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Early View

Original article

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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

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Running Title: Oral Ralinepag for Treatment of Pulmonary Arterial Hypertension

Summary of most important findings: In this randomized, placebo-controlled Phase 2 22-week study of PAH patients on single or dual oral background therapy, ralinepag, an oral IP receptor agonist, significantly reduced PVR.

Abstract

PURPOSE: This Phase 2 study was designed to assess the efficacy, safety and tolerability of immediate-release (IR) orally administered ralinepag, a selective, non-prostanoid prostacyclin receptor (IP) agonist with a 24-hour terminal half-life, compared to placebo in adult patients with symptomatic pulmonary arterial hypertension (PAH).

METHODS: Sixty-one PAH patients who were receiving standard of care, including mono or dual PAH -targeted background therapy were randomized 2:1 to ralinepag (n=40) or placebo (n=21). The starting dose of ralinepag was 10 mcg twice daily (bid). Dosage was then up titrated as tolerated over the course of the 9-week dose-titration period, to a maximum total daily dose of 600 mcg (300 mcg bid). The primary efficacy endpoint was the absolute change in pulmonary vascular resistance (PVR) from baseline to Week 22. Additional endpoints included percentage change in PVR from baseline, other hemodynamic parameters, 6-minute walk distance (6MWD), and safety and tolerability.

RESULTS: Ralinepag significantly decreased PVR by 163.9 dyn.sec/cm^5 compared to an increase of 0.7 dyn.sec/cm^5 with placebo (p=0.02); the least-squares mean change from baseline PVR was -29.8% compared with placebo (p=0.03). 6MWD increased from baseline by 36.2 m with ralinepag and 29.4 m with placebo (p = 0.90). Serious adverse events occurred in 10% of ralinepag patients and 29% of placebo patients. Study discontinuations occurred in 13% of ralinepag patients and 10% of placebo patients.

SUMMARY: Ralinepag reduced PVR compared with placebo in PAH patients on mono (41%) or dual combination (59%) background therapy.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is characterized by vascular remodeling of the small pulmonary arteries that results in elevated pulmonary vascular resistance and right ventricular failure. PAH is thought to be initiated by dysfunction of several key mechanisms influencing vasomotor control, proliferation, inflammation and in situ thrombosis. The vasculopathy is associated with excessive production of growth factors, pro-inflammatory mediators, and vasoconstrictors, and a diminished production of potent vasodilators and inhibitors of platelet aggregation.[1,2]

Prostacyclin is produced in vascular endothelial cells and normally contributes to vasodilation, inhibition of smooth muscle cell proliferation, inhibition of platelet aggregation, and inhibition of inflammation.[3,4] The functions of prostacyclin in the pulmonary circulation are mediated primarily by a specific cell-surface receptor, the prostacyclin receptor (IP), which is expressed on platelets, smooth muscle and endothelial cells and belongs to the G-protein coupled receptor (GPCR) class. The binding of prostacyclin to the receptor triggers the activation of the G-protein and increases intracellular cAMP, which activates downstream signaling to produce the vasoregulatory effects. Activation of the IP receptor, either through the use of prostacyclin analogues or IP receptor activating drugs, is a means of pharmacologically targeting the diminished prostacyclin synthesis that is characteristic of PAH.

Continuous intravenous infusion of prostacyclin (epoprostenol) was the first PAH-targeted treatment to receive regulatory approval and remains the preferred treatment for those who are severely impaired.[5] However, the clinical use of epoprostenol is challenging due to its poor bioavailability and instability in blood, requiring complex and

life changing drug delivery systems. Accordingly, one of the most important priorities in PAH therapeutic research, particularly for patients with less severe disease, has been identification of more chemically stable and bioavailable molecules that specifically target the IP receptor.

Currently approved oral prostacyclin therapies (selexipag and treprostinil) have short half-lives (6.5-13 hrs for active metabolite of selexipag; 4.5 hours for treprostinil) leading to relatively large fluctuations between peak and trough plasma concentrations. These fluctuations stand in contrast to the continuous therapeutic plasma levels and 24 hour IP receptor engagement achieved with continuous intravenous infusion of epoprostenol.

Ralinepag is a next generation, orally available, non-prostanoid, selective, and potent prostacyclin receptor (IP) agonist that has been studied in human pulmonary tissues.[6] *In vitro* studies indicate ralinepag has high binding affinity and selectivity at the human IP receptor. [7] Two earlier phase 1 studies demonstrated a favorable safety and tolerability profile for single and multiple ascending doses of immediate release (IR), orally administered ralinepag in healthy volunteers.[8] Pharmacokinetic data from the SAD/MAD study suggests the IR formulation of ralinepag yields an effective half-life suitable for BID dosing. The present study was designed to investigate the efficacy, safety and tolerability of twice-daily, orally administered ralinepag IR capsules in adult patients with symptomatic PAH.

METHODS

Patients & Study Design

This was a phase 2, multicenter, international, double-blind, placebo-controlled, randomized trial of 22 weeks' duration. Written informed consent was obtained from all study subjects, and protocols were approved by the institutional review board at each participating study site. Data collection and management were conducted by the study sponsor consistent with a pre-determined statistical analysis plan.

