Updates in Pulmonary Arterial Hypertension Therapies

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Objectives

DEFINE PULMONARY HYPERTENSION AND BASIC PATHOPHYSIOLOGY

DISCUSS CHANGES IN EXISTING THERAPIES

EVALUATE NEW THERAPIES

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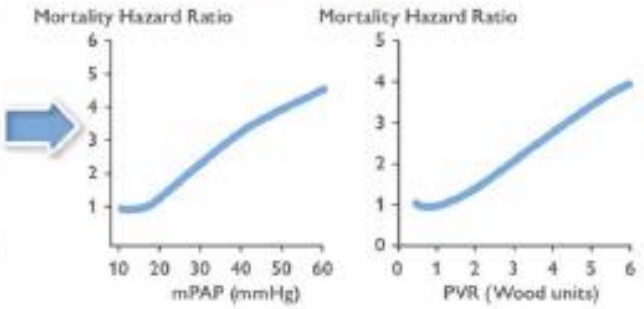
Pulmonary hypertension

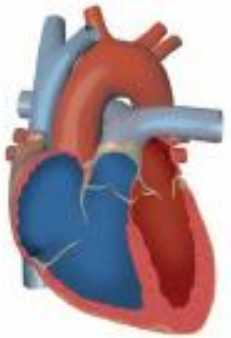
Prevalence

1% Global population

Pulmonary congestion in post-capillary PH

Pulmonary vascular disease / obstruction in pre-capillary PH

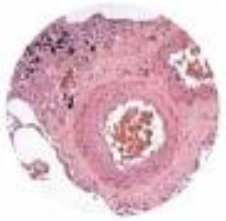




Right heart failure

Clinical Classification

Pulmonary arterial hypertension (PAH)



- Idiopathic/heritable
- Associated conditions

PH associated with left heart disease

- IpcPH
- CpcPH

PH associated with lung disease

- Non-severe PH
- Severe PH

PH associated with pulmonary artery obstructions

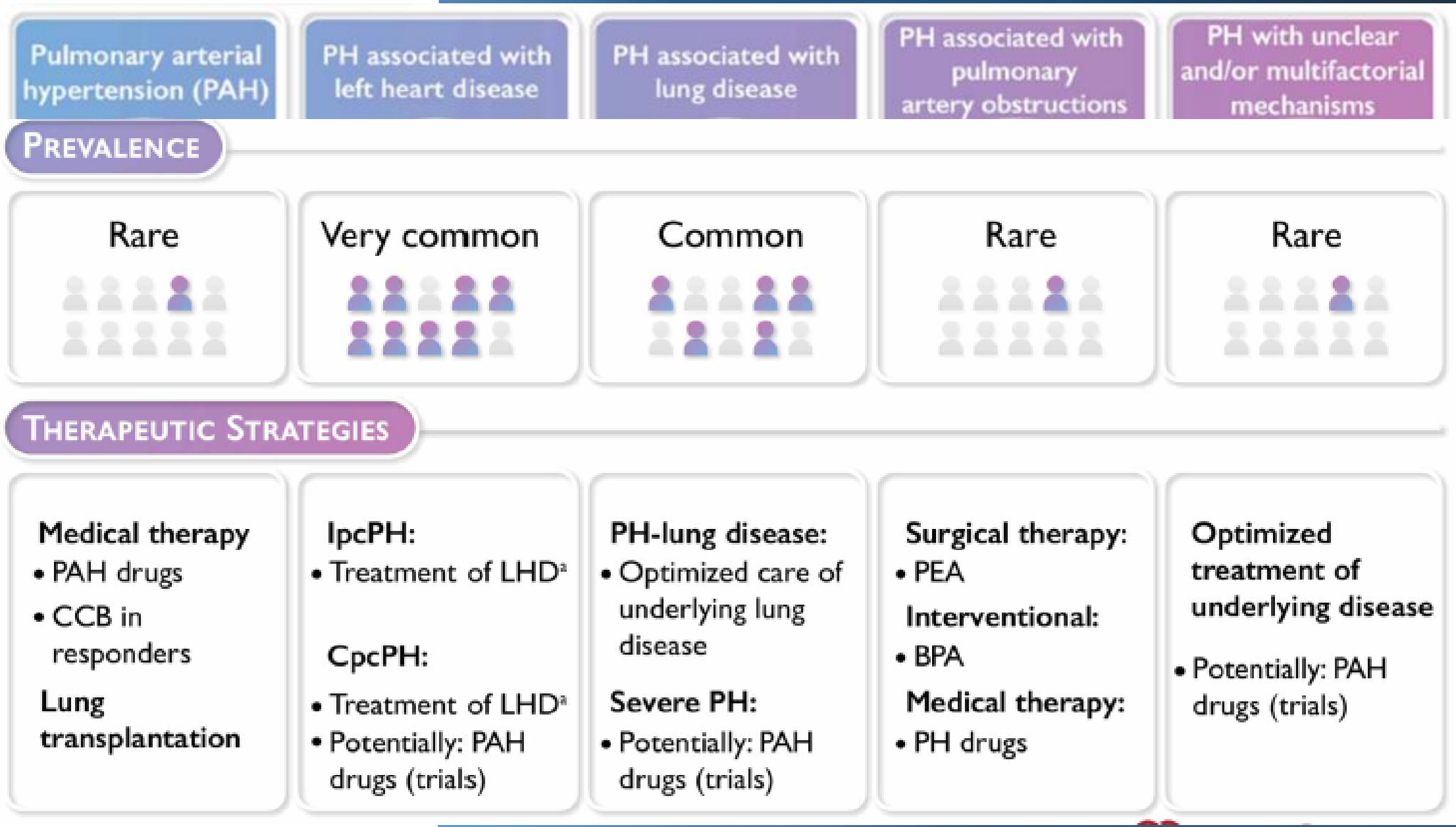
- CTEPH
- Other pulmonary obstructions

PH with unclear and/or multifactorial mechanisms

?

- Haematologic disorders
- Systemic disorders

Eur Respir J 2022;
in press: 2200879
https://doi.org/10.1183/13993003.00879-2022



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PH Defined

TABLE 5 Haemodynamic definitions of pulmonary hypertension

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ⩽15 mmHg PVR >2 WU
IpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR ⩽2 WU
CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

