

Hemodynamic Effects of the Oral Prostacyclin Receptor (IP) Agonist Ralinepag in Pulmonary Arterial Hypertension (PAH)



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Background

- Ralinepag is a novel, next-generation, oral, highly selective prostacyclin receptor agonist¹
- Ralinepag, when formulated as an immediate-release (IR) capsule and given twice-a-day (bid), as done in this study, delivers a favorable PK profile with a low peak-to-trough ratio²
- Ralinepag has a long terminal half-life (~24 hours), supporting the use of once-a-day (qd) dosing with an extended-release (XR) tablet formulation in future clinical studies²

Objective

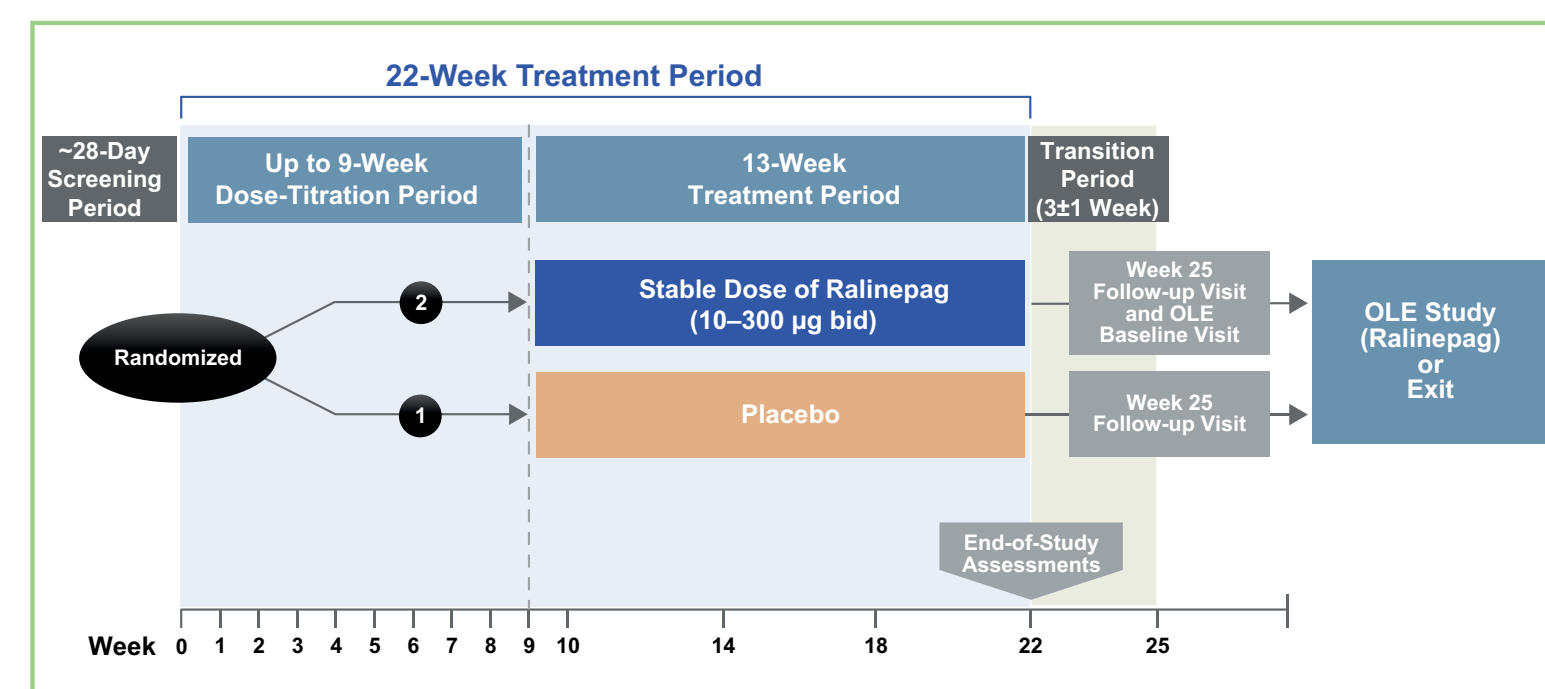
- To evaluate the efficacy, safety, and tolerability of ralinepag in a multicenter, double-blind Phase 2 study