The study population included male and female patients between the ages of 18 and 75 years diagnosed with symptomatic PAH of idiopathic or heritable origin; induced by drugs and toxins; or associated with connective tissue disease, human immunodeficiency virus infection or surgically repaired congenital systemic-pulmonary shunt. Patients were required to be on a stable dose of an oral disease-specific PAH therapy, with either an ERA and/or a PDE5 inhibitor or sGC stimulator, for at least 3 months and had to remain on stable doses for the duration of the study. Eligible patients demonstrated WHO/NYHA functional class II-IV symptoms and a 6MW distance of ≥100 meters and ≤500 meters. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and its amendments, consistent with Good Clinical Practices and local regulatory requirements.

Study Procedures

Eligible patients were randomized 2:1 to ralinepag or placebo. Randomization was stratified by baseline WHO/NYHA functional class (II versus III or IV). All patients were instructed to take their assigned study drug with food.

Optimal dosing of IP agonists in PAH patients requires titration on an individualized basis up to a maximum tolerated dose (MTD) in order to mitigate potentially severe side effects (e.g. nausea, headache, flushing, lightheadedness). The present study consisted of a dose titration period followed by a maintenance period. The dose titration period occurred during the first 9 weeks of the study and was followed by a 13-week maintenance period. A follow-up visit was to occur approximately 3 weeks after the end of the maintenance period (Week 25). (Figure 1) Over the course of the 9-week dose-titration period, dosages were up titrated weekly according to each patient's tolerance, with a maximum daily dose of 600 mcg (300 mcg bid). The titration schedule was to begin relatively slowly with 10 mcg/day increases ending with 200 mcg/day increases during the last 2 weeks of the titration period (titration schedule [total daily dose, mcg] 20, 30, 40, 60, 80, 120, 160, 200, 400, 600). Doses were permitted to be reduced based on tolerability, however the final dose attained during the titration period was required to be maintained during the 13-week treatment period prior to evaluation at Week 22. Patients were instructed to continue the same dose and regimen of disease-specific PAH medications for the duration of the study.

During the study, the following clinical assessments of efficacy were performed: hemodynamic parameters by right heart catheterization (RHC), 6MWD, assessment of clinical worsening, N-terminal prohormone of B-type natriuretic peptide (NT-proBNP)

levels, and WHO/NYHA functional class. Safety was assessed by evaluating adverse events (AEs), clinical safety laboratory tests (hematology, serum chemistry, urinalysis), vital signs, 12-lead ECGs, and physical examinations. Samples for measurement of NT-ProBNP were frozen, batched and sent to a central independent laboratory facility for analysis.

Right heart catheterization was performed prior to study Day 1 of the dose titration period and at the end of the maintenance period (Week 22), approximately 4 hours after the last dose of study drug. The 6MWD was conducted according to the modified guidelines issued by the American Thoracic Society without specific attention to timing after the prior dose of study drug. Investigators evaluated each patient for indications of clinical worsening throughout the study, based on the pre-defined criteria of death occurring ≤14 days after study drug discontinuation, hospitalization for heart-lung or lung transplantion or atrial septostomy, addition or change in dose of PAH specific medications, or the combined occurrence of ≥20% decrease in 6MWD from baseline with worsening in WHO/NYHA functional class and worsening of signs of right heart failure that did not respond to optimized oral diuretic therapy.

Details related to any serious AEs were collected for up to 30 days after the last dose of randomized study medication for patients that withdrew from the study or discontinued randomized, blinded study treatment.

Study Endpoints

The primary efficacy endpoint was absolute change in pulmonary vascular resistance (PVR) from baseline to week 22 with ralinepag compared with placebo. Secondary

endpoints included percentage change from baseline in PVR; 6MWD, time to clinical worsening; safety and tolerability. Exploratory endpoints included changes in other hemodynamic parameters, changes in NT-proBNP, and change in WHO/NYHA functional class.

Pharmacokinetic assessments were conducted from blood samples collected and processed for determination of ralinepag plasma concentrations during both the dose titration and maintenance periods. Blood samples (~3mL) were collected predose and at 4 hours postdose at each study visit where dose escalation was planned during the dose titration period and during each study visit within the maintenance treatment period.

Statistical Analysis

The sample size estimation of 60 patients was based on the assumption of a between-treatment group difference of 350 dyn.sec/cm^5 mean change in PVR from baseline to Week 22. At this sample size, the study would be powered at 90% to detect a between-treatment group difference (assuming a 2:1 randomization ratio) based on a two-sided t-test at the 5% significance level.

For PVR, assessments measured at Week 22 or early withdrawal were included in the analysis.

Missing data at Week 22 was imputed using a multiple imputation method. Lastly, to further assess the impact of missing data on the primary analyses, analyses without data imputation using the completers population was performed and compared with additional sensitivity analyses. Baseline assessments were not carried forward.

An analysis of covariance (ANCOVA) model with baseline PVR as a covariate and factors for treatment, baseline WHO/NYHA functional class (II versus III or IV), and baseline background PAH therapy (with ERA versus without ERA) was used to assess the effect of ralinepag versus placebo on change in PVR from baseline. Least-squares (LS) means for the treatments and the treatment effect and the LS mean difference between treatments was calculated with 95% confidence intervals (CIs) and a 2-sided p-value. The normality of the model residuals was assessed using the Shapiro-Wilk test. Continuous variables were summarized using number of observations (n), mean, SD, median, minimum, and maximum. Frequencies and percentages were reported for all categorical data. All analyses and tabulations were performed using SAS (Version 9.3). Ralinepag plasma concentrations were limited to predose (C_{min}) and 4 hours postdose at designated study visits. Ralinepag plasma steady-state was determined by regressing C_{min} values over time and the resultant slope tested for its difference from zero.

