Efficacy and Safety of the Oral Prostacyclin Receptor (IP) Agonist Ralinepag in Pulmonary Arterial Hypertension (PAH)

HW Farber, MD[1], AD Ristic, MD, PhD[2], SA Turner, PhD[3], C Cabell, MD[3], E Parsley, MD[3], A Keogh, MD[4], RJ Oudiz, MD[5], A Ghofrani, MD[6]

[1]Professor of Medicine and Director of the Pulmonary Hypertension Center, Boston University School of Medicine, Boston, MA, USA;
[2]Belgrade University School of Medicine, Belgrade, Serbia; [3]Arena Pharmaceuticals, San Diego, CA, USA; [4]St Vincent's Hospital, Darlinghurst, NSW, Australia;
[5]Department of Medicine, Division of Cardiology, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA;
[6]University of Giessen and Marburg Lung Center, Giessen, Germany

Background

- Ralinepag is a novel, next-generation, oral, nonprostanoid, highly selective prostacyclin receptor agonist[1]
- Ralinepag is formulated to deliver a favorable PK profile, with low peak-to-trough blood levels[2]
- Ralinepag has a long half-life (~24 hours), supporting once-a-day (qd) dosing in future clinical studies[2]

Objective

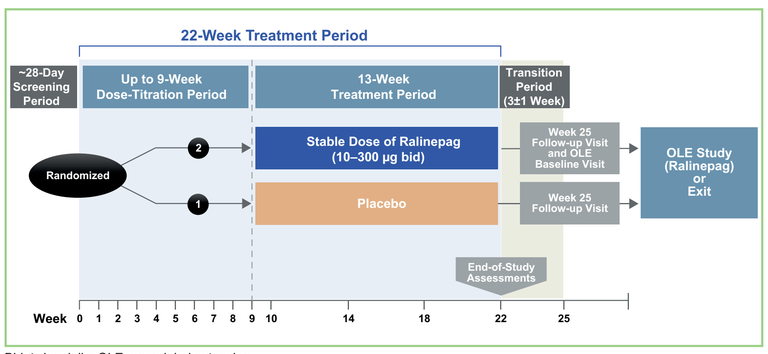
- To evaluate the efficacy, safety, and tolerability of ralinepag in a multicenter, double-blind Phase 2 study

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 data set, and then results were pooled

Results

Patient Characteristics

- Patients (40 ralinepag; 21 placebo) had FC II/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 (SD)	49.4 (13.0)	46.2 (12.3)	55.6 (12.1)
Sex, n (%) Female	53 (87)	33 (83)	20 (95)
Race, n (%) White Other	57 (93) 4 (7)	38 (95) 2 (5)	19 (91) 2 (10)
PVR, dyn·s·cm^{-5}; mean (median)	717 (576)	780 (705)	598 (480)
6MWD, m; mean	378	393	351
WHO FC, %* II III IV	 56 43 2	 55 43 3	 57 43 0
NT-proBNP, pg/mL; mean (median)	980 (343)	792 (335)	1362 (343)

*Percentages 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) Median	 3.9 (4.9) 2.0	 4.4 (5.4) 2.2	 2.9 (3.7) 1.8
PAH classification, n (%) Idiopathic PAH Heritable PAH Drug or toxin induced Associated PAH, n (%)	 32 (53) 5 (8) 4 (7) 20 (33)	 21 (53) 4 (10) 4 (10) 11 (28)	 11 (53) 1 (5) 0 (0) 9 (43)
Background PAH Therapy, (%) Monotherapy Combination therapy	 41 59	 35 65	 52 48
Monotherapy, n (%) ERA PDE5i	 6 (10) 19 (31)	 2 (5) 12 (30)	 4 (19) 7 (33)
Combination therapy, n (%) ERA + PDE5i ERA + SGCS	 34 (56) 2 (3)	 24 (60) 2 (5)	 10 (48) 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.

