.54; *P*<0.0001) (Figure). For safety outcomes, the proportions of participants experiencing ≥1 adverse event (AE), ≥1 serious AE or an AE leading to treatment discontinuation were generally similar between the 0 or ≥1 CMC subgroups in both the sotatercept- and placebo-treated groups (Figure).

Conclusion: Time to a first clinical worsening event was longer with sotatercept (vs placebo), with a generally well tolerated and consistent safety profile across CMC subgroups in HYPERION.

Figure. Baseline characteristics, time to a first clinical worsening event and safety summary for participants with 0 and ≥1 comorbidities in HYPERION

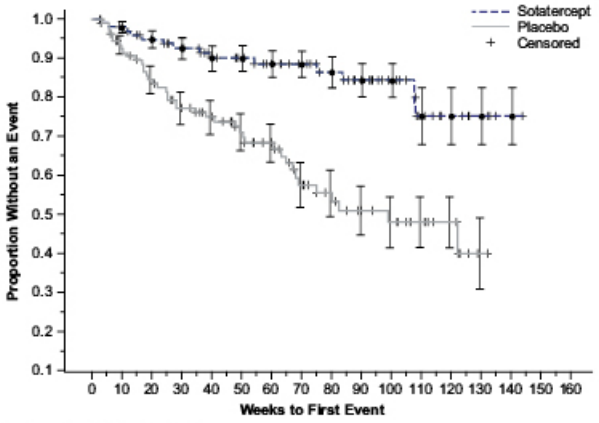
Participants with 0 comorbidities		
0 comorbidities (n=109)	**Sotatercept (n=58)**	**Placebo (n=51)**
Baseline characteristics		
Female, %	88	77
Median age, years	51	43
WHO FC II/III, %	26/74	25/75
Double background therapy, %	78	65
Primary endpoint: Time to a first clinical worsening event		
Median (range) duration of follow-up, months	13.6 (1.4–35.0)	13.8 (2.1–34.4)
N (%) participants with ≥1 event	3 (5)	18 (35)
Events per 100 person-months	0.3	2.7
HR (95% CI)†	**0.13 (0.04–0.43); *P*<0.0001**	
N (%) participants with any components of the primary endpoint‡		
Death from any cause§	2 (3)	0
Unplanned hospitalisation lasting ≥24 h for worsening of PAH	1 (2)	4 (8)
Atrial septostomy	0	0
Lung transplantation	0	0
Deterioration in exercise performance due to PAH‖	0	16 (31)
Safety summary		
≥1 AE, n (%)	54 (93)	44 (86)
≥1 serious AE, n (%)	11 (19)	10 (20)
An AE leading to treatment discontinuation, n (%)	2 (3)	0



Number of participants at risk

Placebo	51	45	38	34	29	27	26	19	15	11	10	4	4	4	2	0	0
Sotatercept	58	55	50	45	39	33	30	23	22	17	14	12	11	5	3	1	0

Participants with ≥1 comorbidities		
≥1 comorbidities (n=211)	**Sotatercept (n=102)**	**Placebo (n=109)**
Baseline characteristics		
Female, %	68	67
Median age, years	64	61
WHO FC II/III, %	21/79	17/83
Double background therapy, %	70	75
Primary endpoint: Time to a first clinical worsening event		
Median (range) duration of follow-up, months	16.4 (0.7–33.2)	11.1 (0.7–30.4)
N (%) participants with ≥1 event	14 (14)	41 (38)
Events per 100 person-months	0.9	3.1
HR (95% CI)†	**0.29 (0.16–0.54); *P*<0.0001**	
N (%) participants with any components of the primary endpoint‡		
Death from any cause§	5 (5)	6 (6)
Unplanned hospitalisation lasting ≥24 h for worsening of PAH	2 (2)	10 (9)
Atrial septostomy	0	0
Lung transplantation	0	0
Deterioration in exercise performance due to PAH‖	8 (8)	30 (28)
Safety summary		
≥1 AE, n (%)	89 (87)	100 (92)
≥1 serious AE, n (%)	28 (27)	35 (32)
An AE leading to treatment discontinuation, n (%)	3 (3)	0



Number of participants at risk

Placebo	109	97	84	72	63	52	43	31	25	20	16	12	7	1	0	0	0
Sotatercept	102	96	86	80	70	62	57	52	41	36	25	14	9	5	1	0	0

Intention-to-treat population.
†Estimates calculated using unstratified Cox regression and one-sided *P*-value based on log-rank test.
‡A participant is included in more than one component if multiple events meeting the definition of the primary endpoint were observed.
§All deaths are included, regardless of adjudication and regardless of whether they occurred during or after HYPERION, except for those occurring after enrolment in SOTERIA.
‖Defined as a decrease in 6-minute walking distance on two consecutive tests performed at least 4 h apart, accompanied by worsening of WHO FC, signs/symptoms of increased right ventricular failure or addition/change of a background PAH therapy.
AE, adverse event; CI, confidence interval; FC, functional class; HR, hazard ratio; PAH, pulmonary arterial hypertension; WHO World Health Organization.