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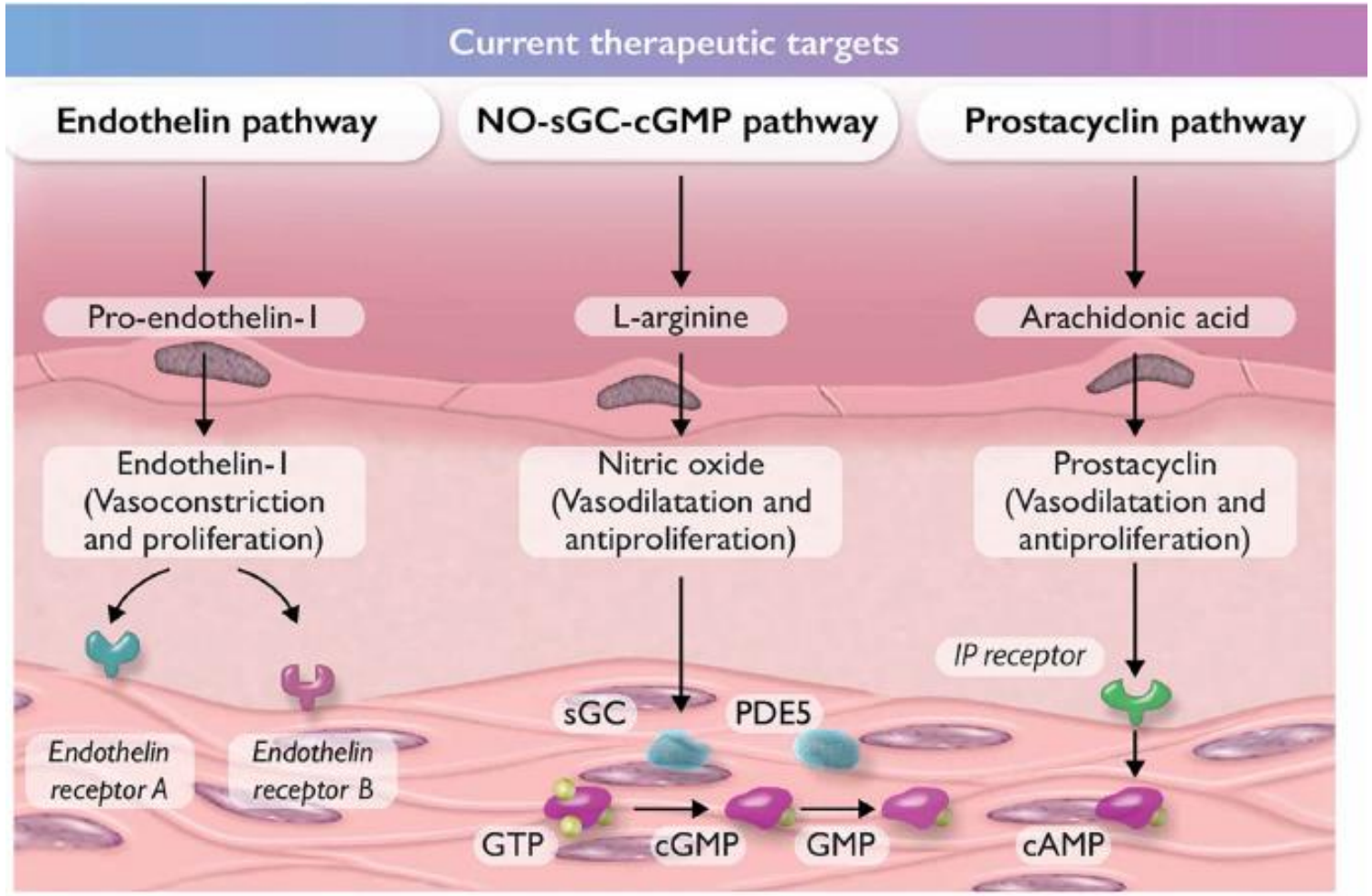
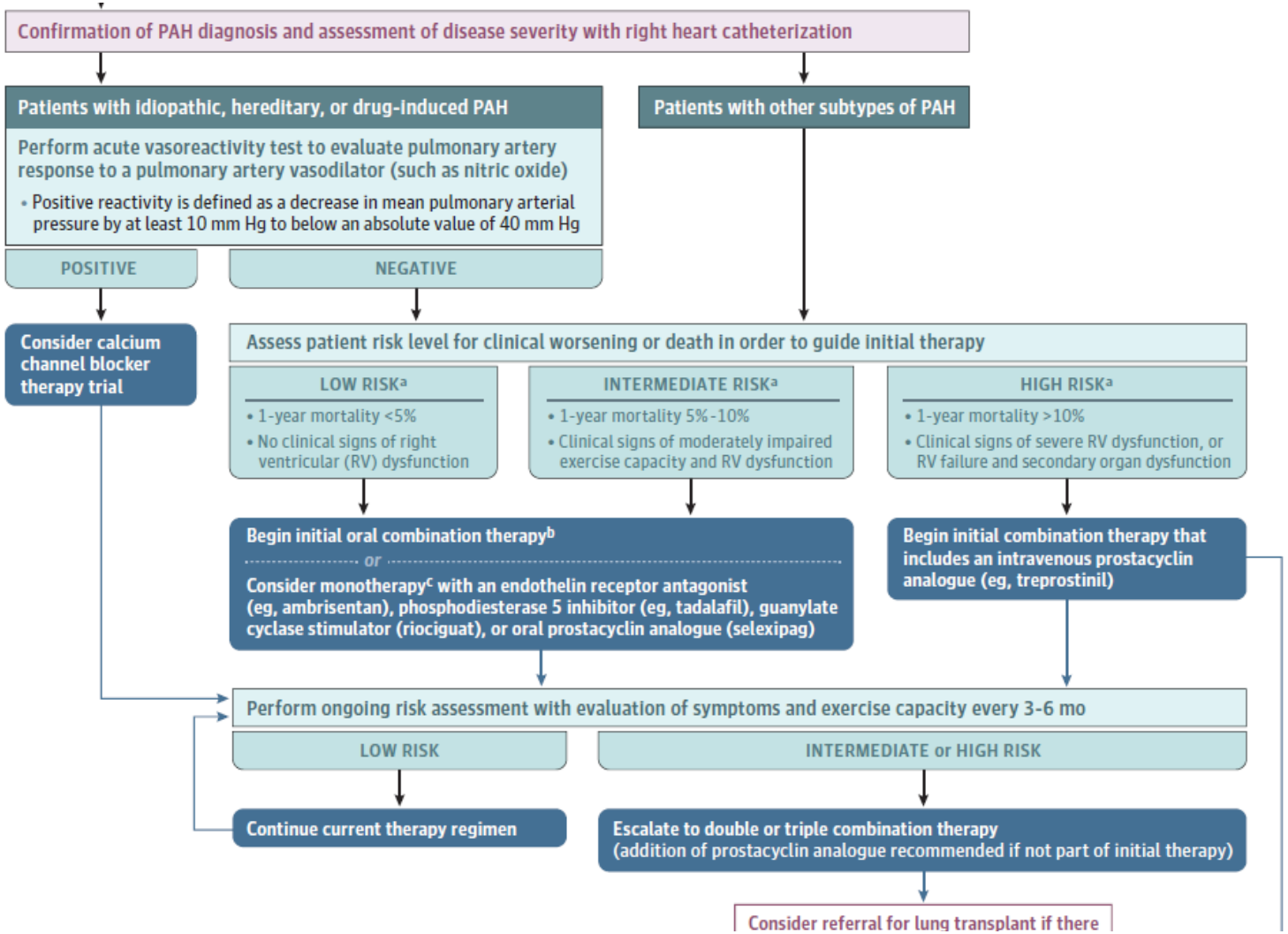


Targeted Drug Therapy

Eur Respir J 2022; in press: 2200879
https://doi.org/10.1183/13993003.00879-2022



Treatment Algorithm

JAMA. 2022;327(14):1379-1392.
doi:10.1001/jama.2022.4402

Pharmacotherapy

	Starting dose	Target dose
Calcium channel blockers		
Amlodipine	5 mg o.d.	15–30 mg o.d.[a]
Diltiazem	60 mg b.i.d.[b]	120–360 mg b.i.d.[b]
Felodipine	5 mg o.d.	15–30 mg o.d.[a]
Nifedipine	10 mg t.i.d.	20–60 mg b.i.d. or t.i.d.
Endothelin receptor antagonists (oral administration)		
Ambrisentan	5 mg o.d.	10 mg o.d.
Bosentan	62.5 mg b.i.d.	125 mg b.i.d.
Macitentan	10 mg o.d.	10 mg o.d.
Phosphodiesterase 5 inhibitors (oral administration)		
Sildenafil	20 mg t.i.d.	20 mg t.i.d.[c]
Tadalafil	20 or 40 mg o.d.	40 mg o.d.
Prostacyclin analogues (oral administration)		
Beraprost sodium	20 µg t.i.d.	Maximum tolerated dose up to 40 µg t.i.d.
Beraprost extended release	60 µg b.i.d.	Maximum tolerated dose up to 180 µg b.i.d.
Treprostinil	0.25 mg b.i.d. or 0.125 mg t.i.d.	Maximum tolerated dose
Prostacyclin receptor agonist (oral administration)		
Selexipag	200 µg b.i.d.	Maximum tolerated dose up to 1600 µg b.i.d.
Soluble guanylate cyclase stimulator (oral administration)		
Riociguat[d]	1 mg t.i.d.	2.5 mg t.i.d.
Prostacyclin analogues (inhaled administration)		
Iloprost[e]	2.5 µg 6–9 times per day	5.0 µg 6–9 times per day
Treprostinil[e]	18 µg 4 times per day	54–72 µg 4 times per day
Prostacyclin analogues (i.v. or s.c. administration)		
Epoprostenol i.v.	2 ng/kg/min	Determined by tolerability and effectiveness; typical dose range at 1 year is 16–30 ng/kg/min, with wide individual variability
Treprostinil s.c. or	1.25 ng/kg/min	Determined by tolerability and effectiveness; typical dose range