Methods

Patient Population and Study Design

- This study enrolled 61 adults with stable functional class (FC) II–IV, Group 1 PAH, and 6-minute walk distance (6MWD) of 100–500 m
 - 39 patients were from Europe, 12 from the US, and 10 from Australia
- Patients were randomized 2:1 to receive ralinepag or placebo in a 9-week titration phase followed by 13-week maintenance (Figure 1)
- Ralinepag treatment was initiated at 10 µg bid and titrated weekly up to 300 µg bid, as tolerated (Figure 1)
- Right heart catheterization was performed at baseline and at Week 22
- All patients received background PAH treatment with an endothelin receptor agonist (ERA), phosphodiesterase-5 (PDE5i), or soluble guanylate cyclase stimulator (eg, riociguat), alone or in combination

Figure 1. Study Design: Ralinepag Phase 2 Randomized, Placebo-Controlled Trial in World Health Organization Group 1 PAH



Bid, twice daily; OLE, open-label extension.

Outcomes

Primary Efficacy Endpoint

- Absolute change in pulmonary vascular resistance (PVR) from baseline to Week 22

Secondary Endpoints

- Changes in 6MWD and hemodynamics
- Percentage change in PVR
- Safety and tolerability

Exploratory Endpoints

- Changes in N-terminal prohormone of B-type natriuretic peptide (NT-proBNP)

Imputation Strategy for Primary Endpoint Analysis

- Missing PVR values were populated using a conservative multiple imputation approach
- Analysis of covariance (ANCOVA) was run on each imputed data set, and then results were pooled

Results

Patient Characteristics

- Patients (40 ralinepag; 21 placebo) had FC III/IV (56%/42%/2%) PAH and mean (± standard deviation [SD]) 6MWD of 378 m (104 m) (Table 1)
- Baseline median PVR was 705 (ralinepag) and 480 (placebo) dyn·s·cm⁻⁵ (Table 1)
- At baseline, 65% of ralinepag-treated patients and 48% of patients given placebo were receiving background combination PAH treatment (Table 2)

Table 1. Demographics and Baseline Characteristics

	All Patients (N=61)	Ralinepag (n=40)	Placebo (n=21)
Age, years			
Mean (range)	49.4 (19–73)	46.2 (19–68)	55.6 (29–73)
Sex, n (%)			
Female	53 (87)	33 (83)	20 (95)
Race, n (%)			
White	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)
6MWD, m; mean	378	393	351
WHO FC, n (%) ^a			
II	34 (56)	22 (55)	12 (57)
III	26 (43)	17 (43)	9 (43)
IV	1 (2)	1 (3)	0
NT-proBNP, pg/mL; mean (median)	980 (343)	792 (335)	1362 (343)

^aPercentages may not sum to 100 due to rounding. FC, functional class; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; 6MWD, 6-minute walk distance; SD, standard deviation; WHO, World Health Organization.

Table 2. Patients' Medical History

	All Patients (N=61)	Ralinepag (n=40)	Placebo (n=21)
Duration of PAH, years			
Mean (SD)	3.9 (4.9)	4.4 (5.4)	2.9 (3.7)
Median	2.0	2.2	1.8
PAH classification, n (%)			
Idiopathic PAH	32 (53)	21 (53)	11 (53)
Heritable PAH	5 (8)	4 (10)	1 (5)
Drug or toxin induced	4 (7)	4 (10)	0 (0)
Associated PAH, n (%)	20 (33)	11 (28)	9 (43)
Background PAH therapy, %			
Monotherapy	41	35	52
Combination therapy	59	65	48
Monotherapy, n (%)			
ERA	6 (10)	2 (5)	4 (19)
PDE5i	19 (31)	12 (30)	7 (33)
Combination therapy, n (%)			
ERA + PDE5i	34 (56)	24 (60)	10 (48)
ERA + SGCS	2 (3)	2 (5)	0 (0)
New PAH treatment within 3–6 months of Day 1, n (%)	13 (21)	5 (13)	8 (38)

ERA, endothelin receptor antagonist; FC, functional class; PDE5i, phosphodiesterase-5 inhibitor; SGCS, soluble guanylate cyclase stimulator; SD, standard deviation.

