Combination Therapy with Oral Treprostinil for Pulmonary Arterial Hypertension: A Double-Blind, Placebo-Controlled Study

Online Data Supplement

Committee Members

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Supplemental Methods

Inclusion Criteria

A subject was eligible for inclusion in this study if all the following criteria applied:

1. The subject voluntarily gave informed consent to participate in the study.

2. The subject was 18 to 75 years of age (inclusive) at Screening (date of providing written informed consent).

3. Women of childbearing potential (WOCBP) included any female who had experienced menarche and who had not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or was not postmenopausal (defined as amenorrhea for at least 12 consecutive months). Women of childbearing potential must have practiced true abstinence from intercourse when it was in line with their preferred and usual lifestyle, or used 2 different forms of highly effective contraception for the duration of the study, and for at least 30 days after discontinuing the study medication. Medically acceptable forms of effective contraception included: (1) approved hormonal contraceptives (such as birth control pills), (2) barrier methods (such as a condom or diaphragm) used with a spermicide, (3) an intrauterine device, or (4) partner vasectomy. For WOCBP, a negative urine pregnancy test was required at Screening and Baseline phases prior to initiating the study medication.

4. Male subjects must have consented to use a condom during intercourse for the duration of the study, and for at least 48 hours after discontinuing the study medication.

5. The subject had a diagnosis of symptomatic idiopathic or heritable pulmonary arterial hypertension (PAH), PAH associated with connective tissue disease (CTD), PAH associated with HIV infection, PAH associated with repaired congenital systemic-to-pulmonary shunt (with at least 1 year since repair respective to the date of informed consent), or PAH associated with appetite suppressant or toxin use.

6. The subject, if known to be positive for human immunodeficiency virus (HIV) infection, had a CD4 lymphocyte count of at least 200 cells/mm^3 assessed at Screening and was receiving current standard of care anti-retroviral or other effective medication for the treatment of HIV infection.

7. The subject had a baseline 6-Minute Walk Distance (6MWD) greater than or equal to 150 m in the absence of a concurrent injury, illness (other than PAH or a PAH-related condition), or other confounding factor including, but not limited to, use of an aid for ambulation (e.g., use of a cane or walker) or connection to a non-portable machine, that would have prevented the accurate assessment of the subject's exercise capacity.

8. The subject was optimally treated with conventional pulmonary hypertension therapy (e.g., oral vasodilators, oxygen, digoxin, diuretics, anticoagulants as deemed appropriate by the Investigator) with no additions, discontinuations, or dose changes for a minimum of 10 days prior to randomization. The exceptions were the discontinuation or dose changes of anticoagulants and/or dose change of diuretics.

9. The subject was receiving a PAH-approved oral monotherapy at a minimum dose that complied with the approved prescribing information for the product for at least 30 days prior to randomization and was receiving a stable dose for at least 10 days prior to randomization.

The subject who had previously received 2 PAH-approved oral therapies at the same time (specifically, a phosphodiesterase type 5 inhibitor [PDE5-I], endothelin receptor antagonist [ERA], or soluble guanylate cyclase stimulate [sGC] stimulator) was eligible provided they had received these medications concomitantly for less than or equal to 90 days cumulatively. The subject must have taken only 1 PAH-approved therapy for at least 30 days prior to randomization and must have been receiving a stable dose for at least 10 days prior to randomization.

10. The subject had previously undergone a cardiac catheterization within 3 years prior to the start of Screening or during the Screening Period, and the most recent assessment documented a pulmonary artery pressure mean of at least 25 mmHg, a pulmonary capillary wedge pressure (PCWP) (or in the event a PCWP could not be reliably obtained, a left ventricular end diastolic pressure [LVEDP]) less than or equal to 15 mmHg, and absence of unrepaired congenital heart disease (other than patent foramen ovale). If a reliable PCWP or LVEDP were unable to be obtained during cardiac catheterization, subjects with clinically normal left heart function and absence of clinically relevant mitral valve disease on echocardiography were eligible for enrollment.

11. The subject underwent echocardiography with evidence of clinically normal systolic and diastolic left ventricular function and absence of any clinically significant left-sided heart disease (e.g., mitral valve disease). Subjects with clinically insignificant left ventricular diastolic dysfunction due to the effects of right ventricular overload (i.e., right ventricular hypertrophy and/or dilatation) were eligible.

12. The subject had a previous ventilation perfusion lung scan, high-resolution computerized tomography scan of the chest, and/or pulmonary angiography that were consistent with the

diagnosis of PAH (e.g., low probability of pulmonary embolism, absence of major perfusion defects).

13. The subject had pulmonary function tests conducted within 6 months before Screening or during the Screening Period to confirm the following:

    a. Total lung capacity was at least 60% (predicted value) assessed by either whole body plethysmography or helium dilution or nitrogen washout technique

    b. Forced expiratory volume at 1 second was at least 50% (predicted value).

14. In the opinion of the Principal Investigator, the subject was able to communicate effectively with study personnel and was considered reliable, willing, and likely to cooperate with protocol requirements, including attending all study visits.