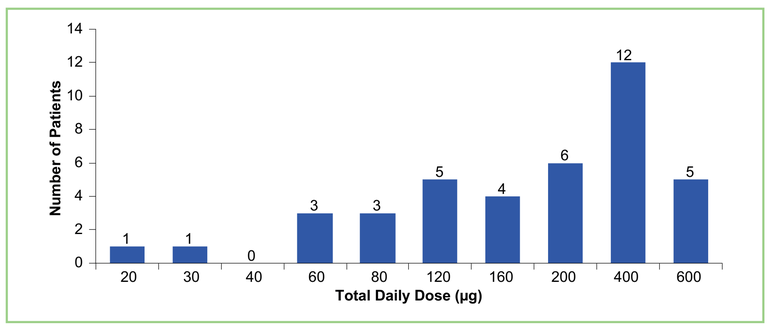
Patient Disposition

- 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 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



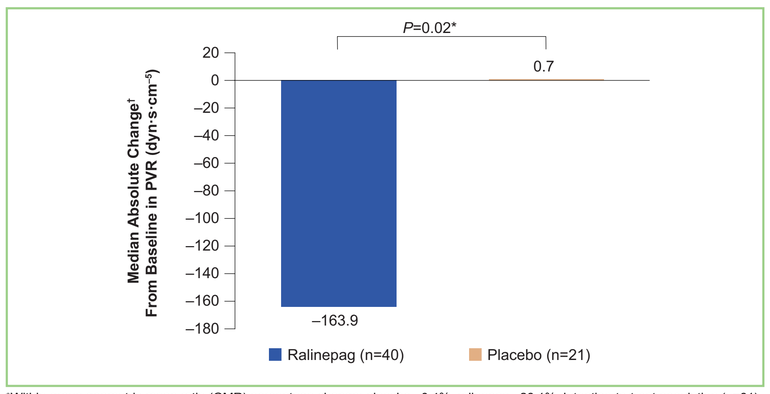
Primary Endpoint: Absolute Change in PVR

- 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

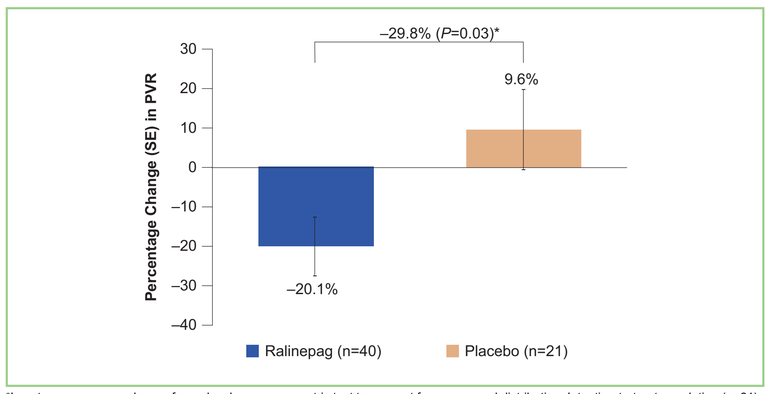
- There was a 29.8% reduction in PVR compared with placebo (*P*=0.03), and a 20.1% decrease from baseline for ralinepag (**Figure 4**)

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



*Within-group geometric mean ratio (GMR) percentage change: placebo –0.4%, ralinepag –26.1%. Intention-to-treat population (n=61), imputation of missing values.
†Median 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



*Least-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*		*P*-value†
	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·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

*Least-squares mean (standard error) change from baseline.
†*P*-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 by 36.2 m for ralinepag compared with 29.4 m for the placebo group, but this was not significantly different
- There was a significant increase in least-squares mean 6MWD from baseline for patients treated with ralinepag (*P*=0.003)

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

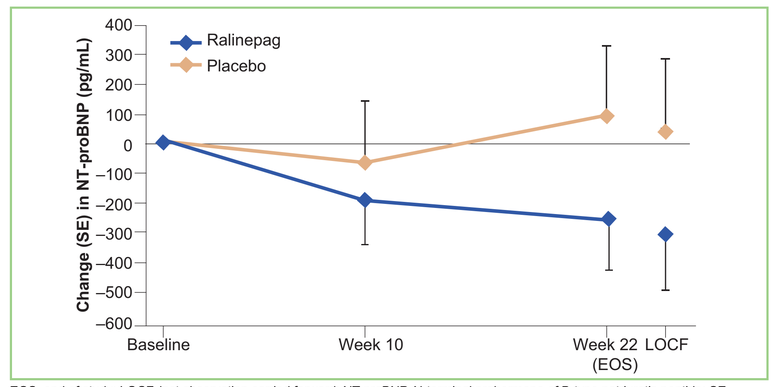
Serious Adverse Events and Discontinuations

- 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 increased 6MWD from baseline to Week 22 – not statistically significant from 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**

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Disclosures

SA Turner, C Cabell, and E Parsley 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, Bellerophon.

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