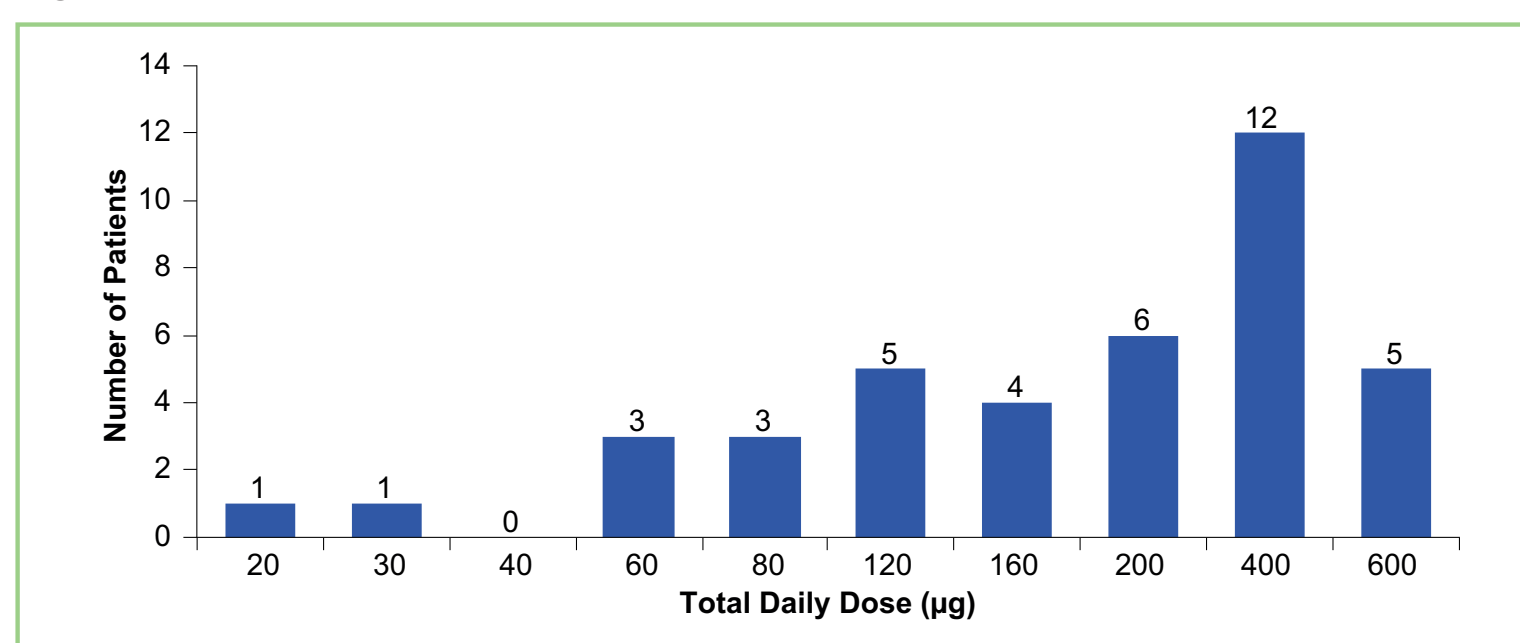
Patient Disposition

- In this Phase 2 study, 107 patients were screened
 - 46 patients were excluded and 61 were randomized
- Of the initial 40 patients in the ralinepag group, 34 completed the study
 - Five patients withdrew because of adverse events, and one was withdrawn due to investigator decision
- In the placebo group, 19 out of 21 patients completed the study and two patients withdrew due to adverse events