Exclusion Criteria

Subjects were not eligible for inclusion in this study if any of the following criteria applied:

1. The subject was pregnant or lactating.

2. The subject had previously received oral treprostinil.

3. The subject had received a PGI_2 (except if used during acute vasoreactivity testing) within 30 days prior to randomization or had previous intolerance or significant lack of efficacy to any PGI_2 or PGI_2 analogue that resulted in discontinuation or inability to titrate that therapy effectively.

4. The subject had any background conventional therapies for PAH added, removed, or dose-adjusted (including but not limited to oxygen, vasodilators, diuretics, digoxin, anticoagulants)

within 10 days prior to randomization. The exceptions were removal or dose adjustments of anticoagulants and/or dose adjustments of diuretics.

5. The subject received their first dose of a PAH-approved oral monotherapy less than 30 days prior to randomization, or had their PAH-approved oral monotherapy dose changed within 10 days prior to randomization, or the subject discontinued any PAH-approved therapy within 30 days prior to Screening, or the subject had previously received 2 PAH-approved oral therapies at the same time (specifically, a PDE5-I, an ERA, or a sGC stimulator) concomitantly for more than 90 days cumulatively.
6. The subject had any disease associated with PAH other than CTD, HIV infection, repaired (for at least 1 year) congenital systemic-to-pulmonary shunt, PAH associated with appetite suppressant/toxin use (e.g., portal hypertension, chronic thromboembolic disease, pulmonary veno-occlusive disease, etc), or had an atrial septostomy.
7. The subject had a current diagnosis of uncontrolled sleep apnea as defined by their physician.
8. The subject had a history of ischemic heart disease, including a previous myocardial infarction or symptomatic coronary artery disease within 6 months prior to Screening or a history of left-sided myocardial disease as evidenced by a mean PCWP (or a LVEDP) greater than 15 mmHg or left ventricular ejection fraction less than 40% as assessed by either multigated angiogram, angiography, or echocardiography.
9. The subject had uncontrolled systemic hypertension as evidenced by systolic blood pressure (BP) greater than 160 mmHg or diastolic BP greater than 100 mmHg.

10. The subject had alanine aminotransferase or aspartate aminotransferase levels at least 3 times greater than the upper limit of normal, clinically significant liver disease/dysfunction, or known Child-Pugh Class C hepatic disease at Screening.

11. The subject had any other disease or condition that would interfere with the interpretation of study assessments.

12. The subject had a musculoskeletal disorder (e.g., arthritis affecting the lower limbs, recent hip or knee joint replacement, artificial leg), was using a device to assist walking (e.g., cane or walker), or any disease that was likely to limit ambulation, or was connected to a machine that was not portable.

13. The subject had an unstable psychiatric condition or was mentally incapable of understanding the objectives, nature, or consequences of the study, or had any condition which in the Investigator's opinion would constitute an unacceptable risk to the subject's safety.

14. The subject was receiving an investigational drug, had an investigational device in place, or had participated in an investigational drug or device study within 30 days prior to Screening.

15. The subject had chronic renal insufficiency as defined by either a Screening creatinine value greater than 2.5 mg/dL (221 μmol/L) or the requirement for dialysis.

16. Subject did not have 3 or more of the following left ventricular disease/dysfunction risk factors:

    - Body Mass Index of at least 30 kg/m^2
    - History of essential hypertension
    - Diabetes mellitus (any type)

- Historical evidence of significant coronary artery disease established by any 1 of the following: history of myocardial infarction, percutaneous coronary intervention, or angiographic evidence of coronary artery disease (more than 50% stenosis in at least 1 coronary artery); positive stress test with imaging; previous coronary artery bypass graft; or stable angina.

Components of the Primary End Point and Definitions

Clinical worsening (adjudicated) was defined as the occurrence of any 1 of the following events:

- Death (all causes)
- Hospitalization due to worsening PAH defined as:
    - Non-elective hospitalization lasting at least 24 hours in duration caused by clinical conditions directly related to PAH and/or right heart failure or
    - Lung or heart/lung transplantation or
    - Atrial septostomy
- Initiation of an inhaled or infused PGI_2 for the treatment of worsening PAH
- Disease progression (all criteria required):
    - A decrease in 6MWD of at least 15% from baseline (or too ill to walk) directly related to PAH progression with other comorbidities ruled out, confirmed by two 6-Minute Walk Tests (6MWTs) performed on different days (confirmatory 6MWTs were required to be conducted within 30 days of the qualifying decrease in 6MWD; however, confirmatory 6MWTs that occurred outside of this window

were considered to have met the definition of clinical worsening and sent to the adjudication committee for review).