RESULTS

Patient Disposition

A total of 61 patients were enrolled between January 2015 and June 2017 at 28 study centers in 9 countries including the United States, Australia, Poland, Romania, Bulgaria, Serbia, Spain, Hungary, and Czech Republic. Of the 61 patients, 52% had idiopathic PAH, 8% had heritable PAH, 7% had drug or toxin induced PAH and 33% had associated PAH. Patients were predominantly female (86%) with a mean age of 49.4

years and body weight of 73.2 kg at enrollment. The mean baseline 6MWD was 378.4 meters (SD 103.9) and mean baseline PVR was 717.4 dyn.sec/cm^5 (SD 414.8). Forty patients were randomized to receive ralinepag and 21 to receive placebo (Figure 2). Demographics and baseline characteristics of treatment groups are presented in Table 1.

Thirty-four (85.0%) patients in the ralinepag group and 19 (90.5%) in the placebo group completed the study. PVR was imputed for six ralinepag and two placebo patients for the primary endpoint.

The overall mean duration of treatment exposure including dosing interruptions was comparable between the ralinepag versus placebo groups; 168.70 (SD 46.5) versus 180.1 (SD 13.8) days, respectively. Ralinepag total daily maintenance doses were titrated as high as 600 mcg, with the most common dose being 400 mcg.

Efficacy

Following 22 weeks of treatment, a significant reduction in PVR of 163.9 dyn.sec/cm^5 (median) was observed in the ralinepag treated patients, compared with an increase of 0.7 dyn.sec/cm^5 (median), p = 0.02, observed with placebo (Figure 3), meeting the primary end point of the study. These results, which imputed values for missing final data, were corroborated by the completers analysis and other sensitivity analyses, in which a reduction in PVR of 169.7 dyn.sec/cm^5 (median) for ralinepag and 3.1 dyn.sec/cm^5 for placebo were observed. In the completers analysis, a statistically

significant reduction from baseline in PVR by 19.8% was observed (p<0.0001) in the ralinepag patients.

There was a 29.8% reduction in PVR (least-squares mean) compared with placebo (p=0.03), which included a 20.1% decrease from baseline for ralinepag treated subjects.

At week 22, changes from baseline in 6MWD with ralinepag were not significantly different than placebo, with least-squares mean 6MWD increases of 36.2 m for ralinepag treated patients and 29.4 m for placebo (p = 0.90).

The proportion of patients with clinical worsening was lower with ralinepag versus placebo (2.5% versus 9.5%), but the difference between the groups was not statistically significant (p=0.26). Notably, significantly fewer ralinepag- than placebo-treated patients deteriorated in WHO/NYHA functional class (2.5% versus 19.0%; p=0.03).

Exploratory analyses demonstrated that ralinepag treatment trended toward a reduction in mean NT-proBNP (-304.9 versus 35.4 pg/mL; p=0.25) compared with placebo, but the treatment group differences were not statistically significant. (Figure 4)

Patients treated with ralinepag demonstrated significant reductions relative to placebo in mean pulmonary arterial pressure (PAP) (mmHg; ralinepag: –6.1, placebo: 2.9; p=0.028), systemic vascular resistance (SVR) (dyn.sec/cm^5; ralinepag: -258.7, placebo +152.9; p=<0.001), and arterial blood pressure (mmHg; ralinepag -8.2, placebo -2.7; p=0.001) (Table 2). Cardiac index was higher with ralinepag compared with placebo, but the treatment effect was not statistically significant.

Safety and Adverse Events

Not unexpectedly, both SVR and systemic blood pressure decreased with ralinipag, but symptomatic hypotension was not observed. No other clinically rmeaningful changes in vital signs or laboratory tests from baseline to week 22 were observed. The most common reason for study withdrawal among both groups was an adverse event. A summary of adverse events that occurred in ≥30% of patients is presented in Table 3. All patients (100%) in the ralinepag-treated group and 90.5% patients in the placebo group had at least one AE. Overall, 78.7% of AEs were considered related to study drug, 95.0% in the ralinepag group and 47.6% in placebo. Of the AEs related to study treatment, 20% of AEs in the ralinepag group and 28.6% in placebo patients were mild in severity (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated) and 47.5% were considered moderate in severity (minimal, local or noninvasive intervention indicated) for ralinepag and 14.3% for placebo. Related events noted as severe (medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling) occurred in 37.5% and 28.6% of ralinepag and placebo patients, respectively.

For patients treated with ralinepag, the most common AEs reported during the study were headache (n= 31, 78%), nausea (n=20, 50%), and diarrhea (n=19, 48%).

When the AE data were analyzed in 4 week periods (figure 5), a notable decline in AEs was observed during the maintenance phase (Week 10 to Week 22) relative to the dose titration phase (weeks 1-9). For example, the percentage of patients that experienced a headache was lower during weeks 10-14 of the maintenance phase (44.4%) relative to weeks 4-9 of the dose titration phase (75%) and continued to decline through the end of the study. Similar trends were observed for nausea and diarrhea. For patients treated

with placebo, the frequency of events was similar over the dose titration period compared with the maintenance period.