Ralinepag Dosing

- Ralinepag total daily maintenance doses were titrated as high as 600 µg, with the most common dose being 400 µg (Figure 2)

Figure 2. Distribution of Maintenance Dose



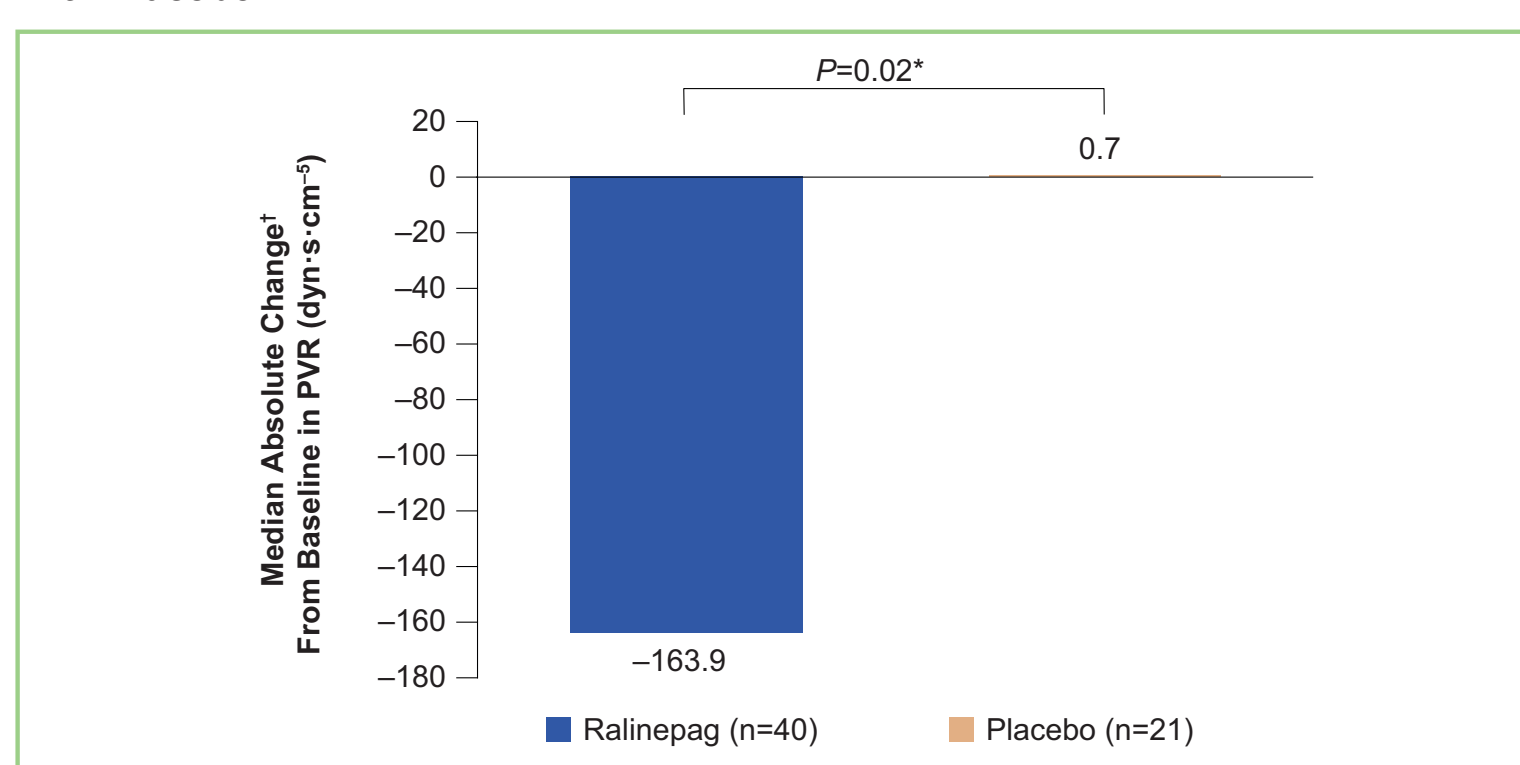
Primary Endpoint: Absolute Change in PVR