- Worsening of PAH symptoms, which included either:
  - An increase in World Health Organization functional class (WHO FC) from baseline or
  - Appearance or worsening of symptoms of right heart failure since baseline

- Unsatisfactory long-term clinical response (all the following criteria required):
  - Randomized to receive study drug for at least 24 weeks
  - A decrease from baseline in 6MWD at Week 24 and beyond at 2 consecutive visits on different days (confirmatory 6MWTs were required to be conducted within 30 days of the qualifying decrease in 6MWD; however, confirmatory 6MWTs that occurred outside of this window were considered to have met the definition of clinical worsening and sent to the adjudication committee for review).
  - Sustained WHO FC III or IV symptoms for at least 24 weeks consecutively

Table E1. Change from Baseline in REVEAL 2.0 Risk Score

Study Group*	Baseline	Week 12		Week 24		Week 36	
	Mean (SD)	Mean (SD) Change from Baseline	Mean Difference (SE) *P* Value*	Mean (SD) Change from Baseline	Mean Difference (SE) *P* Value*	Mean (SD) Change from Baseline	Mean Difference (SE) *P* Value*
Placebo (N=344)	5.83 (2.6)	0.05 (1.5)	-0.42 (0.13) *P*=0.0015	0.03 (1.59)	-0.53 (0.15) *P*=0.0003	-0.01 (1.88)	-0.6 (0.19) *P*=0.002
Oral TRE (N=346)	6.3 (2.43)	-0.37 (1.73)		-0.51 (1.83)		-0.61 (2.15)	

Definition of Abbreviations: SD = standard deviation; SE = standard error; TRE = treprostinil
Data are available for N oral treprostinil/placebo participants: N=301/300 at Week 12, N=277/271 at Week 24, and N=217/222 at Week 36. No data were imputed.
*P values obtained from two-sample t-test.

REVEAL 2.0 score calculated with the following: WHO Group I subgroup, demographics, comorbidities (eGFR), NYHA/WHO functional class, vital signs, 6MWD, and NT-proBNP. Higher values indicate greater overall risk for clinical worsening or mortality.

Table E2. Summary of Deaths at Study Closure (all causes) – Sensitivity Analysis

Timepoint	Oral Treprostinil (N=346)		Placebo (N=344)		
	n	%	n	%	*P* Value*
Known deaths at study closure	38	11%	60	17.4%	0.016
Known and assumed deaths (in unknowns) at study closure	43	12.4%	65	18.9%	0.021

*P values obtained from Fisher's exact test.

Vital status is unknown for 74 participants, including 43 participants assigned to oral treprostinil and 31 assigned to placebo. Although the overall group of oral treprostinil participants had a substantially higher risk for mortality at baseline as compared to those assigned placebo, these 43 oral treprostinil participants with unknown vital status were at identical risk for mortality as compared to the 31 placebo participants with an unknown status. Thus, we did a sensitivity analysis assuming that 11% of 43 unknown oral treprostinil participants (n=5) and 17.4% of 31 unknown placebo participants (n=5) died. The analysis also holds to a routine definition of 'unlikely due to chance' ($P<0.05$) if we assume up to 8 unknown oral treprostinil participants as dead with only 5 unknown placebo participants as dead.

Table E3. Summary of Deaths (all causes) Adjusted for Baseline Risk

Timepoint	Oral TRE (N=346)	Placebo (N=344)	Prespecified Analysis		Post-Hoc Analysis	
			HR (95% CI) *P* Value*	*P* Value†	HR (95% CI) *P* Value‡	*P* Value§
Deaths at end of randomized treatment, n (%)	17 (4.9)	18 (5.2)	1.0 (0.52, 1.95) 0.99	0.98	0.87 (0.44, 1.71) 0.68	0.72
Deaths in randomized study and the open-label extension, n (%)	30 (8.7)	42 (12.2)	0.80 (0.50, 1.28) 0.36	0.43	0.71 (0.44, 1.15) 0.17	0.16
Deaths at study closure, n (%)	38 (11.0)	60 (17.4)	0.63 (0.42, 0.95) 0.03	0.03	0.58 (0.38, 0.89) 0.01	0.01

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; TRE = treprostinil

Death events were evaluated up to the end of the double-blind treatment period for subjects who transitioned to the open label extension study or up to 30 days after last dose of study drug (unless lost to follow-up). The subjects who discontinued from the study early have their time to death censored at the subjects' last visit. Subjects who survived have their time to death censored at the date of the last study assessment.

Vital status was collected at the study closure for all subjects including subjects who rolled over to the open label extension study and who discontinued early from the study. For subjects whose vital status was not available at the study closure, their time to death was censored at the subjects' last known date to be alive. Subjects who were alive at the study closure have their time to death censored at the last contact date. Vital status remained unknown for 74 participants (11%).

*Hazard ratio, 95% CI, and P value are calculated with proportional hazard model with treatment, background PAH therapy and baseline 6MWD as explanatory variables.

†*P* value is calculated with Log-rank test stratified by background PAH therapy and baseline 6MWD category.

‡Hazard ratio, 95% CI, and P-value are calculated with proportional hazard model with treatment and baseline risk criteria as explanatory variables.

§*P* value is calculated with Log-rank test stratified by baseline non-invasive risk criteria (the same adjustment shown in Figure 2B for the primary endpoint). The oral treprostinil participants started at a higher risk for death and thus the hazard ratio drops further when accounting for this imbalance.

