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Combination Therapy with Oral Treprostinil for Pulmonary Arterial Hypertension
A Double-Blind Placebo-controlled Clinical Trial

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Abstract

Rationale: Oral treprostinil improves exercise capacity in patients with pulmonary arterial hypertension (PAH), but the effect on clinical outcomes was unknown.

Objectives: To evaluate the effect of oral treprostinil compared with placebo on time to first adjudicated clinical worsening event in participants with PAH who recently began approved oral monotherapy.

Methods: In this event-driven, double-blind study, we randomly allocated 690 participants (1:1 ratio) with PAH to receive placebo or oral treprostinil extended-release tablets three times daily. Eligible participants were using approved oral monotherapy for over 30 days before randomization and had a 6-minute-walk distance 150 m or greater. The primary endpoint was the time to first adjudicated clinical worsening event: death; hospitalization due to worsening PAH; initiation of inhaled or parenteral prostacyclin therapy; disease progression; or unsatisfactory long-term clinical response.

Measurements and Main Results: Clinical worsening occurred in 26% of the oral treprostinil group compared with 36% of placebo participants (hazard ratio, 0.74; 95% confidence interval, 0.56–0.97; P = 0.028). Key measures of disease status, including functional class, Borg dyspnea score, and N-terminal pro-brain natriuretic peptide, all favored oral treprostinil treatment at Week 24 and beyond. A noninvasive risk stratification analysis demonstrated that oral treprostinil–assigned participants had a substantially higher mortality risk at baseline but achieved a lower risk profile from Study Weeks 12–60. The most common adverse events in the oral treprostinil group were headache, diarrhea, flushing, nausea, and vomiting.

Conclusions: In participants with PAH, addition of oral treprostinil to approved oral monotherapy reduced the risk of clinical worsening. Clinical trial registered with www.clinicaltrials.gov (NCT01560624).

Keywords: pulmonary arterial hypertension; oral treprostinil; clinical study; combination therapy; sequential therapy

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Pulmonary arterial hypertension (PAH) is a rare, but progressive and often fatal, pulmonary vascular disease. Treatment options have expanded greatly in the past 20 years (1), and two event-driven studies of sequential combination therapy have established the durable benefit of the endothelin receptor antagonist (ERA) macitentan (2) and the prostacyclin receptor agonist selexipag (3). Epoprostenol, the endogenous agonist for the prostacyclin receptor, is highly effective in PAH, but it is short acting and requires continuous intravenous infusion (4). Selexipag was thus a significant addition to treatment options as a long-acting and orally available, selective prostacyclin IP receptor agonist. Oral extended-release treprostinil diolamine tablets improved exercise capacity when dosed twice daily in treatment-naive patients with PAH (5). Oral treprostinil dosed three times daily had a better pharmacokinetic profile, allowed participants to achieve a higher total daily dose, and substituted for parenteral treprostinil in a cohort of carefully selected participants with PAH (6). Therefore, the FREEDOM-EV study hypothesized that combination therapy with oral treprostinil would reduce the risk of clinical worsening events in patients who had recently started oral monotherapy for PAH. Preliminary results of this study have been previously reported in the form of conference abstracts (7–9).

**Methods**

**Study Design**

The FREEDOM-EV trial was a multicenter, randomized, double-blind, placebo-controlled, event-driven study. Investigators from 152 centers across 23 countries conducted the study between June 2012 and June 2018. The steering committee, in collaboration with the sponsor, designed the study protocol (see the online supplement), and the institutional review board at each center approved the protocol. The sponsor collected and analyzed the data according to a prespecified statistical analysis plan. An independent data monitoring committee supervised the study, and all authors had access to the source-verified data and attest to the accuracy and completeness of this report.