- Ralinepag decreased PVR by 163.9 dyn·s·cm⁻⁵ from baseline to Week 22, compared with an increase of 0.7 dyn·s·cm⁻⁵ with placebo, P=0.02 (Figure 3)

Secondary Endpoint: Percentage Change in PVR

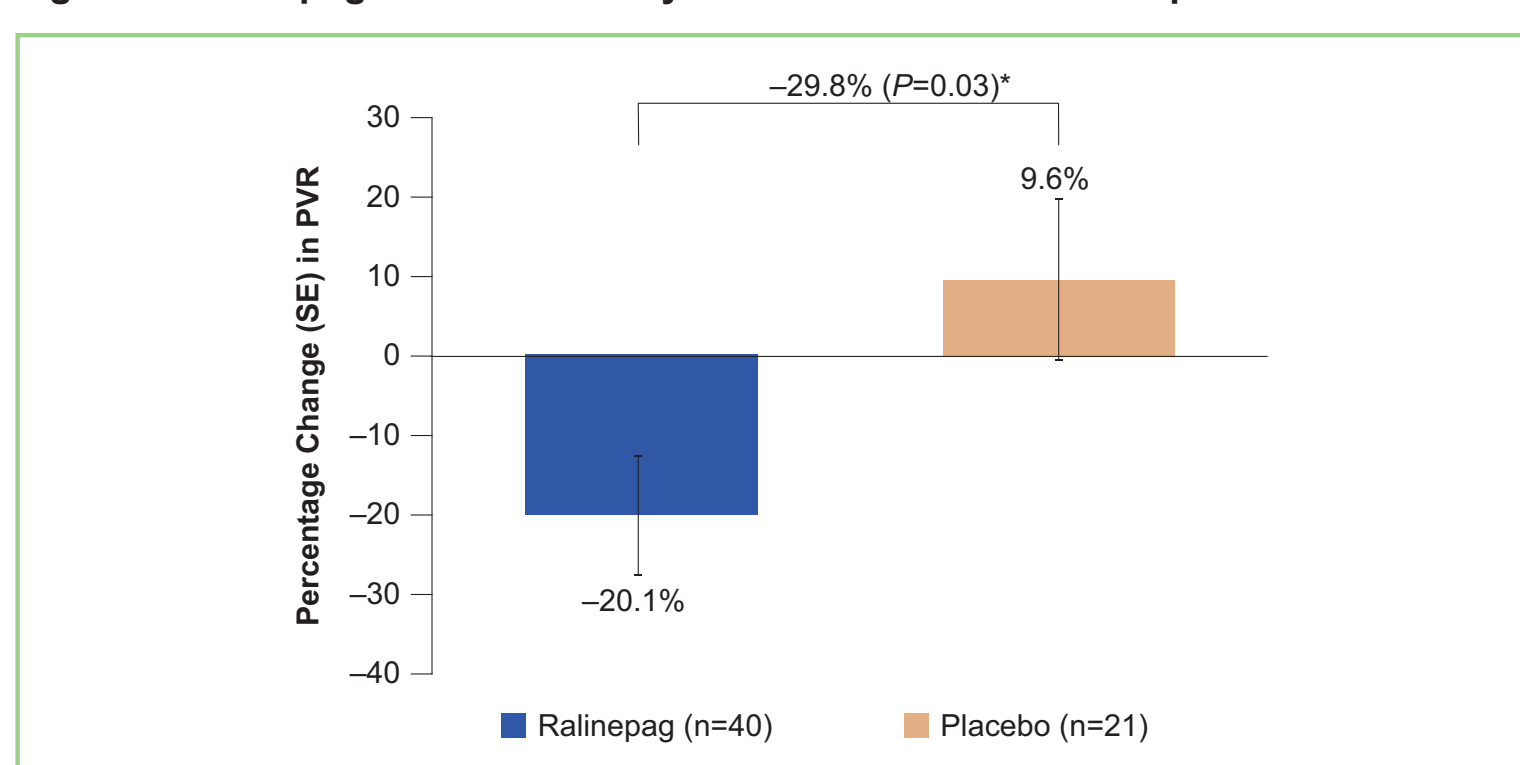
- There was a 29.8% reduction in PVR compared with placebo (P=0.03), and a 20.1% decrease from baseline for ralinepag (Figure 4)