Table E4. Hemodynamic Sub-study – Baseline Data

Parameter	Oral Treprostinil		Placebo	
	N	Baseline	N	Baseline
Age at randomization, years	34	44.1 ± 14.1	27	40.1 ± 14.6
Female, %	34	67.6	27	85.2
Race, % White Black or African American Asian	34	 79.4 0 20.6	27	 66.7 11.1 22.2
Weight, kg*	34	78.53 ± 20.47	27	64.82 ± 20.38
Height, cm*	34	164.4 ± 7.7	27	158.4 ± 7
PAPm, mmHg	34	49.15 ± 14.46	27	49.37 ± 16.1
RAPm, mmHg	34	7.68 ± 3.59	27	7.89 ± 5.62
SAPm, mmHg	33	90.18 ± 14.92	27	86.74 ± 16.13
PCWPm, mmHg	34	9.97 ± 3.02	26	9.23 ± 4.19
CI, L/min/m^2	26	3.1 ± 1.11	22	3 ± 1.07
SVR, dynes*sec/cm^5	29	1456.52 ± 751.21	24	1473.55 ± 637.21
PVR, dynes*sec/cm^5	30	720.23 ± 542.98	24	781.41 ± 462.15
CO, L/min	30	5.3 ± 1.99	24	4.82 ± 1.86

Data are represented as mean ± SD, unless otherwise indicated.
*$P<0.05$; P values are calculated using Wilcoxon rank sum test for continuous variables and Fisher's exact test for categorical variables.

We do not have detailed historical values as part of the database – the eCRF only required that the hemodynamic criteria be met (no source data) and the monitors only confirmed that source data supported enrollment (i.e., source data were checked to make sure that an enrolled participant met eligibility hemodynamic criteria, but the actual data was not entered). Baseline hemodynamic data are available for 61 participants from the hemodynamic sub-study.

Supplemental Figure Legends

Figure E1. Dosing in Study, Through Week 48. The plots show median and IQR. Median dose of both oral treprostinil and placebo continued to increase throughout the course of the study. At Week 24, the median dose of oral treprostinil was 3.563 mg three times daily. At Week 36, the median dose was 4.000 mg three times daily, and at Week 48, the median dose was 4.750 three times daily. Median doses for placebo were higher at all time points.

Figure E2. Forest Plot on Subgroup Analyses of Time to Adjudicated Clinical Worsening Events. The *P*-value is from the test statistic for testing the interaction between the treatment and any subgroup variable. When analyzed by baseline subgroup, oral treprostinil therapy (compared with placebo) significantly reduced the risk of a clinical worsening event in subjects with idiopathic and heritable PAH (Cox proportional hazard model: HR [95% CI]: 0.68 [0.49, 0.94]; *P*=0.0211), subjects in WHO FC III or IV (HR [95% CI]: 0.58 [0.39, 0.86]; *P*=0.0072), subjects that were less than 65 years old (HR [95% CI]: 0.70 [0.51, 0.94]; *P*=0.0187), and subjects treated in North America (HR [95% CI]: 0.37 [0.15, 0.89]; *P*=0.0274). There were no subgroups in which treatment with oral treprostinil was associated with greater likelihood for clinical worsening; whether or not statistically significant, clinical worsening events were always numerically less likely with oral treprostinil.

Figure E3. Analysis of 6MWD Over Time Using Mixed Model Repeated Measurement. Data are from Mixed Model Repeated Measurement (MMRM) with the change from baseline in 6MWD as dependent variable, treatment, week, treatment by week interaction, background PAH therapy as the fixed effects, baseline 6MWD as covariate. An unstructured variance/covariance structure shared across treatment data groups was used to model the within-subject errors. The change from baseline in 6MWD at Week 24 in the oral treprostinil group was not statistically

significantly different from the placebo group when analyzed using MMRM (7.49 m; *P*=0.1411; 95% CI: -2.5, 17.48). However, treatment difference (oral treprostinil – placebo) in 6MWD was statistically significant at both Week 36 (MMRM; 12.86 m; 0=0.0356; 95% CI: 0.87, 24.86) and Week 48 (MMRM; 21.69 m; *P*=0.0015; 95% CI: 8.33, 35.04). For this figure, the 'anchor point' of the MMRM analysis is week 48 (instead of the data with Week 24 as the anchor point, which was presented in the text). Missing values are not imputed for MMRM, so this is an 'observed case' analysis.

Figure E4. Hodges-Lehmann Estimate of Treatment Effect for 6MWD Through Week 48. For those patients who withdrew early due to death, were too ill to walk, or had no 6MWD measure due to clinical worsening event, the 6MWD is set to 0; for all other withdrawals without Week 48 measurement, last observation carried forward (LOCF) is used to impute. The *P*-value is obtained from nonparametric ANCOVA adjusted for PAH background therapy and baseline 6MWD measurement. The change from baseline in 6MWD at Week 24 in the oral treprostinil group was not statistically significantly different from the placebo group when analyzed by a nonparametric ANCOVA (Hodges-Lehmann estimate of location shift: 7.0; *P*=0.0913). However, treatment difference (oral treprostinil – placebo) in 6MWD was statistically significant at both Week 36 (Hodges-Lehmann estimate of location shift: 13.0; *P*=0.0094) and Week 48 (Hodges-Lehmann estimate of location shift: 21.0; *P*=0.0008).