**Selection of Participants**

Participants were 18–75 years of age, met the 2013 consensus definition of World Health Organization (WHO) Group 1 pulmonary hypertension (10), and had a 6-minute-walk distance (6MWD) 150 m or greater at the screening visit. Historical right heart catheterization within 3 years (or during the screening period) must have demonstrated a mean pulmonary artery pressure of 25 mm Hg or greater and a pulmonary artery wedge pressure of 15 mm Hg or less. Based on the AMBITION study (11), protocol amendment 5 excluded participants who had three or more of the following risk factors for heart failure with preserved ejection fraction: 1) body mass index of 30 kg/m² or greater; 2) essential hypertension; 3) diabetes mellitus; or 4) clinically significant coronary artery disease. The initial protocol sought to enroll participants soon after they began oral monotherapy (between 30 and 90 d of beginning an approved dose and schedule of sildenafil, tadalafil, bosentan, ambrisentan, macitentan, or riociguat). Subsequent amendments expanded the monotherapy treatment window to address slow enrollment. The full set of protocol entry criteria are provided in the online supplement. All the participants provided written informed consent.

**Trial Procedures**

Randomization (1:1) was stratified by type of background therapy (i.e., phosphodiesterase type 5 [PDE5] inhibitor or soluble guanylate cyclase [SGC] stimulator vs. ERA) and by baseline 6MWD breakpoint (≤350 m). Participants initially took oral treprostinil or matching placebo 0.125 mg three times daily (spaced carefully every 6–8 h with food). The protocol allowed daily up-titration in 0.125 mg increments for the first 4 weeks and 0.25-mg daily titration thereafter to a maximum dose of 12 mg three times daily. We instructed investigators to increase doses steadily and to assess the need for dose adjustment during weekly telephone calls, attempting to balance the expected adverse drug effects with the apparent clinical benefits (i.e., a reduction in the signs and symptoms of PAH).

**Outcome Measures**

The primary endpoint was the time to first adjudicated clinical worsening event, which was defined as death from any cause, hospitalization for worsening PAH, disease progression, initiation of inhaled or infused prostacyclin therapy, or unsatisfactory...
long-term clinical response (definitions provided in the online supplement). Three disease experts (not otherwise participating in the study) formed a blinded, independent clinical event committee, which adjudicated all clinical worsening events using a narrative that was stripped of information about adverse events or dosing that might cue them to treatment assignment.

Investigator teams met participants at Weeks 4, 8, and 12, and then at 12-week intervals throughout the study to conduct efficacy assessments, including 6MWD, Borg dyspnea score, plasma N-terminal pro–brain natriuretic peptide (NT-proBNP) levels, and WHO functional class. Before the final statistical analysis plan was submitted to the U.S. Food and Drug Administration and before unblinding, we planned a risk analysis using three noninvasive variables as previously proposed (12) and validated (13) (e.g., 6MWD, NT-proBNP, and WHO functional class). Safety assessments included evaluation of adverse events and clinical laboratory parameters. Beginning in 2015, with protocol amendment 6, we collected vital status by phone every 6 months for those who discontinued the study; survival analysis was prespecified in the statistical plan submitted to the Food and Drug Administration.

Figure 1. Patient disposition. *Includes one subject in the oral treprostinil group and one subject in the placebo group who experienced clinical worsening events due to urgent hospitalization for treatment of worsening pulmonary arterial hypertension. †Includes one subject in the oral treprostinil group and one subject in the placebo group who experienced clinical worsening events due to fatal serious adverse events, and one subject in the oral treprostinil group who discontinued treatment due to an adverse event, but remained in the study until death (which did not qualify as a clinical worsening event).

Statistical Analysis
The final power calculation estimated that 205 adjudicated events would provide at least 90% power (type I error rate, 0.05; two-tailed) to detect a difference in the time to adjudicated clinical worsening event between treatment groups, assuming exponential distributions and an underlying hazard ratio of 0.62. We assumed a placebo event rate of 23% at Month 12 and accrual of subjects over 3 years with 10% attrition. These assumptions indicated a sufficient sample size would be 610–850 participants; we closed enrollment at 690 participants when we approached the required 205 events. The primary efficacy endpoint had been tested at an interim analysis when approximately 75% of the total adjudicated events had occurred with a prespecified decision to stop if the interim type I error was less than 0.02; this required that the final analysis have an α of less than 0.044 for an overall type I error rate at 0.05. The main analyses for the primary and secondary endpoints were performed in the entire population. For the primary efficacy analysis of time to adjudicated clinical worsening event, data were summarized by treatment group using product-limit estimates calculated by the Kaplan-Meier method. The log-rank test adjusted for the type of background PAH therapy (PDE5 inhibitor or SGC stimulator vs. ERA), and the baseline 6MWD (breakpoint ≈350 m) was used to calculate significance for treatment differences in the intention-to-treat population. The risk of clinical worsening was also compared between treatment groups using a Cox proportional hazards regression model to estimate a hazard ratio and its 95% confidence interval (CI), also adjusting for background PAH therapy and baseline 6MWD. All safety analyses were also performed in the entire population.