Of the ralinepag treated patients, 5 withdrew from the study due to AEs determined to be at least possibly related to study drug by the investigator (myalgia, headache, nausea, pain of skin, eyelid edema, exfoliative dermatitis, face edema, decreased appetite, and ECG QT prolongation). Fewer patients treated with ralinepag (n=4, 10%) experienced SAEs as compared to placebo (n=6, 28.6%). SAEs in the placebo and ralinepag-treated groups were deemed unrelated to study drug by the study investigator with the exception of ECG QT prolongation in one ralinepag patient. This patient had evidence of an intraventricular conduction disturbance (IVCD) at baseline and throughout the trial as evidenced by intermittent incomplete right bundle branch block. In patients with IVCD, repolarization duration is increased, thereby confounding interpretation of the impact of exogenous factors (e.g. study drug exposure). Two ex-placebo subjects had fatal AEs: One subject died from hypovolemic shock (approximately 29 days after the last dose of randomised study drug - placebo) and one subject had myocardial infarction and cardio-respiratory arrest (approximately 7 days after the last dose of randomised study drug - placebo).

Pharmacokinetics

Ralinepag IR capsules were administered for the complete study. In patients receiving ralinepag, the mean total daily dose at Week 22 (end of maintenance period) in this study was 259 (SD 168) mcg. In general, mean ralinepag plasma concentrations at both evaluated time points increased during the dose titration period and then reached

approximate steady-state levels that were maintained throughout the maintenance period (Figure 6. Overall, the mean steady-state Week 22 plasma levels of ralinepag pre-dose and at 4 hours post-dose were 3.23 ng/mL and 5.60 ng/mL, respectively. The ralinepag plasma levels reflected by a mean total daily dose of 259 mcg appear similar (dose adjusted) to what was observed in the Phase 1 study of healthy volunteers after twice-daily dosing. (SAD, MAD data on file).

DISCUSSION

This study was designed to assess the efficacy, safety and tolerability of twice-daily, orally administered ralinepag in a cohort of adult patients with PAH. Although some imbalances were observed between the treatment groups in several baseline measures, these are not surprising in light of the small sample size and 2:1 randomization scheme. Imbalances were detected between ralinepag versus placebo in the mean duration of PAH, PAH classification, ERA monotherapy, ERA and PDE5 inhibitor combination therapy, age, and mean NT-proBNP. While baseline PVR was higher in the ralinepag group, perhaps suggesting greater disease severity, baseline 6MW was also higher and NT-ProBNP levels were lower in the ralinipag group; thus, no clear pattern of imbalance that might affect the interpretation of the results was identified. Similar findings were observed in the Phase 2 trial of selexipag in PAH.[9]

The study demonstrated a statistically significant absolute change in PVR, meeting the primary efficacy endpoint. Expressed as percent change relative to placebo, a 29.8% difference was observed, including a 20.1% decrease from baseline for ralinepag treated group. These reductions in PVR in the ralinepag group were observed despite

patients already receiving either mono (35%) or dual (65%) combination PAH specific background therapy. These findings are similar to those reported in the Phase 2 study with selexipag;[9] while oral treprostinil did not significantly reduce PVR in a single-center, open label study.[10] Additional signals of efficacy were also observed by assessing other hemodynamic parameters:ralinepag treatment led to greater mean reductions in both systolic and mean PAP when compared with placebo. While cardiac index and stroke volume index trended to increase with ralinepag compared with placebo, these treatment effects were not statistically significant; this result may have also been limited by the small sample size. Although SVR and BP significantly decreased with ralinepag compared with placebo, there was no evidence of a significant compensatory increase in heart rate from baseline to Week 22.

A statistically significant treatment effect in 6MWD was not observed (+36.2 m ralinepag; +29 m placebo; P=0.90). This result was not unexpected since the study was not powered to detect a difference in 6MWD. However, the 29.0 m increase in the placebo group was an unusual result. Similar phase 2 studies of imatinib[11], treprostinil [12]and selexipag[9] also failed to observe a statistically significant treatment effect in 6MWD relative to placebo. Notably, in each of these studies, the changes in 6MWD observed in the placebo group were relatively small (-1.0 m, +0.4 m, +4.8 m for imatnib, selexipag, and treprostinil, respectively). A post-hoc analysis that examined differences in timing of new treatments prior to study start revealed significantly more patients in the placebo group relative to the ralinepag group had started a new PAH specific background therapy within 3-6 months of study start (placebo N=8, 38%; ralinepag N=5, 13%; *P*=0.045). In two previous studies utilizing tadalafil [13] or riociguat, [14] 6MWD

continued to improve beyond week 12, suggesting the possibility that further improvement may be gained beyond 3 months after initiation of a new PAH specific treatment

Twenty-two weeks of treatment with ralinepag was well tolerated by most patients in this study and treatment-related adverse events were generally consistent with the known safety profile of prostacyclin receptor agonists.[15] In order to optimize the benefit of treatment and prevent discontinuation due to intolerable adverse events, therapies targeting the prostacyclin pathway are initiated at low doses and up-titrated to a maximum tolerated maintenance dose. [16] In line with previous studies with prostacyclin analogues and IP receptor agonists, patients in the present study treated with ralinepag reported more frequent adverse events during the dose-titration phase from Week 4 to Week 9, when compared with the maintenance period after Week 9, indicating improvements in tolerability over time. The design of the 9-week dose titration scheme starts with low doses, which are increased weekly in small increments until a total daily dose of 200 mcgs, divided equally in two doses, is reached. The following week required a doubling of the dose to 400 mcgs, followed by an increase to 600 mcgs in the final week. Dose limiting adverse events triggered by aggressive titration may have caused patients to reach lower maximum tolerated doses than if a more gradual dose titration scheme was utilized.