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Changes in Existing Therapies

Macitentan + tadalafil combination tablet

Macitentan 75mg tablet

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Macitentan + Tadalafil

Generic product

A DUE Study + OLE trial

Filed with FDA for approval

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Efficacy and safety of macitentan tadalafil fixed dose combination in pulmonary arterial hypertension: results from the randomized controlled phase III A DUE study

Kelly Chin[1], Pavel Jansa[2], Fenling Fan[3], Jakob Hauser[4], Cheryl Lassen[4], Matthieu Pannaux[5], Hany Rofael[6], Ekkehard Grünig[7]

[1]UT Southwestern Medical Center, Dallas, TX, USA; [2]Charles University and General University Hospital, Prague, Czech Republic; [3]First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China; [4]Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson, Allschwil, Switzerland; [5]Cytel Inc, Cambridge, MA, USA; [6]Janssen Research and Development, LLC, Titusville, NJ, USA; [7]Thoraxklinik at Heidelberg University Hospital, Heidelberg, Germany

A DUE Study

Study Rationale:

Macitentan 10mg + tadalafil 40mg/d is a common dual therapy regimen

A fixed dose single tablet would create a simpler treatment approach

Study Goal:

Evaluate efficacy and safety of the fixed tablet versus monotherapy with macitentan and tadalafil

Design

30 day run in period depending on prior treatment

Randomization to 3 treatment arms, 16 week blinded study:

- Macitentan 10mg/d
- Fixed combination tablet
- Tadalafil 40mg/d

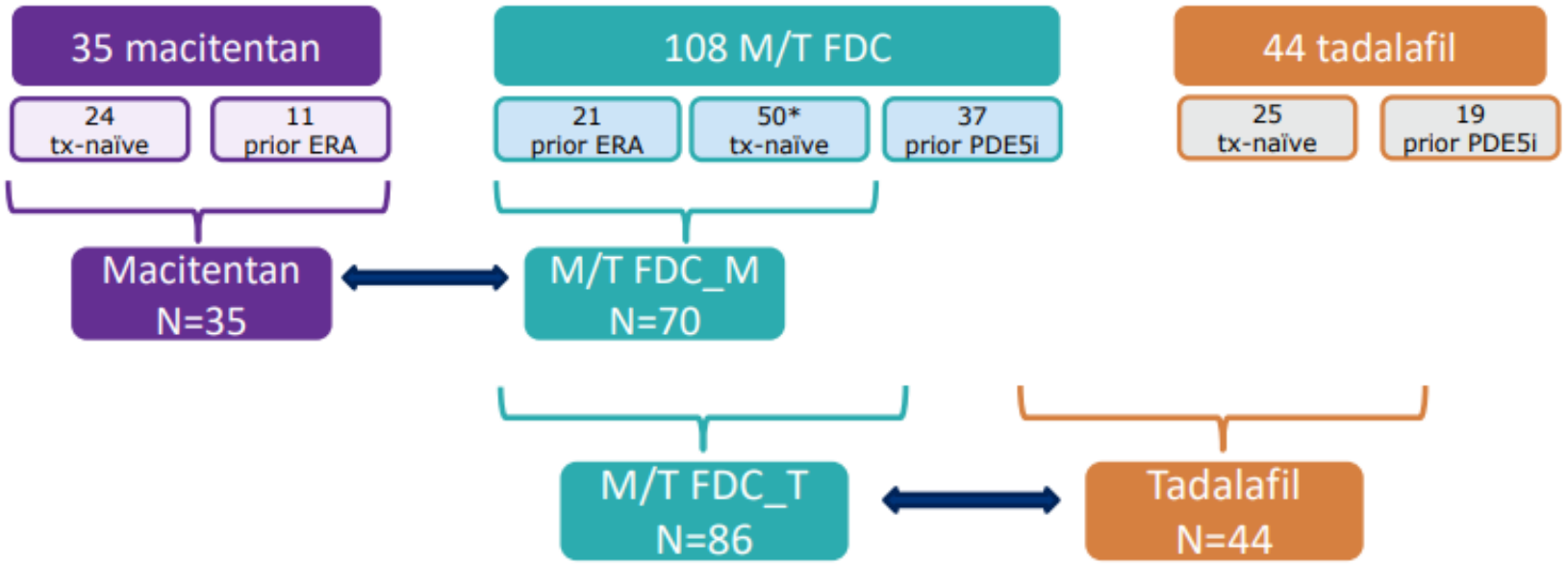
Patients and Outcomes

Adult PAH patients with WHO FC II or III

Endpoints

- Primary – change in peripheral vascular resistance
- Secondary – change in 6 minute walk test, PAH SYMPACT Score, absence of worsening WHO FC
- Treatment effect calculations:
  - M/T FDC vs macitentan monotherapy
  - M/T FDC vs tadalafil monotherapy

M/T monotherapies versus FDC



Chin et al. Mar 2023. ACC.23/WCC Presentation Slides | (A DUE)

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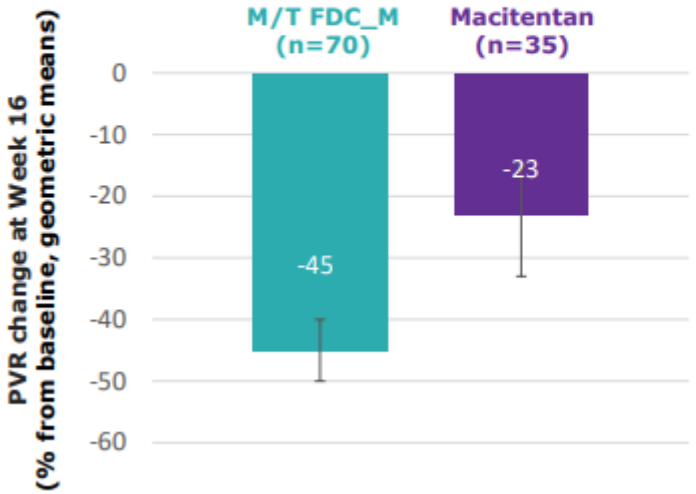
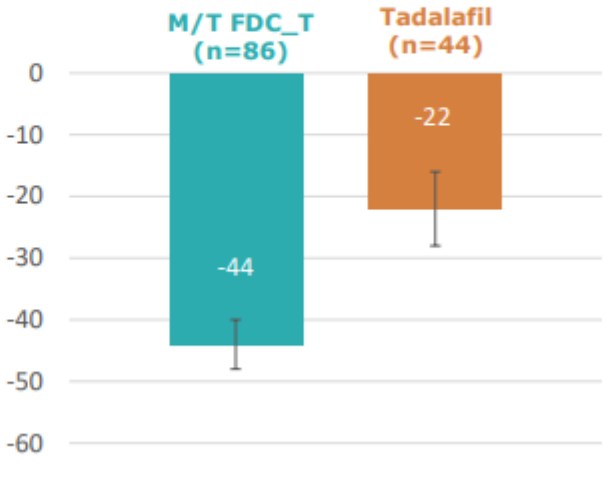
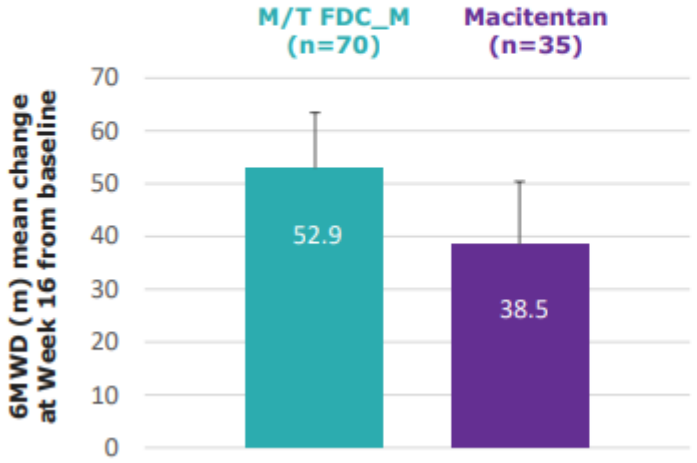
M/T FDC_M vs Macitentan: PVR reduction 29%
Ratio of geometric means (95% CL):
0.71 (0.61, 0.82), **P≤0.0001**