Figure E5. Combined 6MWD/Borg Dyspnea Score Ranking at Week 24. The methodology involves ranking all participants by the change from baseline in Borg dyspnea score and ranking all participants for the change from baseline in 6MWD. The average of these 2 ranks is the overall rank, and this figure shows the likelihood of a given rank by treatment group. When the changes from baseline in 6MWD and Borg dyspnea scores at Week 24 were simultaneously

compared, the oral treprostinil group showed a significant improvement (nonparametric ANCOVA: P=0.0057) over the placebo group. The results demonstrated that oral treprostinil subjects, at nearly every given rank, were more likely to have a larger reduction in perceived dyspnea for a given increase in 6MWD.

Figure E6. Kaplan-Meier Plot of Time to Participant Discontinuation from the Study Due to Adverse Events. *P value is calculated with Log-rank test. †Hazard ratio, 95% CI, and P value are calculated with proportional hazard model.

Figure E1

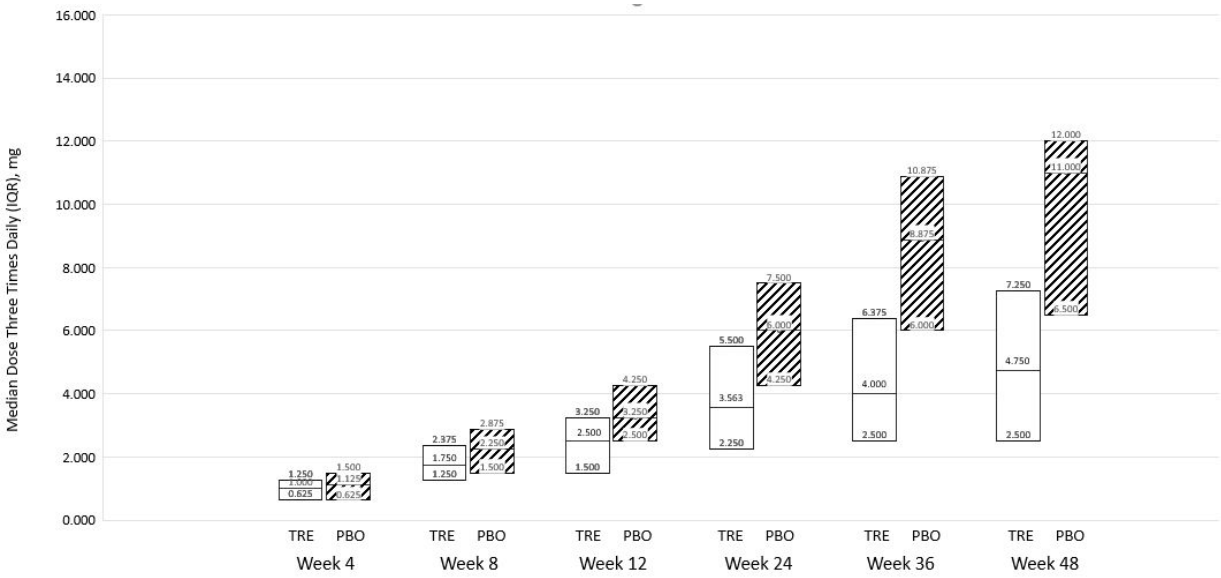

Median Dose Three Times Daily (IQR), mg
16.000
14.000
12.000
10.000
8.000
6.000
4.000
2.000
0.000
1.250
1.000
0.625
1.500
1.125
0.625
2.375
1.750
1.250
2.875
2.250
1.500
3.250
2.500
1.500
4.250
3.250
2.500
5.500
3.563
2.250
7.500
6.000
4.250
6.375
4.000
2.500
10.875
8.875
6.000
7.250
4.750
2.500
12.000
11.000
6.500
TRE PBO
Week 4
TRE PBO
Week 8
TRE PBO
Week 12
TRE PBO
Week 24
TRE PBO
Week 36
TRE PBO
Week 48