Significantly fewer ralinepag- than placebo-treated patients deteriorated in WHO/NYHA functional class (1/40 2.5% versus 4/21 19.0%; p = 0.02). The WHO/NYHA functional class is one of the most powerful predictors of survival for PAH, not only at diagnosis, but also during follow-up.[16]

In the current study of ralinepeg, NT-proBNP was chosen as an exploratory biomarker measure, since changes correlate with other predictors of survival in PAH patients.[17,18] Although analyses demonstrated a greater mean reduction from baseline to Week 22 with ralinepag versus placebo for NT-proBNP, the differences between treatment groups were not statistically significant (p= 0.286 and p=0.253, respectively). Since this study was not powered to detect differences in this parameter, these results were not entirely unexpected.

Pharmacokinetic studies of ralinepag have demonstrated a long half-life of approximately 24 hours resulting in minimal fluctuation between peak and trough plasma concentrations at steady-state (SAD MAD data on file). The plasma levels achieved in this study both pre-dose and 4 hours post-dose (3.23 ng/mL, 5.60 ng/mL, respectively) exceeded those that are aassociated with a pharmacologic effect. The pharmacokinetic profile allows for twice daily dosing of ralinipag, which may be advantageous to patients in terms of convenience and maintenance of the treatment effect throughout the dosing interval, and potentially minimizing prostanoid-related adverse effects by reducing peaks in blood levels.

Our study has several limitations. The sample size was small and there were several imbalances at baseline between the two treatment arms. Additionally, the placebo group experienced a substantial increase in 6-minute walk test , which is unusual and unexplained. Finally, while the PVR was significantly decreased with ralinepag (the primary endpoint) as was pulmonary artery pressure, changes in other parameters were not significantly changed. Accordingly, these results should be considered preliminary and interpreted with caution.

In conclusion, ralinepag, a next-generation, orally available, non-prostanoid selective prostacyclin receptor agonist significantly reduced PVR compared with placebo in patients with moderately symptomatic PAH. This effect was observed in subjects who were taking either monotherapy or combination therapy at the time of enrollment. Additional studies, including larger and more long-term clinical trials, are needed to confirm these findings.

Captions:

Figure 1: Study Design

Figure 2: Patient Disposition

Figure 3: Ralinepag Significantly Reduced PVR Compared with Placebo

Figure 4: Change in NT-proBNP

Figure 5: Frequency of patient-reported Adverse Events (AEs) as a function of time on ralinepag .

Figure 6: Mean (SEM) plasma ralinepag steady-state plasma concentrations at pre-dose (trough) and 4 hrs post-dose during the 9-week dose titration and subsequent 13-week maintenance periods of the study (22-week total dosing duration).

Footnotes:

Adverse Event classification of severity:

Mild - asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Moderate - minimal, local or noninvasive intervention indicated.

Severe - medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling.

