Ralinepag Plasma Levels Correlate With Improvements in Functional and Hemodynamic Parameters in Patients With Pulmonary Arterial Hypertension (PAH)

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Background

- Ralinepag is a next-generation, oral, selective and potent prostacyclin receptor agonist with a high binding affinity (K_i) of 3.4 nM for the human prostacyclin receptor in development for pulmonary arterial hypertension (PAH)[1,2]
- In a Phase 2 study, ralinepag significantly improved pulmonary vascular resistance (PVR) compared with placebo in patients on monotherapy (35%) or dual (65%) background therapy
- The tolerability and adverse event profile in this study was consistent with the known side effects of prostacyclin receptor agonists

Rationale

- There is evidence of a dose-response relationship for some drugs targeting the prostacyclin receptor; however, the relationship between drug plasma levels and hemodynamic parameters is unknown
- Prostacyclin receptor therapies are typically initiated at low doses and up-titrated slowly until an effective and well-tolerated maintenance dose is achieved
- Understanding the relationship between plasma levels and clinical response helps to define optimal dose levels

Study Aim

- This *post hoc* analysis of the Phase 2 study evaluated whether ralinepag plasma levels correlated with improvements in functional and/or hemodynamic parameters, and/or serum biomarkers, including PVR, 6-minute walk distance (6MWD), and B-type natriuretic peptide (BNP)

Methods

Patient Population and Study Design

- This Phase 2 study enrolled 61 adults with stable functional class (FC) II–IV, Group 1 PAH, and 6MWD of 100–500 m
  - 39 patients were from Europe, 12 from the US, and 10 from Australia
- Patients were randomly assigned 2:1 to receive ralinepag or placebo in a 9-week maximum-tolerated titration phase followed by a 13-week maintenance phase
- Right heart catheterization was performed at baseline (BL) and at Week 22 as per protocol, 4 hours post dose
- All patients were receiving at least one background PAH treatment
- PK sampling was performed at both trough and 4-hour-post-dose levels throughout the study; Only 4-hour levels were used for the plasma level correlations in this poster
  - The relationships between plasma levels and efficacy measures were done by linear regression analysis

Outcomes

Primary Efficacy Endpoint

- Absolute change in PVR from BL to Week 22

Secondary Endpoints

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

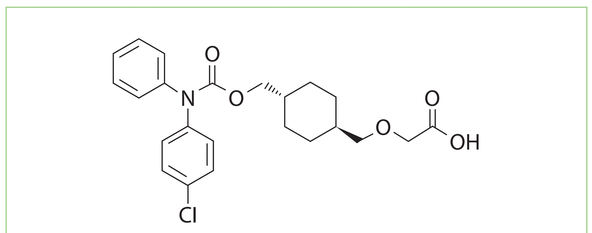
Exploratory Endpoints

- Changes in BNP

Imputation Strategy for Primary Endpoint Analysis

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

Figure 1. Ralinepag: An Oral Prostacyclin Receptor Agonist



Results

Patient Characteristics

- Baseline characteristics of the study population are shown in **Table 1**

Table 1. Baseline Characteristics

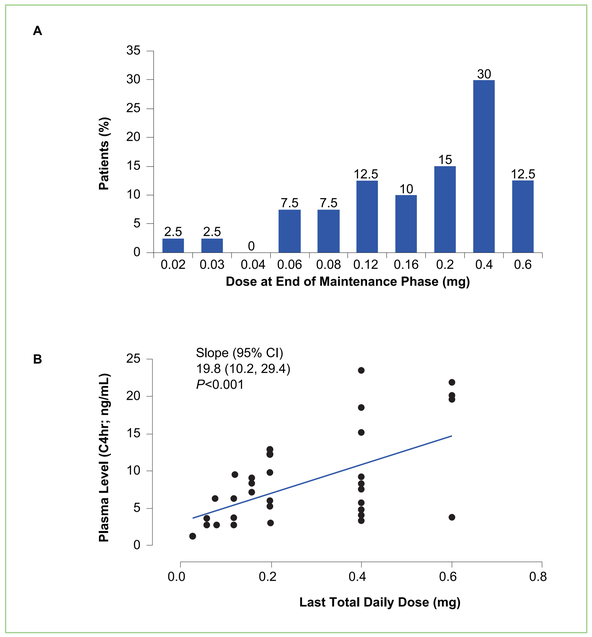
	All Patients (N=61)	Ralinepag (n=40)	Placebo (n=21)
Age, years Median (min, max)	51.0 (19, 73)	46.5 (19, 68)	60.0 (29, 73)
Sex, n (%) Female	53 (87)	33 (83)	20 (95)
Race, n (%)* White Other	57 (93) 4 (7)	38 (95) 2 (5)	19 (91) 2 (10)
PVR, dyn·s·cm^{-5}; mean (median)	717 (576)	780 (705)	598 (480)
6MWD, m (mean)	378	393	351
WHO FC, %* II III IV	56 42 2	55 43 3	57 43 0
BNP, pg/mL; mean (median)	168 (58)	160 (67)	183 (52)
PAH classification, n (%) Idiopathic PAH Heritable PAH Drug or toxin induced Associated PAH, n (%) Scleroderma SLE CHD	32 (53) 5 (8) 4 (7) 20 (33) 13 (21) 5 (8) 2 (3)	21 (53) 4 (10) 4 (10) 11 (28) 6 (15) 3 (8) 2 (5)	11 (53) 1 (5) 0 (0) 9 (43) 7 (33) 2 (10) 0 (0)
Background PAH therapy, n (%) Monotherapy Combination therapy	25 (41) 36 (59)	14 (35) 26 (65)	11 (52) 10 (48)