FIGURE E2

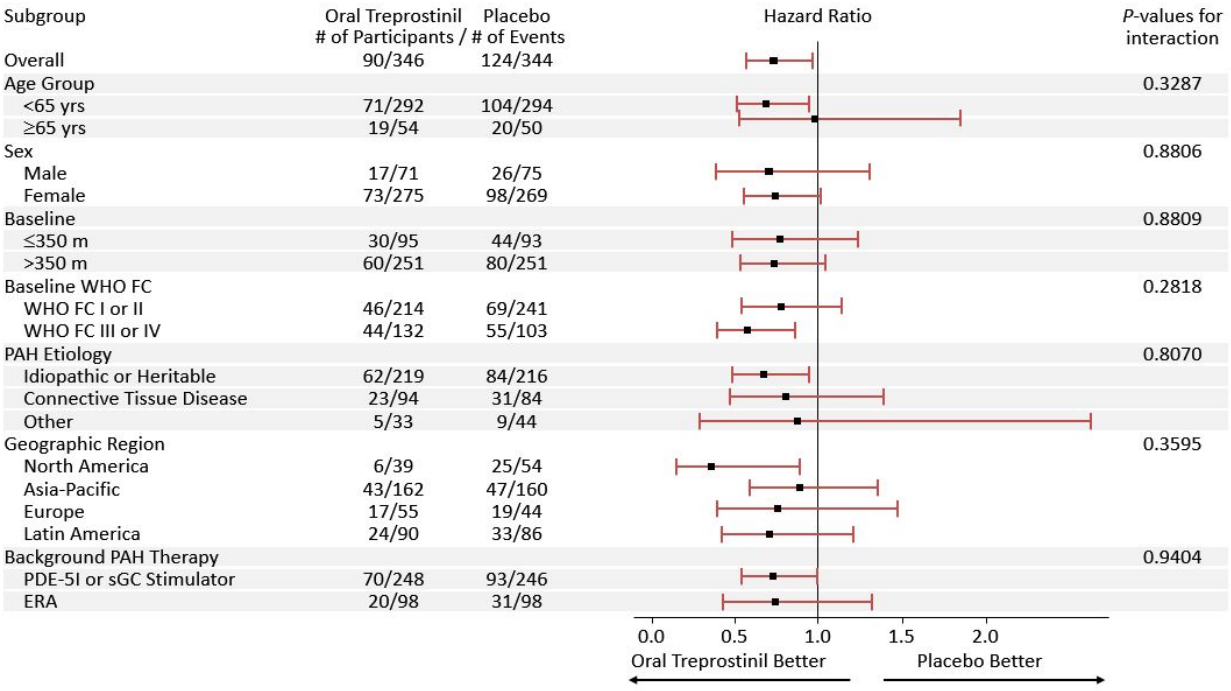

Subgroup
Oral Treprostinil # of Participants / # of Events
Placebo # of Events
Hazard Ratio
P-values for interaction
Overall 90/346 124/344
Age Group 0.3287
<65 yrs 71/292 104/294
≥65 yrs 19/54 20/50
Sex 0.8806
Male 17/71 26/75
Female 73/275 98/269
Baseline 0.8809
≤350 m 30/95 44/93
>350 m 60/251 80/251
Baseline WHO FC 0.2818
WHO FC I or II 46/214 69/241
WHO FC III or IV 44/132 55/103
PAH Etiology 0.8070
Idiopathic or Heritable 62/219 84/216
Connective Tissue Disease 23/94 31/84
Other 5/33 9/44
Geographic Region 0.3595
North America 6/39 25/54
Asia-Pacific 43/162 47/160
Europe 17/55 19/44
Latin America 24/90 33/86
Background PAH Therapy 0.9404
PDE-5I or sGC Stimulator 70/248 93/246
ERA 20/98 31/98
0.0
0.5
1.0
1.5
2.0
Oral Treprostinil Better
Placebo Better