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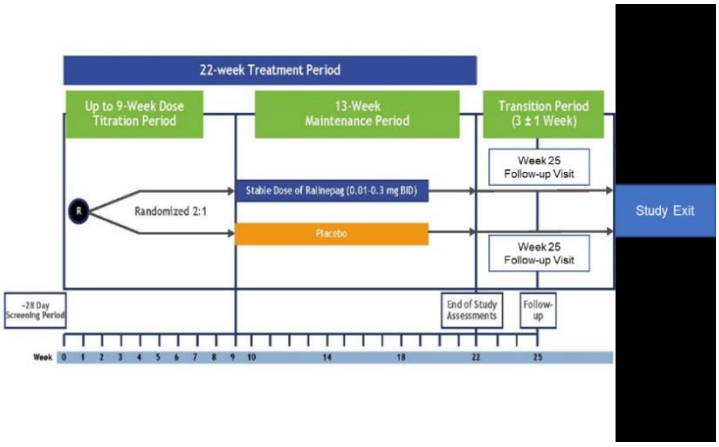
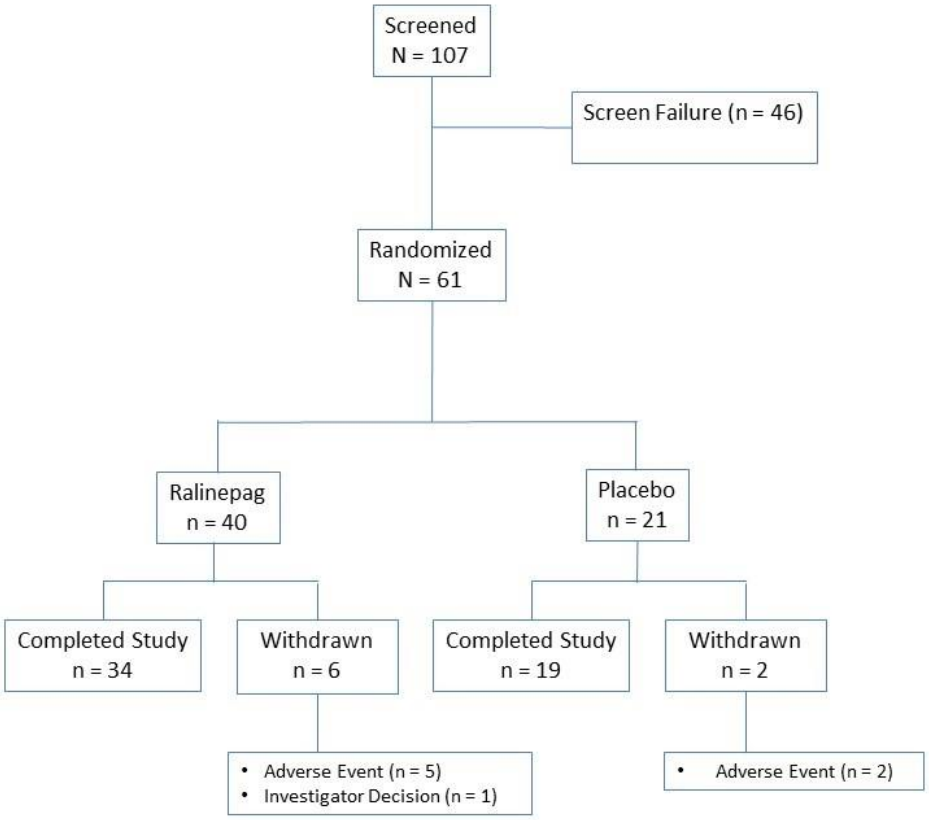
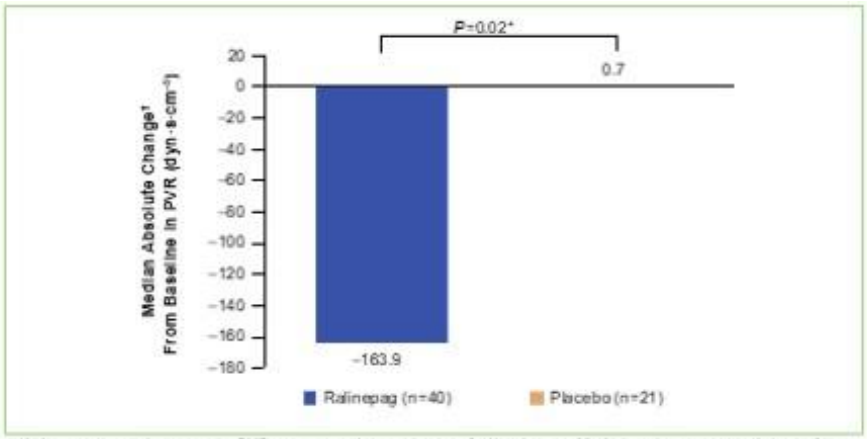
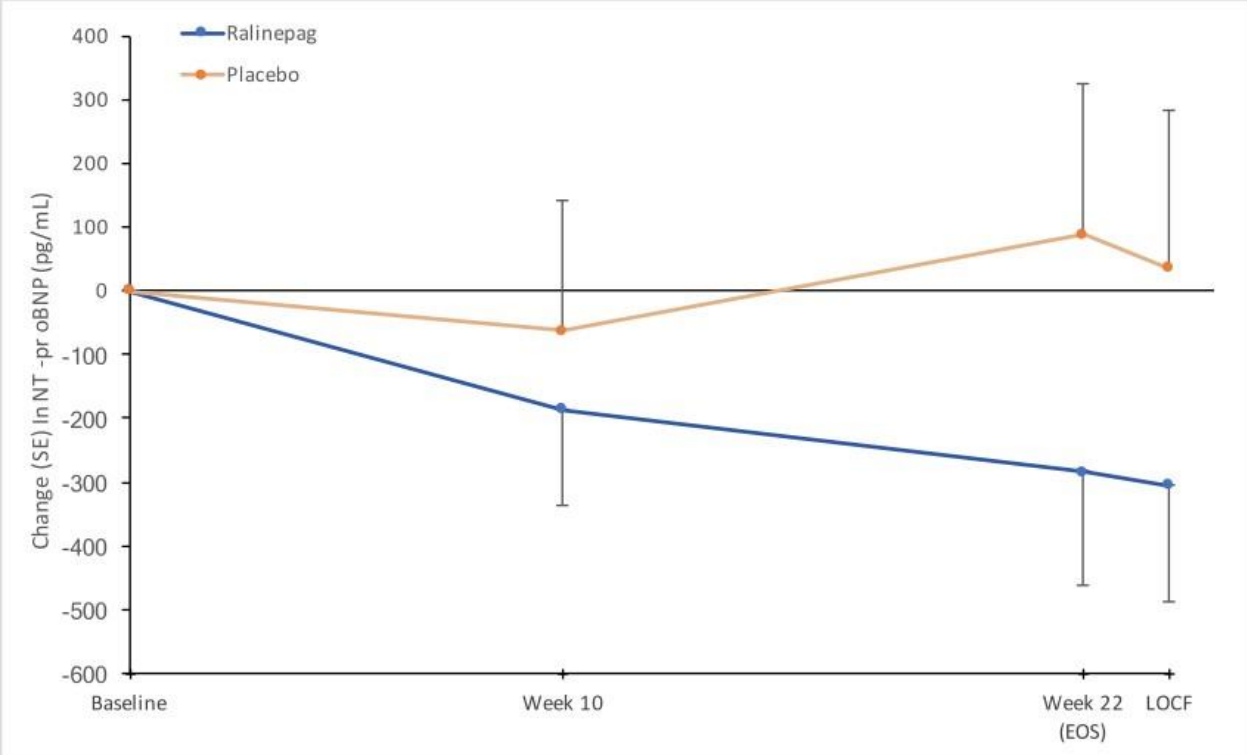
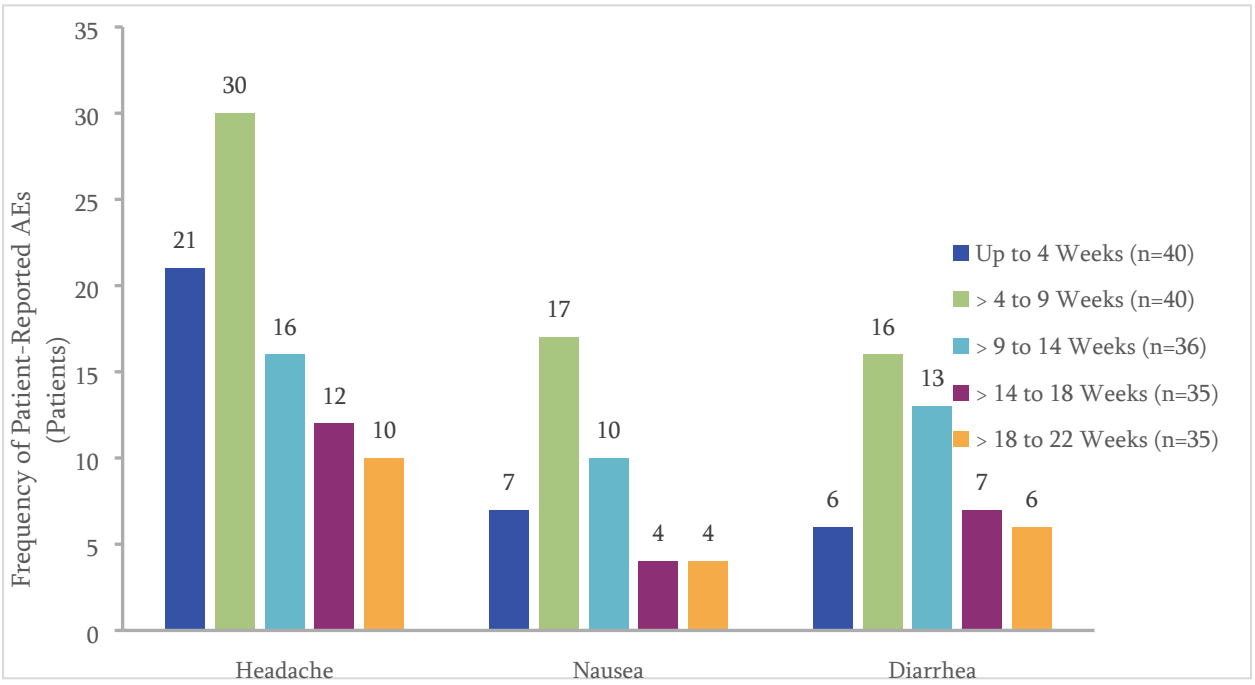