Figure 3. Primary Endpoint: Ralinepag Significantly Reduced PVR Compared With Placebo



^aWithin-group geometric mean ratio (GMR) percentage change: placebo -0.4%, ralinepag -26.1%. Intention-to-treat population (n=61), imputation of missing values. ^bMedian change used due to non-normal distribution; mean absolute change from baseline: placebo 25.5, ralinepag -175.7 dyn·s·cm⁻⁵. PVR, pulmonary vascular resistance.

Figure 4. Ralinepag Reduced PVR by 29.8% From Baseline Compared With Placebo



^aLeast-squares mean change from placebo; nonparametric test to account for non-normal distribution. Intention-to-treat population (n=61). PVR, pulmonary vascular resistance; SE, standard error.

Secondary Endpoint: Change in Hemodynamic Parameters

- There was a significant reduction in mean pulmonary arterial pressure in the ralinepag-treated group (-6.1 mmHg) when compared to the placebo group (-2.9 mmHg) from baseline to Week 22, P=0.028 (Table 3)
- There was also a significant reduction in mean arterial blood pressure in the ralinepag-treated group (-8.2 mmHg) versus the placebo group (2.7 mmHg) from baseline to Week 22, P=0.001 (Table 3)

Table 3. Secondary Hemodynamic Parameters: Change From Baseline to Week 22

Hemodynamic Parameter	Baseline		Change From Baseline to Week 22 ^a		P-value ^b
	Ralinepag (n=34)	Placebo (n=19)	Ralinepag (n=34)	Placebo (n=19)	
Mean pulmonary arterial pressure (SD), mmHg	51.0 (15.26)	43.1 (10.08)	-6.1 (1.5)	-2.9 (2.0)	0.028
Cardiac index (SD), L·min ⁻¹ ·m ⁻²	2.6 (0.60)	2.9 (0.49)	0.31 (0.12)	-0.0 (0.16)	0.183
Mixed venous oxygen saturation (SD), %	65.0 (7.86)	68.0 (6.28)	1.0 (1.05)	0.6 (1.56)	0.412
Right atrial pressure (SD), mmHg	8.1 (6.14)	8.7 (5.06)	-0.3 (0.68)	-2.0 (0.89)	0.118
Pulmonary capillary wedge pressure (SD), mmHg	9.3 (2.93)	10.5 (3.17)	-0.4 (0.59)	-0.3 (0.77)	0.119
Mean arterial blood pressure (SD), mmHg	89.6 (16.13)	86.8 (10.55)	-8.2 (1.83)	-2.7 (2.35)	0.001
Heart rate (SD), bpm	77.1 (13.61)	71.6 (7.87)	0.9 (1.92)	-0.8 (2.49)	0.961

^aLeast-squares mean (standard error) change from baseline. ^bP-value based on a stratified Wilcoxon rank test – ANCOVA model with three factors (treatment, WHO/NYHA functional class, background PAH therapy). bpm, beats per minute; NYHA, New York Heart Association; SD, standard deviation.