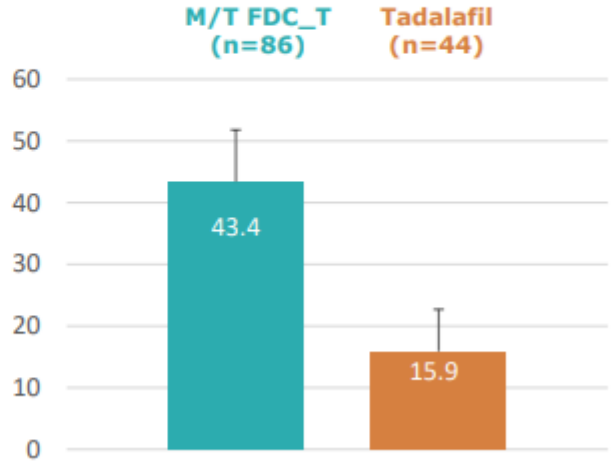
M/T FDC_T vs Tadalafil: PVR reduction 28%
Ratio of geometric means (95% CL):
0.72 (0.64, 0.80), **P≤0.0001**



M/T FDC_M vs Macitentan:
Change in 6MWD (95% CL):
16.04m (-17.00, 49.08), P=0.380



M/T FDC_T vs Tadalafil:
Change in 6MWD (95% CL):
25.37m (-0.93, 51.59), P=0.059



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Safety Analysis

Rate of serious and any adverse effects were similar amongst all 3 groups

Increased incidence in Edema/fluid retention in combination group

M/T FDC: 20.6%	Macitentan: 14.3%	Tadalafil: 15.9%

Increased incidence of anemia/hgb decrease in combination group

M/T FDC: 18.7%	Macitentan: 12.9%	Tadalafil: 2.3%

Chin et al. Mar 2023. ACC.23/WCC Presentation Slides | (A DUE)

Macitentan 75mg tablets

- Rationale: ETb is partially blocked at 10mg
- Studied up to 600mg a day in healthy volunteers
- ETa is 100% blocked at 10mg
- Hgb lowering and hypotension side effects attributed to ETa blockade
- UNISUS PAH study
- MACI-TEPH study

Macitentan 75mg: UNISUS Trial

Goal: Demonstrate superiority of macitentan 75mg in prolonging the time to the first clinical events

Design: Phase III, double blind, randomized prospective study

- Macitentan 10mg vs. 75mg

Objective:

- Primary: time to first morbidity or mortality event
- Secondary: change in 6mw, time to first PH hospitalization or death, change in PAH-SYMPACT score

Timeline: 4 years

https://www.clinicaltrials.gov/study/NCT04273945

Macitentan 75mg: MACiTEPH Trial

Goal: Evaluate the effect of macitentan 75 mg versus placebo on exercise capacity in chronic thromboembolic pulmonary hypertension (CTEPH)

Design: A Prospective, Randomized, Double-blind, Multicenter, Placebo-controlled, Parallel Group, Phase 3 Study With Open-label Extension to Evaluate Efficacy and Safety

- Macitentan 10mg vs. 75mg

Primary Objective: change in 6 minute walk distance

Secondary Objectives: time to clinical worsening, WHO FC improvement, change in PAH SYMPACT score, change in EQ-5D-5L score

Timeline: 28 weeks

https://www.clinicaltrials.gov/study/NCT04271475

New Therapies

Ralinepag

- Phase II trial

Sotatercept

- PULSAR
- STELLAR

Title	Efficacy and safety of ralinepag, a novel oral IP agonist, in PAH patients on mono or dual background therapy: results from a phase 2 randomized, parallel group, placebo-controlled trial
Methods	Phase II study comparing ralinepag versus placebo 61 patients receiving standard of care with PAH background therapy Randomized 2:1 to ralinepag (n=40) or placebo (n=21) Dosing: 10mcg BID titrated to 300mcg BID over 9 week titration period
Objectives	Primary: absolute change in PVR at week 22 Secondary: percentage change in PVR from baseline, 6 minute walk distance, safety , tolerability
Results	Ralinepag significantly decreased PVR by 163.9 dyn.s.cm^{-5} vs. increase of 0.7 dyn.s.cm^{-5} with placebo (p=0.03) 6MWD increase by 36.2m with ralinepag and 29.4m with placebo (p=0.9) Serious adverse events occurred in 10% of ralinepag patients and 29% of placebo patients Discontinuations were slightly higher in the treatment group
Conclusion	Ralinepag reduced PVR compared to placebo in PAH patients on mono (41%) or dual therapy (50%) background therapy

Eur Respir J 2019; 54: 1901030

Baseline Characteristics

TABLE 1 Demographics and baseline characteristics

	All patients	Ralinepag	Placebo	p-value
Subjects n	61	40	21	
Age years[#]	49.4 (19–73)	46.2 (19–68)	55.6 (29–73)	0.0057[+]
Female	53 (87)	33 (83)	20 (95)	
Ethnicity				
Caucasian	57 (93)	38 (95)	19 (91)	
Other	4 (7)	2 (5)	2 (10)	
PVR dyn·s·cm^{-5} mean (median)	717 (576)	780 (705)	598 (480)	0.110[+]
6MWD m mean (median)	378 (400)	393 (405)	351 (367)	
WHO FC[#]				
II	34 (56)	22 (55)	12 (57)	0.800[§]
III	26 (43)	17 (43)	9 (43)	
IV	1 (2)	1 (3)	0	
Aetiology of PAH				
Idiopathic PAH	21 (52.5)	11 (52.4)	32 (52.5)	
Heritable PAH	4 (10.0)	1 (4.8)	5 (8.2)	
Drugs or toxins	4 (10.0)	0 (0.0)	4 (6.6)	
Associated PAH[¶]	11 (27.5)	9 (42.9)	20 (32.8)	
NT-proBNP pg·mL^{-1} mean (median)[#]	980 (343)	792 (335)	1362 (343)	0.700[+]
Background PAH therapy %				
Monotherapy	41	35	52	
Combination therapy	59	65	48	
Monotherapy				
ERA[#]	6 (10)	2 (5)	4 (19)	0.170[f]
PDE5i	19 (31)	12 (30)	7 (33)	
Combination therapy				
ERA+PDE5i	34 (56)	24 (60)	10 (48)	0.420[f]
ERA+sGCS	2 (3)	2 (5)	0 (0)	
New PAH treatment within 3–6 months of day 1	13 (21)	5 (13)	8 (38)	0.049[f]