FIGURE E3

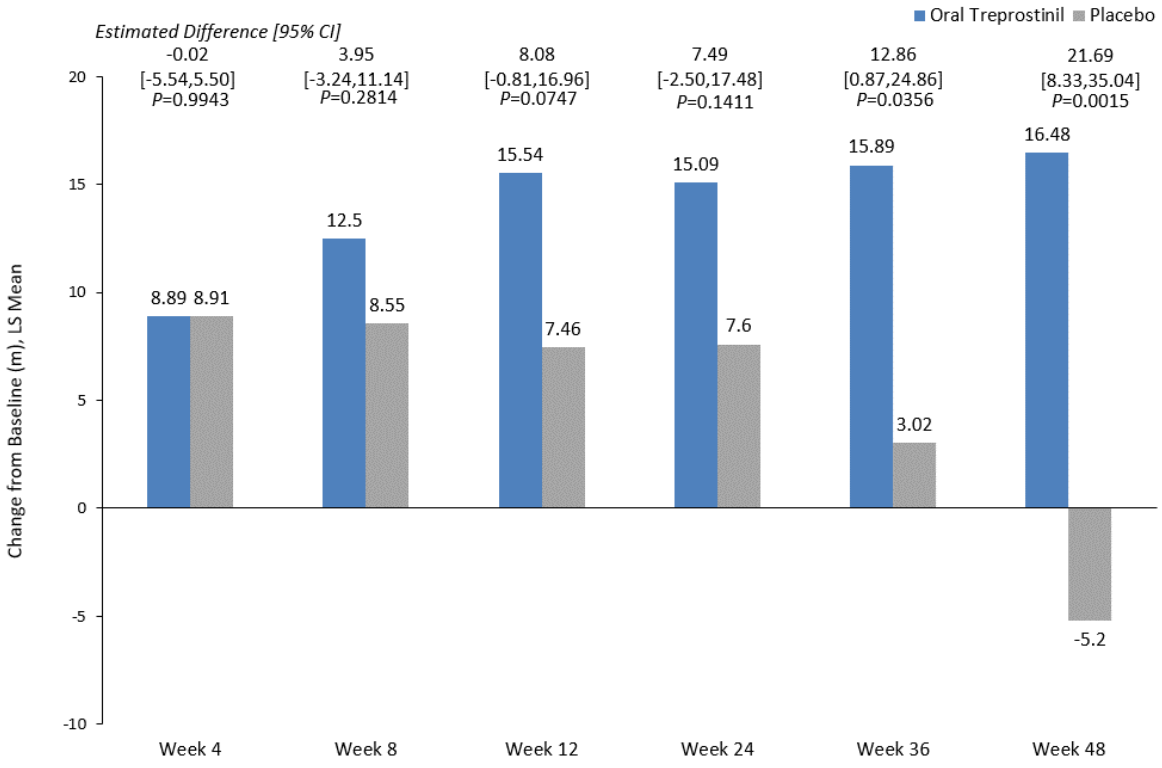

Oral Treprostinil
Placebo
Estimated Difference [95% CI]
-0.02
[-5.54,5.50]
P=0.9943
3.95
[-3.24,11.14]
P=0.2814
8.08
[-0.81,16.96]
P=0.0747
7.49
[-2.50,17.48]
P=0.1411
12.86
[0.87,24.86]
P=0.0356
21.69
[8.33,35.04]
P=0.0015
Change from Baseline (m), LS Mean
20
15
10
5
0
-5
-10
8.89
8.91
12.5
8.55
15.54
7.46
15.09
7.6
15.89
3.02
16.48
-5.2
Week 4
Week 8
Week 12
Week 24
Week 36
Week 48

Figure E4

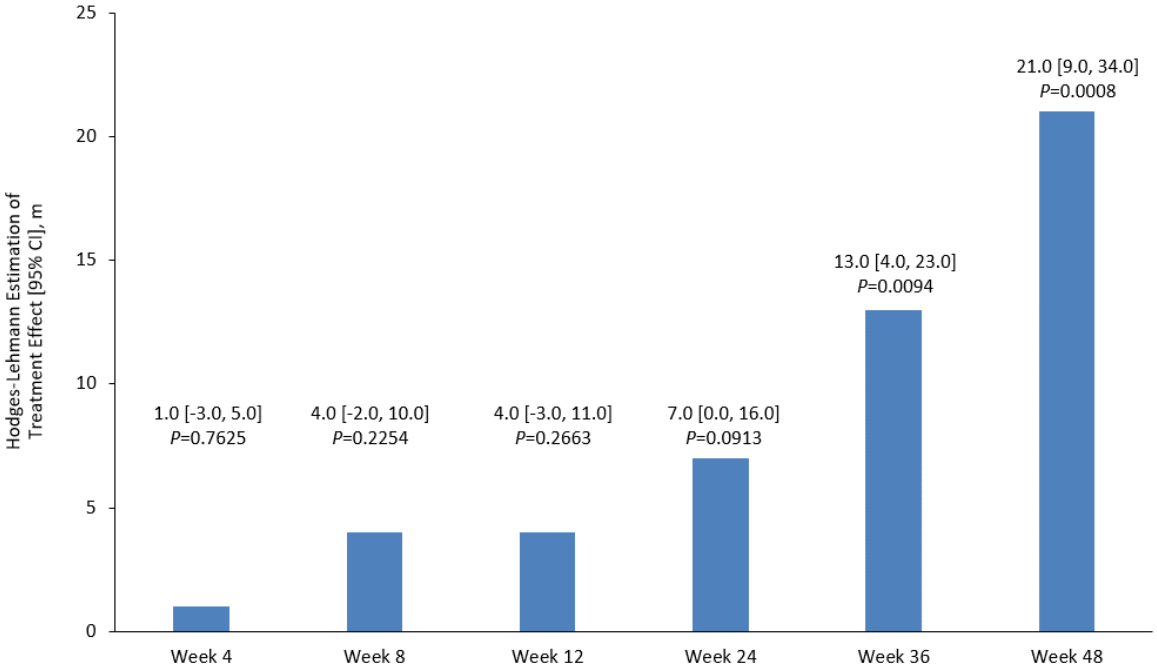

Hodges-Lehmann Estimation of Treatment Effect [95% CI], m
25
20
15
10
5
0
1.0 [-3.0, 5.0]
P=0.7625
4.0 [-2.0, 10.0]
P=0.2254
4.0 [-3.0, 11.0]
P=0.2663
7.0 [0.0, 16.0]
P=0.0913
13.0 [4.0, 23.0]
P=0.0094
21.0 [9.0, 34.0]
P=0.0008
Week 4
Week 8
Week 12
Week 24
Week 36
Week 48