Table 1. Disposition and Baseline Characteristics

| Group                | Number | %     |
|----------------------|--------|-------|
| Placebo              | 344    | 50    |
| Oral Treprostinil    | 346    | 50    |

| Event Type                        | Placebo | Oral Treprostinil |
|-----------------------------------|---------|-------------------|
| Progressive Disease (n=4)         | 4       | 4                 |
| Adverse Event (n=14)†             | 14      | 14                |
| Withdrawal by Subject (n=29)†     | 29      | 29                |
| Protocol Violation (n=4)           | 4       | 4                 |
| Other (n=5)                        | 5       | 5                 |

| Event Type                        | Placebo | Oral Treprostinil |
|-----------------------------------|---------|-------------------|
| Clinical Worsening Event Including Death (Reported by Investigators)†| 133     | 91                |
| Completed the Study Without Clinical Worsening or Early Discontinuation n=155| 155     | 148               |
Table 1. Baseline Characteristics*

| Characteristic | Oral Treprostinil (n = 346) | Placebo (n = 344) | Overall (n = 689) |
|---------------|-----------------------------|-------------------|------------------|
| Age, yr       | 45.6 ± 15.7                 | 44.8 ± 15.4       | 45.2 ± 15.5      |
| Sex, F, n (%) | 275 (79.5)                  | 269 (78.2)        | 544 (78.8)       |
| Race, n (%)   |                             |                   |                  |
| White         | 187 (54.0)                  | 173 (50.3)        | 360 (52.2)       |
| Black or African American | 8 (2.3)   | 13 (3.8)         | 21 (3.0)         |
| Asian         | 150 (43.4)                  | 156 (45.3)        | 306 (44.3)       |
| Unknown       | 1 (0.3)                     | 2 (0.6)           | 3 (0.4)          |
| Region, n (%) |                             |                   |                  |
| North America | 39 (11.3)                   | 54 (15.7)         | 93 (13.5)        |
| Asia-Pacific  | 162 (46.8)                  | 160 (46.5)        | 322 (46.7)       |
| Europe        | 55 (15.9)                   | 44 (12.8)         | 99 (14.3)        |
| Latin America | 90 (26.0)                   | 86 (25.0)         | 176 (25.5)       |
| Median time since diagnosis (IQR), mo | 6.2 (2.4–13.3) | 6.5 (2.28–13.2) | 6.4 (2.3–13.3)  |

Definition of abbreviations: 6MWD = 6-minute-walk distance; ERA = endothelin receptor antagonist; IQR = interquartile range; PAH = pulmonary arterial hypertension; PDE5 = phosphodiesterase type 5; SGC = soluble guanylate cyclase; WHO = World Health Organization.

*Plus/minus values are means ± SD. Testing of baseline characteristics showed that there were no significant between-group differences at baseline, except regarding risk stratification by number of low-risk criteria.

1Low-risk criteria defined as WHO functional class I or II, 6MWD greater than 440 m, and/or NT-pro-brain natriuretic peptide less than 300 pg/ml. Low-risk criteria met were only counted for subjects with all three measures available; n = 337 oral treprostinil, n = 334 placebo.

2P = 0.002; P value was obtained from Fisher’s exact test.

Results

Participants

We randomly allocated 690 participants to oral treprostinil (346 participants) or placebo (344 participants) treatment groups (Figure 1). Table 1 shows the demographic and clinical characteristics of participants; individual characteristics were largely balanced at baseline. We enrolled participants after beginning initial monotherapy (median time, 5.4 mo). Participants were predominantly female; 63% had WHO functional class II symptoms, and 72% were taking a PDE5 inhibitor or SGC stimulator. Median dose of oral treprostinil achieved at Week 24 was 3.56 mg three times daily, which corresponds to titration by approximately 0.125 mg once weekly (288 oral treprostinil participants; see Figure E1 in the online supplement). Median dose of placebo at Week 24 was 6 mg three times daily (289 placebo participants).