Eur Respir J 2019; 54: 1901030

Results

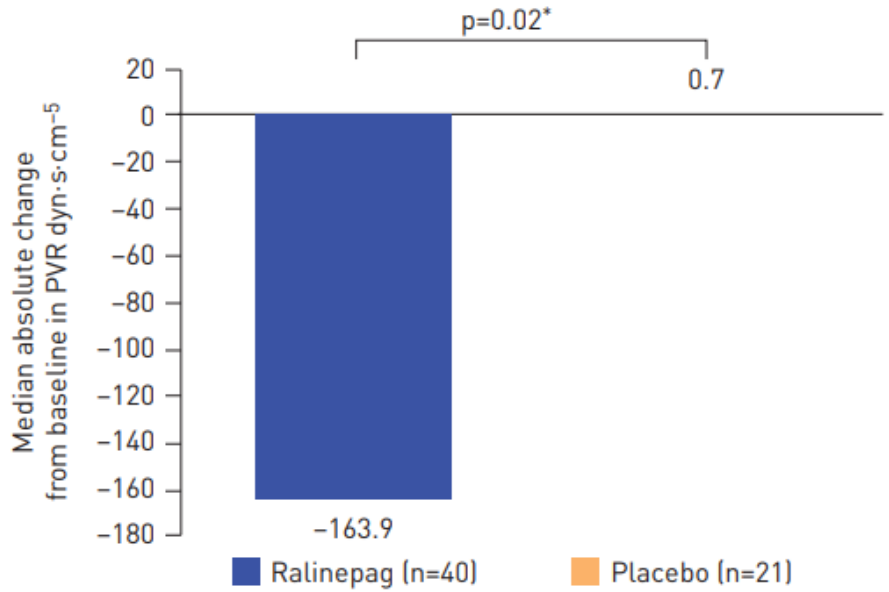

TABLE 2 Secondary haemodynamic parameters: change from baseline to week 22

	Baseline		Change from baseline to week 22#		p-value¶
	Ralinepag	Placebo	Ralinepag	Placebo	
Subjects n	34	19	34	19	
Mean pulmonary arterial pressure mmHg	51.0±15.26	43.1±10.08	−6.1±1.5	−2.9±2.0	0.028
Cardiac index L·min·m^{-2}	2.6±0.60	2.9±0.49	0.31±0.12	−0.0±0.16	0.183
Mixed venous oxygen saturation %	65.0±7.86	68.0±6.28	1.0±1.05	0.6±1.56	0.412
Right atrial pressure mmHg	8.1±6.14	8.7±5.06	−0.3±0.68	−2.0±0.89	0.118
Pulmonary capillary wedge pressure mmHg	9.3±2.93	10.5±3.17	−0.4±0.59	−0.3±0.77	0.119
SVR dyn·s·cm^{-5}	1449.0 ±378.53	1309.9 ±286.65	−258.7 ±286.54	152.9 ±374.47	<0.001
Mean arterial blood pressure mmHg	89.6±16.13	86.8±10.55	−8.2±1.83	−2.7±2.35	0.001
Heart rate bpm	77.1±13.61	71.6±7.87	0.9±1.92	−0.8±2.49	0.961

Eur Respir J 2019; 54: 1901030

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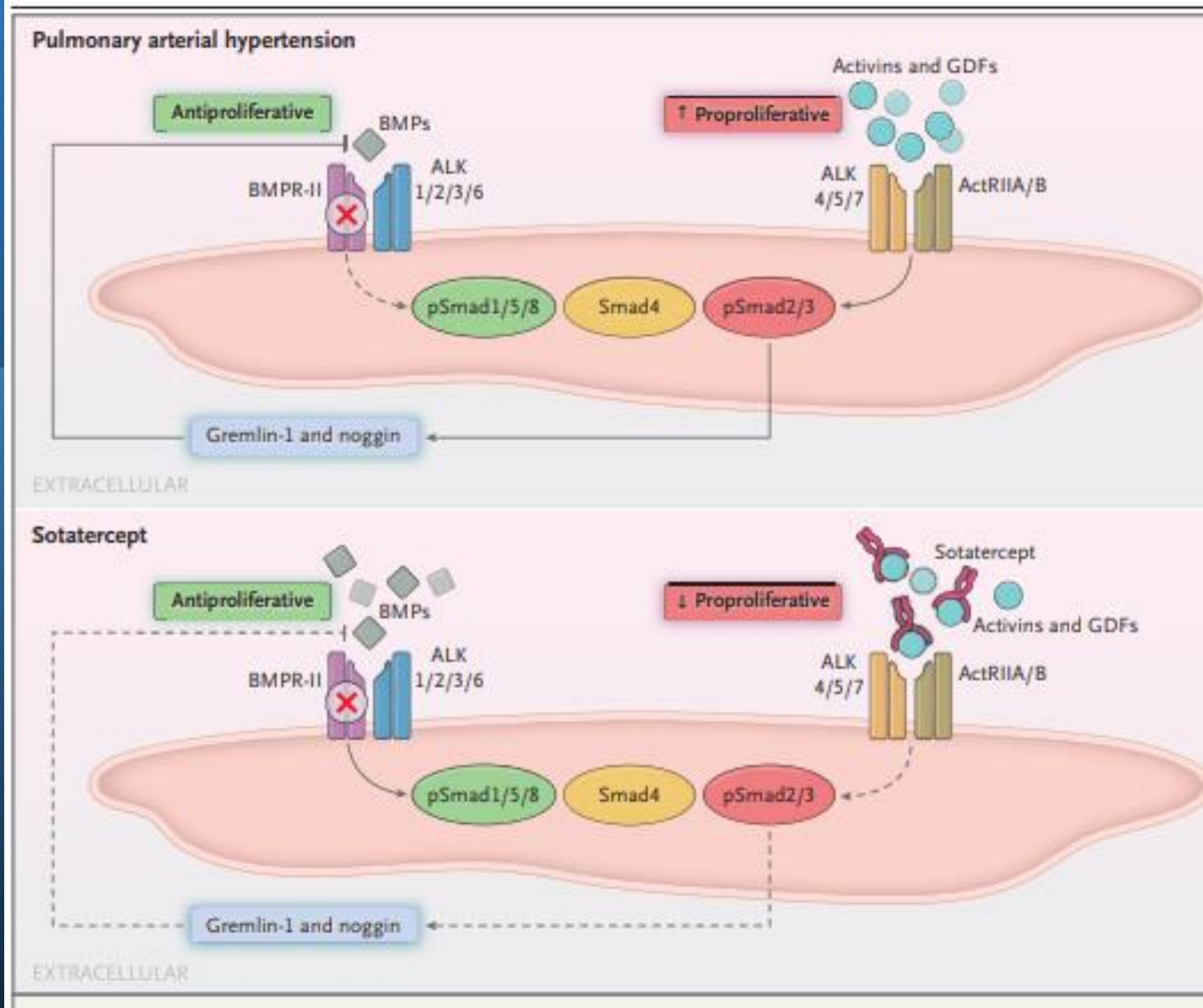
Sotatercept: Proposed Mechanism