22-week Treatment Period
Up to 9-Week Dose Titration Period
13-Week Maintenance Period
Transition Period (3 ± 1 Week)
Week 25 Follow-up Visit
Stable Dose of Ralinepag (0.01-0.3 mg BID)
Randomized 2:1
Placebo
Week 25 Follow-up Visit
Study Exit
~28 Day Screening Period
End of Study Assessments
Follow-up
Week 0 1 2 3 4 5 6 7 8 9 10 14 18 22 25


Screened
N = 107
Screen Failure (n = 46)
Randomized
N = 61
Ralinepag
n = 40
Placebo
n = 21
Completed Study
n = 34
Withdrawn
n = 6
Completed Study
n = 19
Withdrawn
n = 2
• Adverse Event (n = 5)
• Investigator Decision (n = 1)
• Adverse Event (n = 2)



*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.
The geometric mean ratio (GMR) of LS mean changes was 0.7, −25.8% change over compared placebo; p = 0.02.




Frequency of Patient-Reported AEs (Patients)
35
30
25
20
15
10
5
0
21
30
16
12
10
7
17
10
4
4
6
16
13
7
6
Headache
Nausea
Diarrhea
Up to 4 Weeks (n=40)
> 4 to 9 Weeks (n=40)
> 9 to 14 Weeks (n=36)
> 14 to 18 Weeks (n=35)
> 18 to 22 Weeks (n=35)