Primary Efficacy Endpoint

Overall, 90 (26%) participants in the oral treprostinil group experienced an adjudicated clinical worsening event compared with 124 (36%) placebo participants. Kaplan-Meier estimates of the time to adjudicated clinical worsening event suggested group separation before Week 24 (Figure 2A, log-rank test, P = 0.039); the hazard ratio adjusted for background therapy and baseline 6MWD as a continuous variable was 0.74 (95% CI, 0.56–0.97; P = 0.028). When adjusted for baseline 6MWD as a categorical variable (breakpoint ≤350 m), the hazard ratio was 0.75 (95% CI, 0.57–0.99; P = 0.040). The median time to clinical worsening was 46 weeks with oral treprostinil and 37 weeks with placebo. The treatment-attributable difference in clinical worsening was driven by a reduced incidence of disease progression in the oral treprostinil group (hazard ratio, 0.39; 95% CI, 0.23–0.66; P < 0.001). Deaths and hospitalizations were balanced. Subgroup analyses of the primary endpoint, based on age, sex, baseline 6MWD, WHO functional class, PAH etiology, geographic region, and background oral PAH therapy did not show any significant interactions between subgroup and treatment (see Figure E2).

Individual components of the demographics suggested balanced participant characteristics at baseline; however, a prespecified (before unblinding), noninvasive risk stratification (12) indicated that the oral treprostinil–assigned group had a higher mortality risk at baseline. Placebo-assigned participants had more low-risk criteria (e.g., WHO functional class I or II symptoms, 6MWD >440 m, and NT-proBNP <300 pg/ml) compared with the oral treprostinil group (Fisher’s exact test, P = 0.002, Table 1). We thus conducted a post hoc analysis accounting for baseline risk profile (number of low-risk factors, 0–3); the hazard ratio for a clinical worsening event dropped further to 0.61 (95% CI, 0.46–0.81; P < 0.001). Arbitrarily classifying those with two to three low-risk
factors as “lower risk” and those with zero to one low-risk factors as “higher risk” resulted in two groups of similar size (n = 366 vs. 305). We re-estimated Kaplan-Meier time-to-event curves for these two groups, finding that oral treprostinil protected higher-risk participants from clinical worsening events (log-rank, \( P = 0.006; \) Figure 2B).

**Secondary and Exploratory Efficacy Endpoints**

Plasma NT-proBNP levels decreased in the oral treprostinil group beginning at Week 12 (Figure 3). WHO functional class improved significantly for participants in the oral treprostinil group at all visits from Week 12 to Week 48 when compared with the placebo group (Figure 4A). Improvement was observed as both a higher proportion of favorable (“improved”) and a lower proportion of worsening (“deteriorated”) categorical change from baseline. At Week 24, oral treprostinil participants increased their 6MWD 16 m (least squares mean) compared with 8 m in the placebo group (mixed-model repeated measurement [MMRM] estimate of treatment effect, 8 m [95% CI, −2 to 18; \( P = 0.12 \)) (Table 2). By Week 36, treatment difference in 6MWD was clear (MMRM = 13 m [95% CI, 1–25]; \( P = 0.04 \)), and this increased further at Week 48 (MMRM = 22 m [95% CI, 8–35; \( P = 0.002 \)) (Figure 4B). Similarly, the combined 6MWD/Borg dyspnea score ranking, a statistical method for analyzing changes in walk distance and associated changes in Borg dyspnea score, favored the oral treprostinil treatment group at Week 24 (see Figure E5).

We hypothesized a priori (before unblinding) that oral treprostinil applied as sequential combination therapy would improve risk assessments at follow-up. We obtained the necessary variables to define the recently proposed, noninvasive risk assessment at Weeks 12, 24, 36, and 60. At each assessment, the Fisher’s exact analysis of those having categorical change was highly significant (\( P < 0.002 \)), with more oral treprostinil participants having an improved risk profile and fewer having a deteriorated risk profile (Figure 4C). A post hoc analysis using the Reveal 2.0 risk score (14) yielded a similar result beginning at Week 12 (see Table E1).