N Engl J Med 2021;384:1204-15.
DOI: 10.1056/NEJMoa2024277

PULSAR

Title	Sotatercept for the treatment of pulmonary arterial hypertension
Methods	24 week multicenter trial, randomized PAH patients on background tx to SQ sotatercept 0.3 mg/kg every 3 weeks or 0.7mg/kg every 3 weeks vs. placebo
Objectives	• Change in PVR from baseline at 24 weeks (least squares mean difference) • 6 minute walk difference • Change in N-terminal pro-B type natriuretic peptide • Safety analysis
Results	Primary endpoint: PVR Least squares mean difference: • Sotatercept 0.3mg group vs. placebo -145.8 dyn.s.cm^{-5} (p=0.003) • Sotatercept 0.7mg vs placebo -239.5 dyn.s.cm^{-5} (p<0.001) Secondary endpoint: 6 mw Least squares mean difference: • Sotatercept 0.3mg group vs. placebo 29.4m (95% CI 3.8 to 55.0) • Sotatercept 0.7mg vs placebo 21.4m (95%CI -2.8 to 45.7)
Conclusions	Sotatercept reduced PVR in patients receiving background therapy for PAH

N Engl J Med 2021;384:1204-15.
DOI: 10.1056/NEJMoa2024277

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Baseline Characteristics

Table 1. Demographic and Baseline Clinical Characteristics.*

Characteristic	Placebo (N=32)	Sotatercept 0.3 mg/kg (N=32)	Sotatercept 0.7 mg/kg (N=42)	Both Sotatercept Dose Groups (N=74)	Total (N=106)
Female sex — no. (%)	26 (81)	29 (91)	37 (88)	66 (89)	92 (87)
Age — yr	45.6±13.4	49.1±14.3	49.8±15.1	49.5±14.7	48.3±14.3
Race — no. (%)†					
White	30 (94)	31 (97)	37 (88)	68 (92)	98 (92)
Black	0	1 (3)	3 (7)	4 (5)	4 (4)
Other	2 (6)	0	2 (5)	2 (3)	4 (4)
Body-mass index‡	27.3±5.9	26.1±4.9	27.7±6.6	27.0±5.9	27.1±5.9
Time since diagnosis of pulmonary arterial hypertension — yr§	7.7±5.5	7.8±6.0	7.7±5.6	7.7±5.7	7.7±5.6
Classification of pulmonary arterial hypertension — no. (%)					
Idiopathic	19 (59)	13 (41)	29 (69)	42 (57)	61 (58)
Heritable	7 (22)	5 (16)	5 (12)	10 (14)	17 (16)
Associated with connective-tissue disease	3 (9)	9 (28)	6 (14)	15 (20)	18 (17)
Drug-induced or toxin-induced	1 (3)	4 (12)	2 (5)	6 (8)	7 (7)
Associated with corrected congenital shunts	2 (6)	1 (3)	0	1 (1)	3 (3)
WHO functional class — no. (%)¶					
II	17 (53)	15 (47)	24 (57)	39 (53)	56 (53)
III	15 (47)	17 (53)	18 (43)	35 (47)	50 (47)
Standard therapy for pulmonary arterial hypertension — no. (%)‖					
Prostacyclin infusion therapy	10 (31)	11 (34)	18 (43)	29 (39)	39 (37)
Monotherapy	3 (9)	3 (9)	4 (10)	7 (9)	10 (9)
Double therapy	12 (38)	11 (34)	14 (33)	25 (34)	37 (35)
Triple therapy	17 (53)	18 (56)	24 (57)	42 (57)	59 (56)
Hemoglobin — g/dl	13.7±1.8	12.9±1.5	13.5±1.6	13.3±1.6	13.4±1.7

N Engl J Med 2021;384:1204-15.
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Results

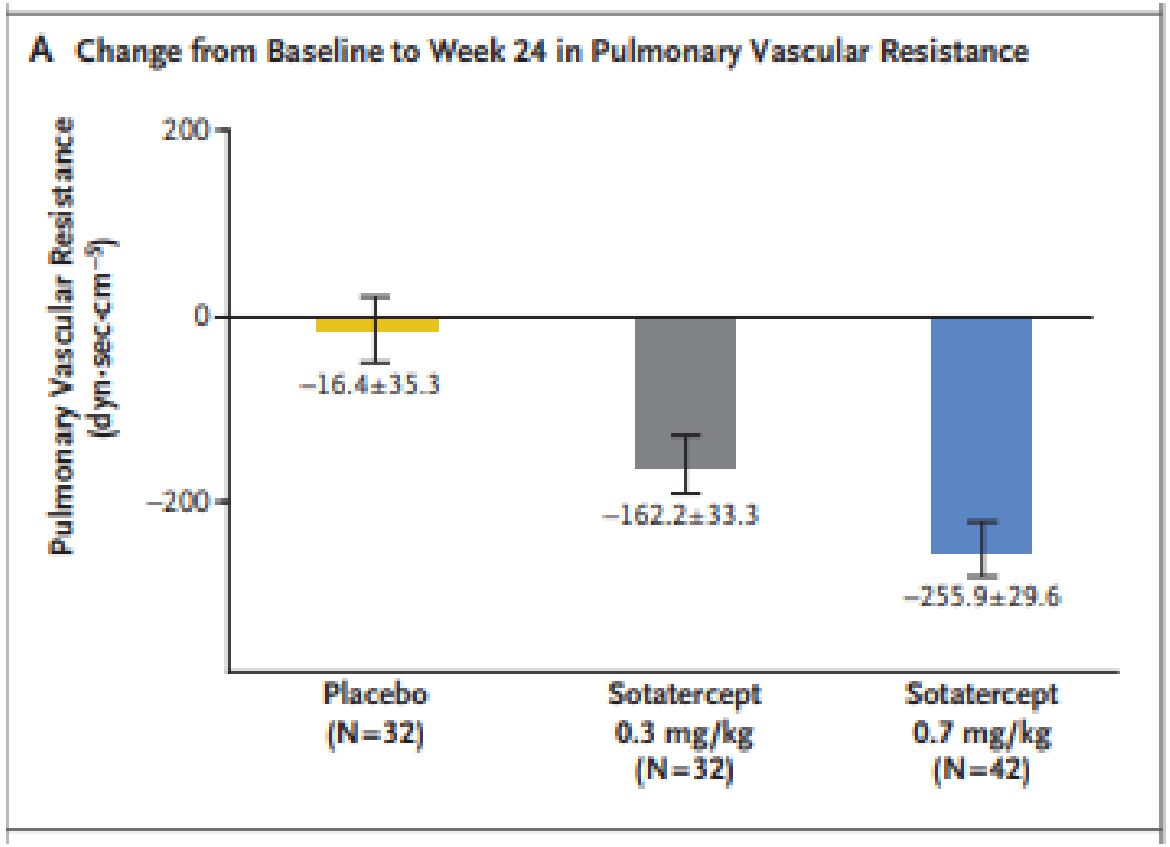

Table 3. Adverse Events and Hematologic Variables through the End of the Placebo-Controlled Treatment Period.*