Figure E5

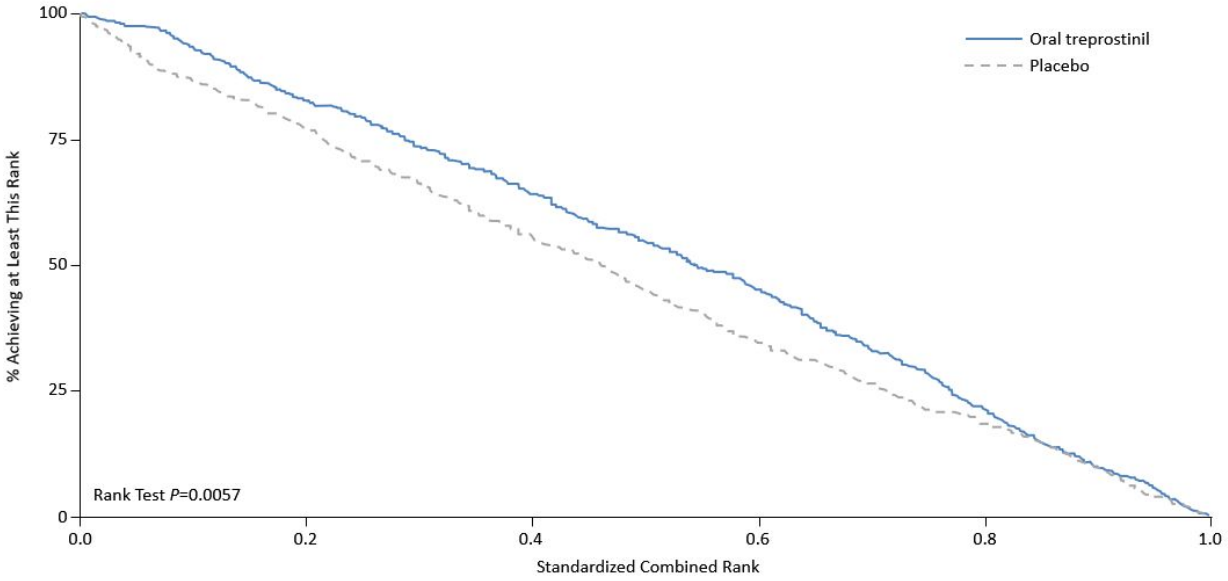
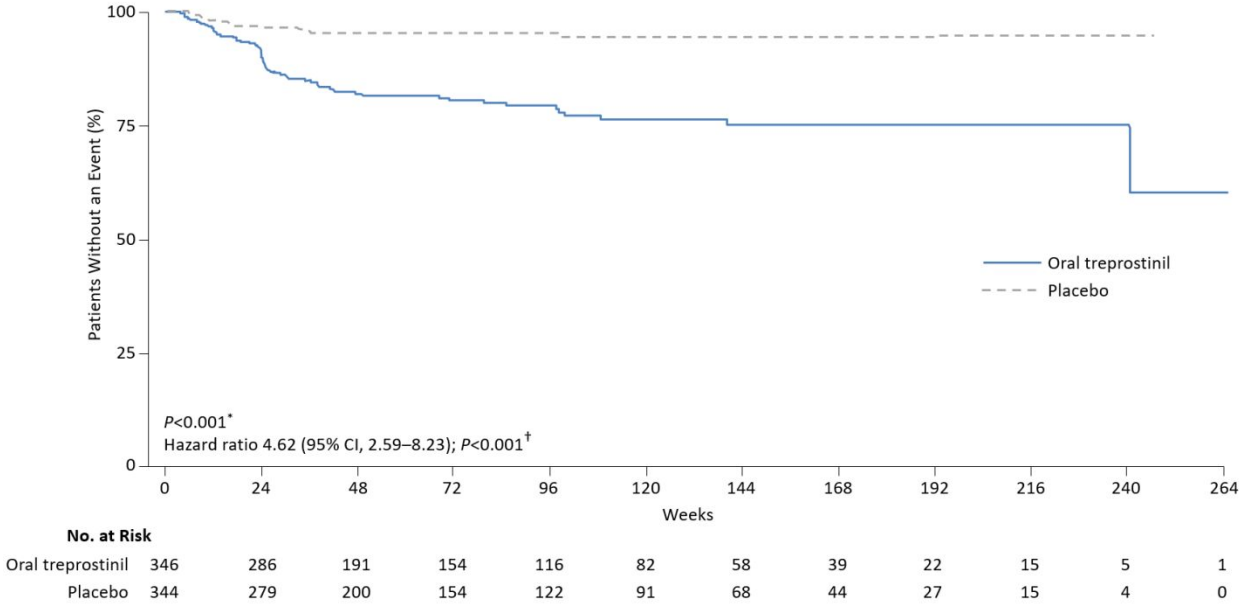

100
75
50
25
0
% Achieving at Least This Rank
Oral treprostinil
Placebo
Rank Test P=0.0057
0.0
0.2
0.4
0.6
0.8
1.0
Standardized Combined Rank

Figure E6



No. at Risk												
Oral treprostinil	346	286	191	154	116	82	58	39	22	15	5	1
Placebo	344	279	200	154	122	91	68	44	27	15	4	0