The initial data collection plan stopped following participants 30 days after discontinuing randomized treatment unless they consented to participate in an open-label follow-up study. An amended protocol issued in 2015 collected vital status every 6 months for consenting participants until final study closure in October 2018. As of October 2018, 38 (11%) participants initially assigned to oral treprostinil were confirmed dead compared with 60 (17.4%) in the placebo group (hazard ratio, 0.63; 95% CI, 0.42–0.95; \( P = 0.026 \)) (Table 2). Because we did not begin collecting vital status until some participants had exited the study (and some investigative sites had closed), survival could not be confirmed for 74 (11%) participants. A sensitivity analysis assuming the observed mortality rate in those with unknown vital status still favored oral treprostinil (see Tables E2 and E3).
components of the primary endpoint. This
deaths were balanced between groups as
of whom were taking an approved oral
disease progression in participants, all
worsening event by reducing the likelihood
three times daily delayed a composite clinical
endpoint of time to
In the present study, oral treprostinil dosed
was substantially more common in oral
events attributed to placebo. Study drug
and were more often severe compared with
commonly attributed to oral treprostinil
and were more often severe compared with
events attributed to placebo. Study drug
discontinuation because of adverse events
was substantially more common in oral
treatment–assigned participants (18.8%)
then in placebo participants (4.1%).
Discontinuation because of an adverse
was more common before Week 24
(see Figure E6) and occurred at a median
(interquartile range) oral treprostinil dose
of 1.4 (0.4–3.0) mg three times daily.

Safety
A total of 334 (96.5%) participants in the
oral treprostinil group and 219 (63.7%)
participants in the placebo group reported
at least one adverse event attributable to study
drug (Table 3). Headache, diarrhea,
flushing, nausea, and vomiting were more
commonly attributed to oral treprostinil
and were more often severe compared with
events attributed to placebo. Study drug
discontinuation because of adverse events
was substantially more common in oral
treatment–assigned participants (18.8%)
then in placebo participants (4.1%).
Discontinuation because of an adverse
was more common before Week 24
(see Figure E6) and occurred at a median
(interquartile range) oral treprostinil dose
of 1.4 (0.4–3.0) mg three times daily.

Discussion
In the present study, oral treprostinil dose
times daily delayed a composite clinical
epoint of time to first adjudicated clinical
worsening event by reducing the likelihood
disease progression in participants, all
of whom were taking an approved oral
monotherapy for PAH. Hospitalizations and
deaths were balanced between groups as
components of the primary endpoint. This
study differs from previous sequential
combination studies (2, 3) in that
participants had a younger age, more recent
diagnosis, less severe symptoms, and better
baseline exercise capacity. Although
prostacyclin-class adverse events were
common and 18.8% of oral treprostinil
participants discontinued therapy because of
adverse events, active treatment facilitated
steady reductions in plasma NT-proBNP,
improved WHO functional class, and
reduced Borg dyspnea score after 6MWT, all
beginning at Week 12. Actual 6MWD
was improved at Weeks 36 and 48 in an analysis
that does not require imputation. Total daily
dose among actively treated participants at
Week 24 was 50% higher than that at Week
16 in the previous combination studies of
oral treprostinil (15, 16), and we postulate
that higher doses were possible, because
time three daily dose reduced
peak–trough excursions in plasma
concentrations of treprostinil (6, 17).

Functional improvements, measured as
part of a multifaceted risk assessment, have
been repeatedly associated with improved
outcomes (12, 13, 18, 19). We prespecified
(before submission of the final statistical
analysis plan) use of the French risk
assessment of subsequent treatment
efficacy. The unexpected imbalance in risk
profiles at baseline indicates that our
randomization strategy failed to create
comparable baseline groups. This may be
because the 350 m or lower breakpoint for
6MWD included less than 30% of the
baseline walks and/or because this 350-m
value is not a recognized transition point
for prognosis (21). The post hoc, risk-
adjusted analysis of the primary endpoint
demonstrating a greater treatment effect
indicates that future studies should
consider stratifying randomization based
upon background therapy and a validated
risk score to create cohorts that have a
similar prognosis at baseline (22). A failure
in this regard could lead to under- or
overestimation of the treatment effect.