Variable	Placebo (N=32)	Sotatercept 0.3 mg/kg (N=32)	Sotatercept 0.7 mg/kg (N=42)
Any adverse event — no. (%)	28 (88)	29 (91)	34 (81)
Adverse event occurring in ≥10% of patients in any group — no. (%)			
Headache	5 (16)	8 (25)	6 (14)
Diarrhea	4 (12)	7 (22)	6 (14)
Peripheral edema	5 (16)	3 (9)	5 (12)
Dizziness	3 (9)	5 (16)	4 (10)
Fatigue	6 (19)	2 (6)	4 (10)
Hypokalemia	4 (12)	3 (9)	5 (12)
Nausea	4 (12)	3 (9)	5 (12)
Adverse event of special interest — no. (%)	0	3 (9)	6 (14)
Leukopenia	0	1 (3)	1 (2)
Neutropenia	0	0	1 (2)
Thrombocytopenia	0	2 (6)	5 (12)
Serious adverse event — no. (%)	3 (9)	2 (6)	10 (24)
Adverse event leading to discontinuation of sotatercept or placebo — no. (%)	1 (3)	2 (6)	3 (7)
Adverse event leading to withdrawal from the trial — no. (%)	2 (6)	1 (3)	3 (7)
Adverse event leading to death — no. (%)	0	0	1 (2)†
Hemoglobin increase reported as an adverse event — no. (%)	0	1 (3)	7 (17)
Change in hematologic variables from baseline to week 24			
No. of patients	30	31	36
Hemoglobin — g/dl	0.0±1.1	1.2±1.2	1.5±1.1
Platelet count — $\times 10^9$ per liter	−6.3±29.1‡	12.1±47.7	−12.1±49.8

N Engl J Med 2021;384:1204-15.
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PULSAR Open Label Extension Trial

Placebo patients in PULSAR were re-randomized 1:1 to sotatercept 0.3mg/kg or 0.7mg/kg

Sotatercept patients in PULSAR continued the same doses

Primary efficacy endpoint: change from baseline to months 18-24 in PVR

Secondary endpoints: 6 minute walk and functional class

Results

- 97/106 partcipants completed the OLE
- The placebo crossed group had significant improvement in primary and secondary endpoints
- Continued-sotatercept patients maintained clinical efficacy

Eur Respir J 2023; 61: 2201347
[DOI: 10.1183/13993003.01347-2022].

STELLAR

Title	Phase 3 Trial of Sotatercept for Treatment of Pulmonary Arterial Hypertension
Methods	Phase 3 double blind trial PAH patients with WHO FC II or III receiving background therapy Randomized 1:1 to receive sotatercept 0.3mg/kg SQ titrated to 0.7mg/kg or placebo every 3 weeks
Objectives	Primary Endpoint: • Change in 6 minute walk distance at 24 weeks Secondary endpoints: • Change in PVR, NT-proBNP, improvement in WHO FC, time to death or clinical worsening, PAH SYMPACT score
Results	• Sotatercept group (n=163), Placebo group (n=160) • Median change in 6mw was 34.4m (95% CI 33.0-35.5) in sotatercept group and 1m in the placebo group (95% CI, -0.3 to 3.5) • First 8 secondary endpoints were significantly improved in the sotatercept group vs. placebo, PAH SYMPACT was not • Sotatercept group experienced more epistaxis, dizziness, telangiectasia, increased hemoglobin, thrombocytopenia and increased blood pressure
Conclusions	PAH patients on background therapy, sotatercept improved exercise capacity greater than placebo

N Engl J Med 2023;388:1478-90.
DOI: 10.1056/NEJMoa2213558

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Baseline Demographics

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Sotatercept (N=163)	Placebo (N=160)	Total (N=323)
Female sex — no. (%)	129 (79.1)	127 (79.4)	256 (79.3)
Age — yr	47.6±14.1	48.3±15.5	47.9±14.8
Geographic region — no. (%)			
North America	49 (30.1)	56 (35.0)	105 (32.5)
South America	13 (8.0)	15 (9.4)	28 (8.7)
Europe	91 (55.8)	77 (48.1)	168 (52.0)
Asia–Pacific	10 (6.1)	12 (7.5)	22 (6.8)
Race — no. (%)†			
White	147 (90.2)	141 (88.1)	288 (89.2)
Black	2 (1.2)	5 (3.1)	7 (2.2)
Asian	1 (0.6)	6 (3.8)	7 (2.2)
Other	7 (4.3)	6 (3.8)	13 (4.0)
Missing	6 (3.7)	2 (1.2)	8 (2.5)
Body-mass index‡	26.1±5.7	26.6±6.1	26.4±5.9
Body-mass index ≥30 — no. (%)‡	36 (22.1)	38 (23.8)	74 (22.9)
Time since diagnosis of pulmonary arterial hypertension — yr§	9.2±7.3	8.3±6.7	8.8±7.0
Classification of pulmonary arterial hypertension — no. (%)			
Idiopathic	83 (50.9)	106 (66.2)	189 (58.5)
Heritable	35 (21.5)	24 (15.0)	59 (18.3)
Associated with connective-tissue disease	29 (17.8)	19 (11.9)	48 (14.9)
Drug-induced or toxin-induced	7 (4.3)	4 (2.5)	11 (3.4)
Associated with corrected congenital shunts	9 (5.5)	7 (4.4)	16 (5.0)
WHO functional class — no. (%)¶			
II	79 (48.5)	78 (48.8)	157 (48.6)
III	84 (51.5)	82 (51.2)	166 (51.4)
Background therapy for pulmonary arterial hypertension — no. (%)‖			
Prostacyclin infusion therapy**	65 (39.9)	64 (40.0)	129 (39.9)
Monotherapy	9 (5.5)	4 (2.5)	13 (4.0)
Double therapy	56 (34.4)	56 (35.0)	112 (34.7)
Triple therapy	98 (60.1)	100 (62.5)	198 (61.3)

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Primary and Secondary Endpoint Results

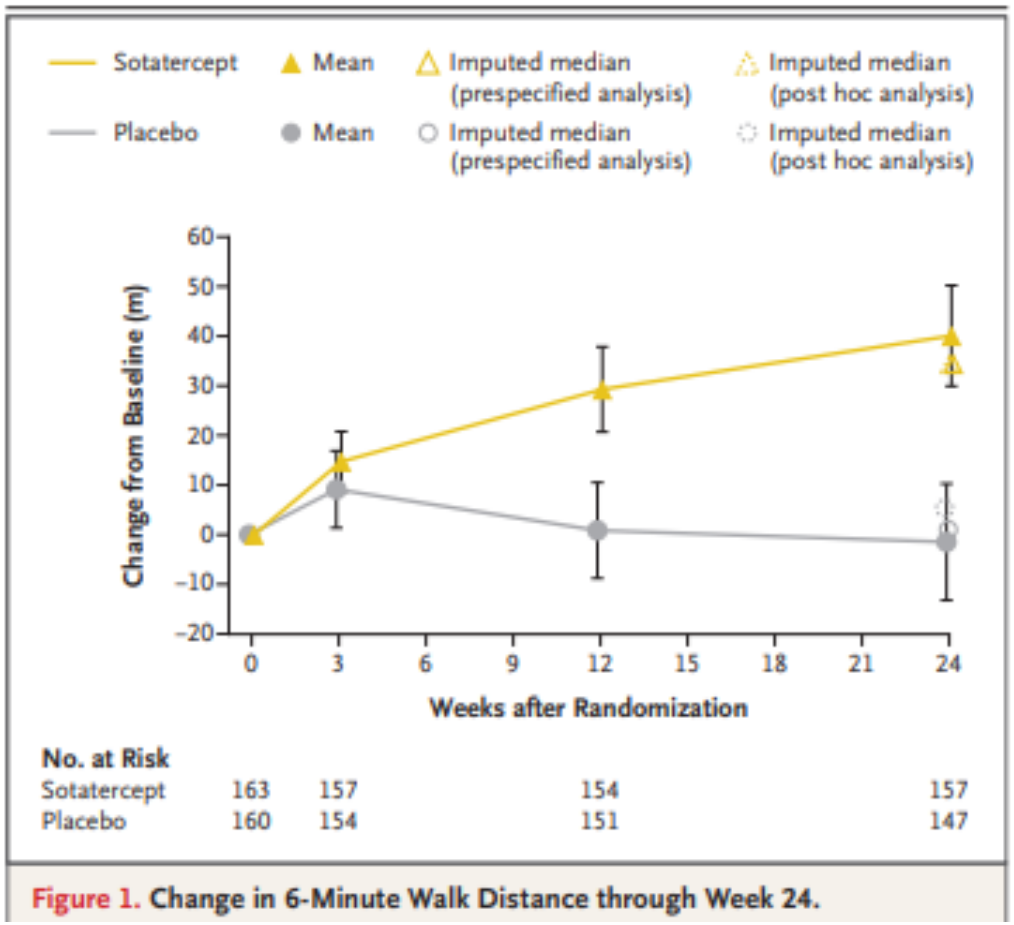

Figure 1. Change in 6-Minute Walk Distance through Week 24.