Secondary Endpoint: Change in 6MWD from Baseline

- Least-squares mean 6MWD increased from baseline by 36.2 m for ralinepag compared with 29.4 m for the placebo group, but these increases were not significantly different
- There was a significant increase in least-squares mean 6MWD from baseline for patients treated with ralinepag (P=0.003), but not for those given placebo (P=0.075)

Secondary Endpoint: Ralinepag Safety and Tolerability

- The most common adverse events were as expected for prostacyclin receptor agonists (Table 4)

Table 4. Most Common Adverse Events

Adverse Events, n (%)	Ralinepag (n=40)	Placebo (n=21)
Headache	31 (78)	6 (29)
Nausea	20 (50)	5 (24)
Diarrhea	19 (48)	3 (14)
Jaw pain	14 (35)	3 (14)
Flushing	13 (33)	1 (5)

- Adverse event frequency appeared to diminish following the 9-week titration phase

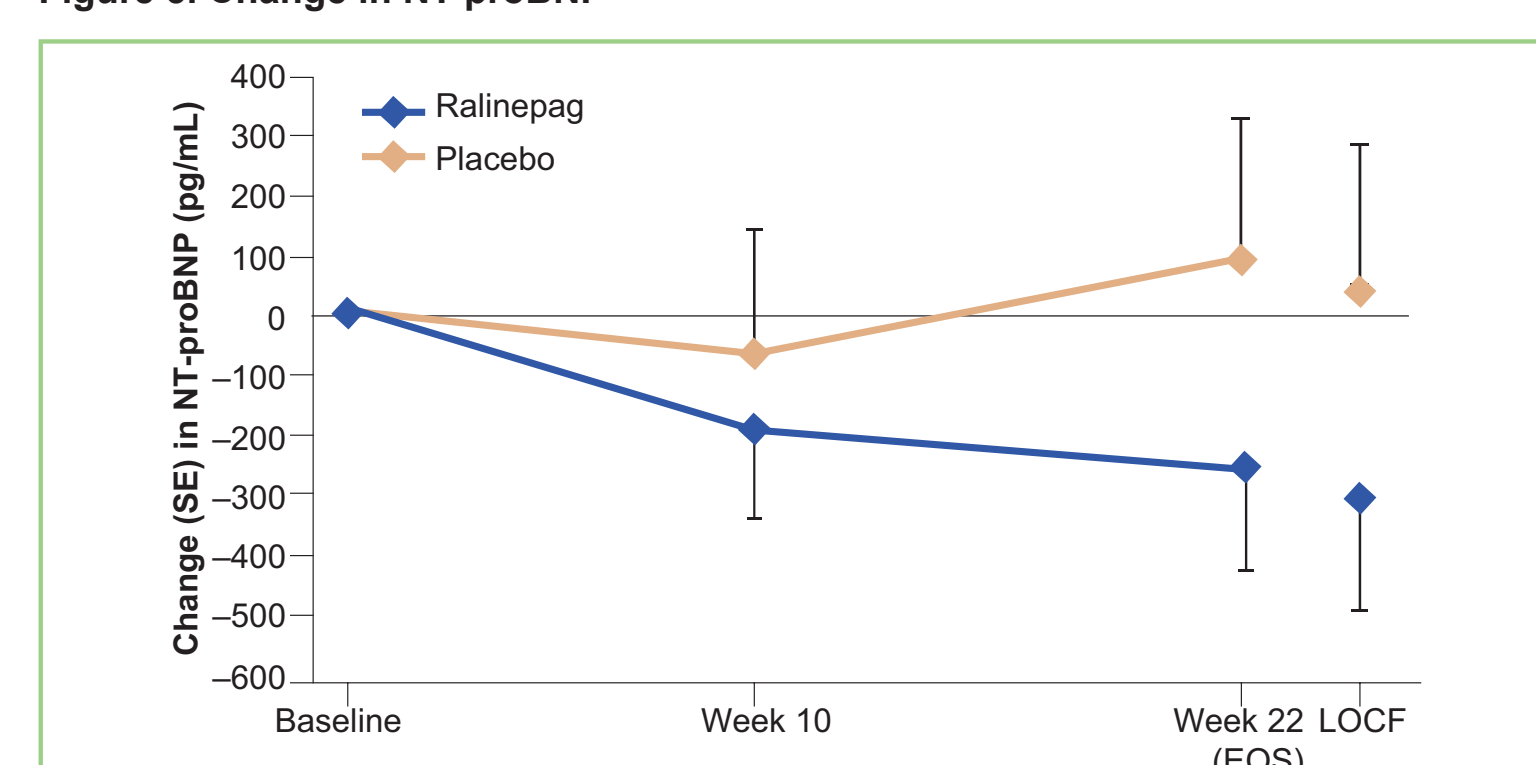
Serious Adverse Events and Discontinuations