*Percentages may not sum to 100 due to rounding. BNP, B-type natriuretic peptide; CHD, coronary heart disease; FC, functional class; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; SLE, systemic lupus erythematosus; WHO, World Health Organization; 6MWD, 6-minute walk distance.

Ralinepag Dosing

- Ralinepag total daily maintenance doses were as high as 0.6 mg, and the most common dose was 0.4 mg (**Figure 2A**)
- Scatter plot of C_{max} and the last ralinepag dose level is seen in **Figure 2B**

Figure 2. Ralinepag Dosing (A) and Correlation Between Ralinepag Plasma Levels and Dose (B)

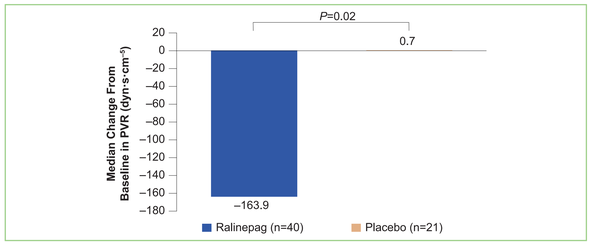


CI, confidence interval; C4hr, concentration at 4-hour levels.

Primary Endpoint: Absolute Change in PVR

- PVR decreased by 163.9 dyn·s·cm^{-5} from BL to Week 22 in patients receiving Ralinepag, compared with an increase in PVR of 0.7 dyn·s·cm^{-5} in patients receiving placebo, *P*=0.02 (**Figure 3**)

Figure 3. Ralinepag Change in PVR

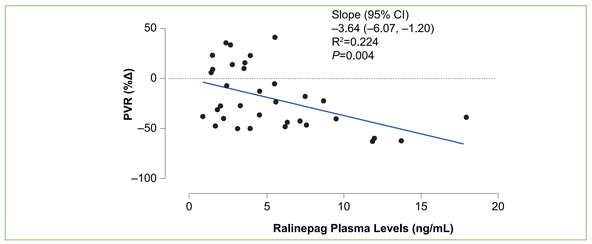


PVR, pulmonary vascular resistance.

Plasma Level Correlations

- There was a significant correlation between ralinepag plasma levels and improvements in PVR (**Figure 4**; *P*=0.004)
- There was no significant correlation between dose and PVR percentage change

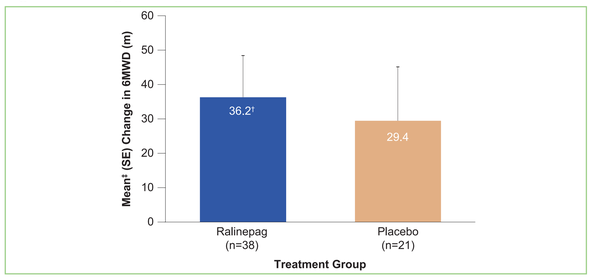
Figure 4. Correlation Between Ralinepag Plasma Levels (Mean Week 9–22, 4 hours Post-Dose) and Change in PVR



CI, confidence interval; PVR, pulmonary vascular resistance.