Table 2. Change from Baseline at Week 24 in Primary and Secondary Efficacy End Points (Intention-to-Treat Population).*

End Point	Sotatercept (N=163)	Placebo (N=160)
Primary end point		
6-Minute walk distance — m		
Median change estimate (95% CI) from baseline at wk 24†	34.4 (33.0 to 35.5)	1.0 (−0.3 to 3.5)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	40.8 (27.5 to 54.1)§¶	
Secondary end points		
Multicomponent improvement		
Patients who met all three criteria for 6-min walk distance, NT-proBNP level, and WHO functional class — no./total no.	63/162‖	16/159‖
Percentage of patients (95% CI)	38.9 (31.3 to 46.9)¶**	10.1 (5.9 to 15.8)
Pulmonary vascular resistance — dyn·sec·cm^{-5}		
Median change estimate (95% CI) from baseline at wk 24†	−165.1 (−176.0 to −152.0)	32.8 (26.5 to 40.0)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−234.6 (−288.4 to −180.8)§¶	
NT-proBNP — pg/ml		
Median change estimate (95% CI) from baseline at wk 24†	−230.3 (−236.0 to −223.0)	58.6 (46.0 to 67.0)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−441.6 (−573.5 to −309.6)§¶	
WHO functional class		
Patients with improvement at wk 24 from baseline — no./total no.	48/163¶**	22/159‖
Percentage of patients (95% CI)	29.4 (22.6 to 37.1)	13.8 (8.9 to 20.2)
Time to first occurrence of death or nonfatal clinical worsening event		
Hazard ratio (95% CI)††	0.16 (0.08 to 0.35)¶‡‡	
French risk score§§		
Patients with a low-risk score with the use of the simplified French model at wk 24 — no./total no.	64/162‖	29/159‖
Percentage of patients (95% CI)	39.5 (31.9 to 47.5)¶**	18.2 (12.6 to 25.1)
PAH-SYMPACT Physical Impacts domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	−0.13 (−0.15 to 0.00)	0.01 (0.00 to 0.13)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.26 (−0.49 to −0.04)¶‖	
PAH-SYMPACT Cardiopulmonary Symptoms domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	−0.12 (−0.14 to −0.08)	−0.01 (−0.03 to 0.00)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.13 (−0.26 to −0.01)¶‖	
PAH-SYMPACT Cognitive/Emotional Impacts domain score¶¶		
Median change estimate (95% CI) from baseline at week 24†	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)
Hodges–Lehmann location shift from placebo estimate (95% CI)‡	−0.16 (−0.40 to 0.08)	

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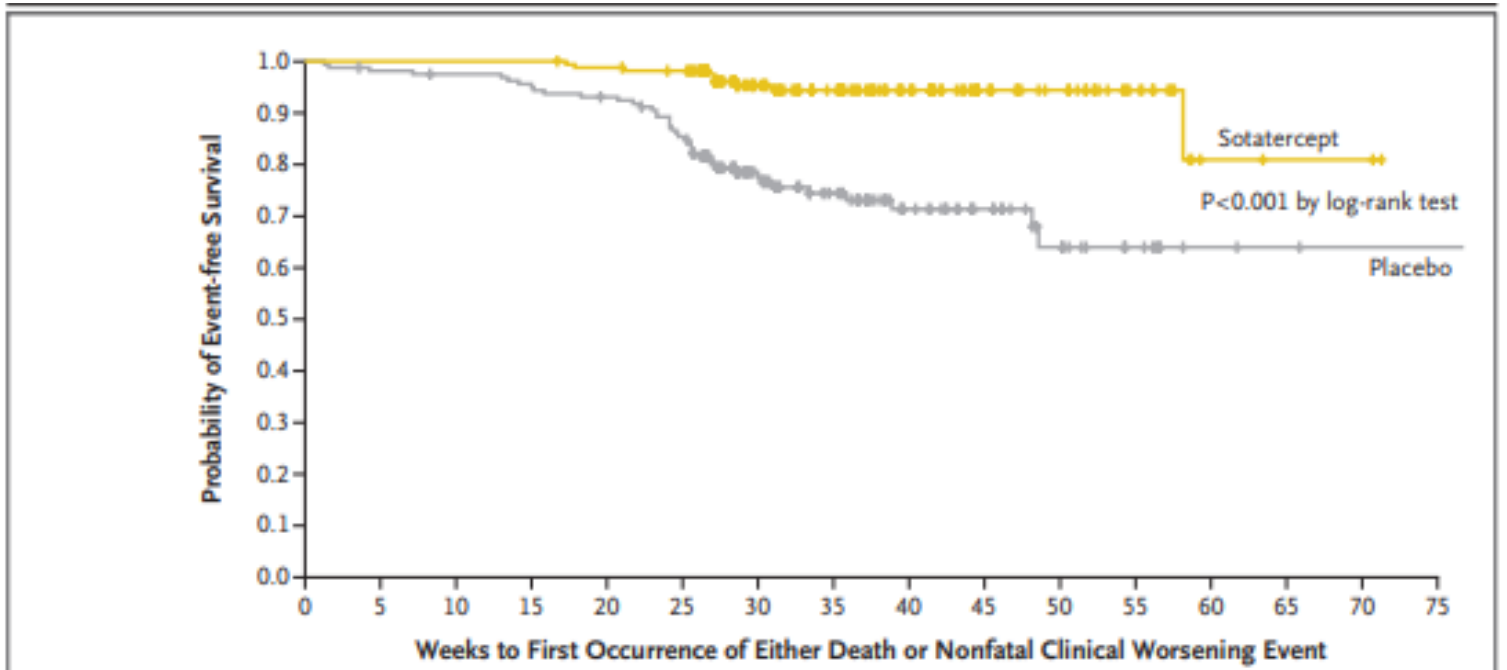
Time to death or clinical worsening event



	Sotatercept (N=163)	Placebo (N=160)
	no. (%)	
Total no. of patients who died or had ≥1 clinical worsening event	9 (5.5)	42 (26.2)
Assessment of first occurrence of either death or nonfatal clinical worsening event		
Death as first event	2 (1.2)	6 (3.8)
Worsening-related listing for lung or heart–lung transplantation	1 (0.6)	1 (0.6)
Initiation of rescue therapy or increase in dose of infusion prostacyclin by ≥10%	2 (1.2)	17 (10.6)
Atrial septostomy	0	0
Pulmonary arterial hypertension–related hospitalization for ≥24 hr	0	7 (4.4)
Worsening of pulmonary arterial hypertension	4 (2.5)	15 (9.4)

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Summary and Conclusions

PAH REMAINS A RARE CONDITION THAT REQUIRES DETAILED DIAGNOSIS

INITIAL THERAPY DIFFERS BASED ON PATIENT'S RISK AND PRESENCE OF COMORBIDITIES

ADVANCES IN THERAPY ARE NEARLY APPROVED AND WILL PROVIDE ADDITIONAL MORBIDITY AND MORTALITY BENEFIT

Updates in Pulmonary Arterial Hypertension Therapies

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