- In this study there were two deaths, both of which were in the placebo group
- Serious adverse events occurred in 10% (4/40) of ralinepag patients and 29% (6/21) of placebo patients
- Discontinuations occurred in 13% (5/40) and 10% (2/21) of patients in the ralinepag and placebo groups respectively

Exploratory Endpoints: Change in NT-proBNP from Baseline

- Patients treated with ralinepag had a numerically greater mean reduction in NT-proBNP (Figure 5) from baseline to Week 22 versus placebo, though this difference was not significantly different

Figure 5. Change in NT-proBNP



EOS, end of study; LOCF, last observation carried forward; NT-proBNP, N-terminal prohormone of B-type natriuretic peptide; SE, standard error.

Conclusions

- Ralinepag significantly reduced PVR compared with placebo in patients with FC II–IV Group 1 PAH on single or dual background therapy
- Ralinepag, but not placebo, significantly increased 6MWD from baseline to Week 22 – but this increase was not statistically significantly different from that seen with placebo
- Tolerability and adverse event profile for ralinepag was consistent with the known effects of prostacyclin receptor agonists
- The clinical benefit of targeting the prostacyclin receptor with ralinepag in patients with Group 1 PAH will be evaluated in a future Phase 3 program testing a once-daily XR tablet formulation

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Disclosures

J Adams, SA Turner, and P Klassen are employees of Arena Pharmaceuticals. HW Farber has received honoraria for advisory boards from Arena Pharmaceuticals related to the submitted work; other relevant commercial interests: advisory boards, honoraria, and/or grant support for Actelion, Gilead, United Therapeutics, Bayer, and Bellerophon. AD Ristić reports personal fees from Arena Pharmaceuticals, Pfizer, Merck, Krka Pharma, Roche Diagnostics, grants from Servier, Actavis, and Bayer AG; grants and personal fees from Boehringer Ingelheim, Berlin-Chemie/Novartis, AstraZeneca, and Hemofarm (STADA). A Keogh participated in clinical trials in PAH for Actelion, Bayer, Pfizer, United Therapeutics, and Reata Pharmaceuticals. F Torres has been a consultant/speaker for Actelion, Bayer, SteadyMed, Genentech, Boehringer Ingelheim, Mallinckrodt, Arena Pharmaceuticals, and Reata Pharmaceuticals. He has received research funding (paid to institution) from United Therapeutics, Medtronic, Bellerophon, the NIH, Arena Pharmaceuticals, and Gilead. VV McLaughlin has served as a consultant and/or advisor for Actelion Pharmaceuticals US, Inc., Bayer, Gilead Sciences, Inc., Medtronic, Merck, St. Jude Medical, and United Therapeutics Corporation. The University of Michigan has received research funding from Actelion Pharmaceuticals US, Inc., Arena Pharmaceuticals, Bayer, and Gilead. P Escribano Subias reports personal fees from Actelion, Bayer, GlaxoSmithKline, and Merck Sharp & Dohme; grants from Actelion, Bayer, GlaxoSmithKline, and Ferrer. N Sood reports participating in a Speaker Bureau for Gilead; and research for Actelion, Bayer, Arena Pharmaceuticals, Reata, and United Therapeutics. L Rubin has received consulting fees from Actelion, Arena Pharmaceuticals, Johnson & Johnson, Karos, SoniVie and MannKind for assistance developing novel therapies for pulmonary vascular diseases.

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