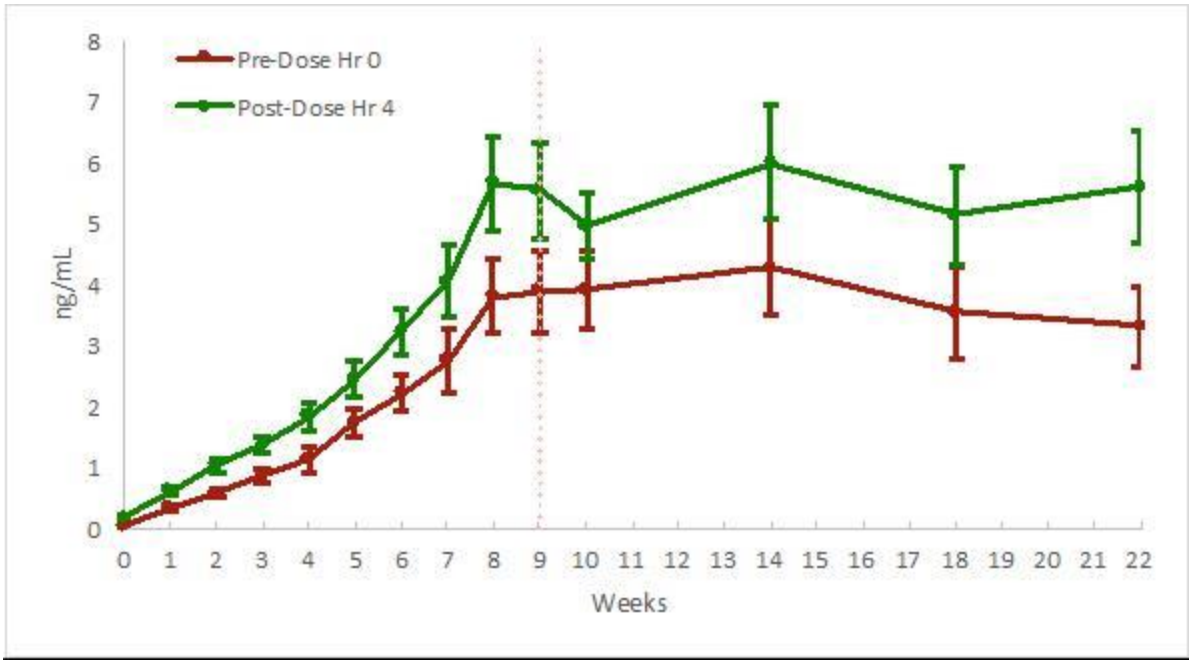

Pre-Dose Hr 0
Post-Dose Hr 4
ng/mL
0
1
2
3
4
5
6
7
8
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Weeks

Table 1: Demographics and Baseline Characteristics

	All Patients (n=61)	Ralinepag (N=40)	Placebo (N=21)	P-value
Age, years* Mean (range)	49.4 (19–73)	46.2 (19–68)	55.6 (29–73)	0.0057[a]
Gender, n (%) Female	53 (87)	33 (83)	20 (95)	
Caucasian, n (%)	57 (93)	38 (95)	19 (91)	
Other, n (%)	4 (7)	2 (5)	2 (10)	
PVR, dyn·s·cm^{5}; mean (median)	717 (576)	780 (705)	598 (480)	0.110[a]
6MWD, m; mean (median)	378 (400)	393 (405)	351 (367)	
WHO FC, n (%)*				
II	34 (56)	22 (55)	12 (57)	0.800[b]
III	26 (43)	17 (43)	9 (43)	
IV	1 (2)	1 (3)	0	
Etiology of PAH, [n (%)]				
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; mean (median)*	980 (343)	792 (335)	1362 (343)	0.700[a]
Background PAH therapy, %				
Monotherapy	41	35	52	
Combination therapy	59	65	48	
Monotherapy, n (%)				
ERA*	6 (10)	2 (5)	4 (19)	0.170[c]
PDE5i	19 (31)	12 (30)	7 (33)	
Combination therapy (%)				
ERA + PDE-5i	34 (56)	24 (60)	10 (48)	0.420[c]
ERA + SGCS	2 (3)	2 (5)	0 (0)	
New PAH treatment within 3–6	13 (21)	5 (13)	8 (38)	0.049[c]

months of Day 1, n (%)

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. Associated (PAH): Connective tissue disease (CTD); or Human immunodeficiency virus (HIV) infection or Congenital systemic-pulmonary shunt (must have undergone surgical correction at least 1 year prior to screening).
* Numerical imbalances were detected between ralinepag versus placebo in PAH classification, ERA monotherapy, ERA and PDE5 inhibitor combination therapy, age, and mean NT-proBNP.
a. P-value by Wilcoxon rank sum test; b. p-value by exact Chi-square test; c. P-value by Fisher's exact test;

Table 2: Secondary haemodynamic Parameters: Change From Baseline to Week 22

Haemodynamic Parameter	Baseline (SD)		Change From Baseline to Week22 (SEM)*		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), $L \cdot min \cdot m^{-2}$	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
Systemic Vascular Resistance (SVR, $dyn.sec/cm^5$)	1449.0 (378.53)	1309.9 (286.65)	-258.7 (286.54)	152.9 (374.47)	<0.001
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; SEM, standard error of the mean.

Table 3: Adverse events occurring in ≥30% of patients in either the ralinepag or placebo groups during the 22-week study

AE % (n)	**Ralinepag (n=40)**	**Placebo (n=21)**
Headache	78% (31)	29% (6)
Nausea	50% (20)	24% (5)
Diarrhoea	48% (19)	14% (3)
Pain in Jaw	35% (14)	14% (3)
Flushing	33% (13)	5% (1)