- 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 (**Figure 5**)
- There was a significant increase in least-squares mean 6MWD from BL for patients treated with ralinepag (**Figure 5**; *P*=0.003), but not for those given placebo (*P*=0.075)

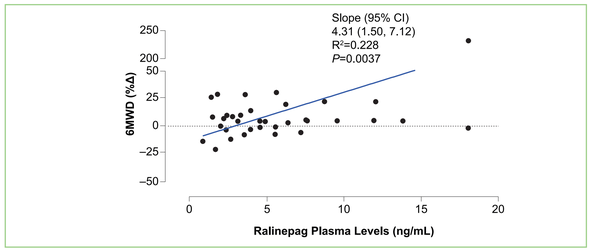
Figure 5. Change in 6MWD



†Significant change from BL within ralinepag group (*P*=0.003). ‡Least-squares mean. 6MWD, 6-minute walk distance; SE, standard error.

- There was a significant correlation between ralinepag plasma levels and improvements in 6MWD (**Figure 6**; *P*=0.0037)

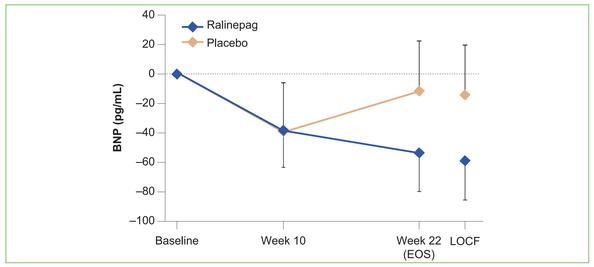
Figure 6. Correlation Between Ralinepag Plasma Levels (Mean Week 9–22, 4 hours Post-Dose) and Change in 6MWD



CI, confidence interval; 6MWD, 6-minute walk distance.

- Patients treated with ralinepag had a numerically greater mean reduction in BNP from BL to Week 22 versus placebo, although this difference was not significantly different (**Figure 7**)

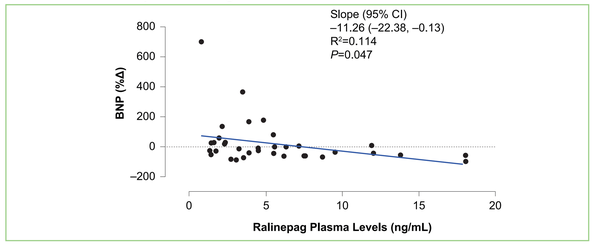
Figure 7. Change in BNP



BNP, B-type natriuretic peptide; EOS, end of study; LOCF, last observation carried forward.

- There was a significant correlation between ralinepag plasma levels and improvements in BNP (**Figure 8**; *P*=0.047)

Figure 8. Correlation Between Ralinepag Plasma Levels (Mean Week 9–22, 4 hours Post-Dose) and Change in BNP



BNP, B-type natriuretic peptide; CI, confidence interval.

Secondary Endpoint: Ralinepag Safety and Tolerability

- The most common adverse events were as expected for prostacyclin receptor agonists and included headaches, nausea, diarrhea, jaw pain, and flushing
- Adverse event frequency decreased following 9-week titration phase

Summary and Conclusions

- **Ralinepag is a next-generation, oral, selective and potent prostacyclin receptor agonist in development for PAH**
- **Ralinepag significantly reduced PVR compared with placebo in patients with FC II–IV Group 1 PAH on single or dual background therapy**
- **This *post hoc* analysis of the Phase 2 study revealed that efficacy better correlated with ralinepag plasma levels than with ralinepag dosing**
- **This is the first study demonstrating a correlation between plasma levels of an oral drug targeting the prostacyclin receptor and hemodynamic parameters, potentially improving the clinical management of optimal dosing**

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Disclosures

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.
N Sood: has participated in a Speaker Bureau for Gilead; and research for Actelion, Bayer, Arena Pharmaceuticals, Reata, and United Therapeutics.
IR Preston: is principal investigator for studies sponsored by Actelion, Bayer, Eiger, Gilead, United Therapeutics (Tufts Medical Center); has received honoraria for consultancies from Actelion, Gilead; and is a member of the adjudication committee for Pfizer clinical trials.
SA Turner, **P Klassen** are employees of Arena Pharmaceuticals.
VF Tapson: has received consulting fees and research funds from Actelion Pharmaceuticals, Bayer, United Therapeutics Corporation, Reata Pharmaceuticals, and Arena Pharmaceuticals; and speaker honoraria from Actelion Pharmaceuticals, Bayer, and United Therapeutics Corporation.
JL Vachiery: reports other from Arena Pharmaceuticals, Bial Portella, Bayer, and MSD; grants from Actelion Pharmaceuticals and GSK
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.
RJ Oudiz: received funding to conduct clinical research and consultancy fees from Arena Pharmaceuticals.

References

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