Participants initially assigned placebo
had a similar rate of death at the end of
randomized treatment. A total of 108 of the
117 participants with an investigator-
reported, nonfatal clinical worsening event
in the primary study began therapy with oral
treprostinil in the extension study. An
apparent increase in survival for those
initially assigned oral treprostinil emerged
late in the study, but this observation must
be treated cautiously, because vital status
was unknown for 74 participants (11%). The
results still favored oral treprostinil,
assuming a proportional mortality among
those with unknown vital status (Tables E2
and E3). We know very little about
participants who discontinued the study.
Only vital status was collected via phone call;
we do not know the causes of death. Deaths
were distributed relatively uniformly
throughout the world with the exception of
India, which had a death rate of
approximately 20%. However, other
countries with less access to expensive,

![Figure 3. Plasma N-terminal pro–brain natriuretic peptide (NT-proBNP) results by study visit. Per protocol, NT-proBNP values were not measured at Week 48. P value was obtained from the analysis of covariance with change from baseline in log-transformed data in NT-proBNP as the dependent variable, treatment as fixed effect, and log-transformed baseline NT-proBNP as a covariate. NT-proBNP assay centrally performed by Covance via the Immulite 2000 on a Siemens platform. The normal range for both sexes over 75 years of age is less than 450 pg/ml. IQR = interquartile range; LS = least squares; PBO = placebo; TRE = oral treprostinil.](image-url)
Figure 4. Categorical changes from baseline in World Health Organization (WHO) functional class, Borg dyspnea score, and risk stratification criteria. (A) WHO functional class categorical change from baseline by study visit; participants who had a missing assessment at Week 24 and had deteriorated were assigned worst case of 10; $P$ value was obtained from Fisher’s exact test. (B) Borg dyspnea score categorical change from baseline by study visit; participants who had a missing assessment at Week 24 and had deteriorated were assigned worst case of 10; $P$ value was obtained from Fisher’s exact test. (C) Risk stratification criteria. $P$ value was obtained from Fisher’s exact test. (D) NT-proBNP dropped markedly with oral treprostinil, and we also observed improvements in investigator-assessed WHO functional class and participants who had a missing assessment at Week 24 and had deteriorated were assigned worst case of 10; $P$ value was obtained from Fisher’s exact test. (E) Borg dyspnea score categorical change from baseline by study visit; participants who had a missing assessment at Week 24 and had deteriorated were assigned worst case of 10; $P$ value was obtained from Fisher’s exact test.
groups.
prognostic score should be considered for variance/covariance structure shared across treatment groups was used to model the within-subject errors.
treatment, week, treatment-by-week interaction, and background PAH therapy as the fixed effects, and baseline 6MWD as the covariate. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.
the dependent variable, treatment, week, and treatment-by-week interaction as the fixed effects, and log-transformed baseline NT-proBNP as the
treatment-related bene-
Subjects who were alive at the study closure have their time to death censored at the last contact date.
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.
**Vital status was collected at the study closure for all subjects including subjects who rolled over to extension study and who discontinued early from the
of this article at www.atsjournals.org.
Author disclosures are available with the text of this article at www.atrsjournals.org.
Table 2. Primary and Secondary Efficacy Endpoints

| Endpoint | Oral Treprostinil (n = 346) | Placebo (n = 344) | Treatment Effect (95% CI) |
|----------|-----------------------------|-------------------|--------------------------|
| Primary endpoint: adjudicated clinical worsening event, n (%) | | | |
| All events | 90 (26.0) | 124 (36.0) | HR, 0.74 (0.56 to 0.97); P = 0.028*; P = 0.039† |
| Death (all causes) | 15 (4.3) | 14 (4.1) |  |
| Hospitalization due to PAH and/or right heart failure | 35 (10.1) | 35 (10.2) |  |
| Initiation of inhaled or infused prostanol | 2 (0.6) | 5 (1.5) |  |
| Disease progression | 19 (5.5) | 50 (14.5) |  |
| Unsatisfactory long-term clinical response | 19 (5.5) | 20 (5.8) |  |
| Secondary endpoints (at Week 24) | | | |
| 6MWD, LS mean change, m | 16 | 8.03 | 7.96 (–2 to 17.92); P = 0.117‡ |
| NT-proBNP, concentration ratio to baseline, LS mean change | 0.82 | 1.16 | 0.71 (0.61 to 0.82); P < 0.001§ |
| Borg dyspnea score, shift from baseline, n (%) | | | |
| Improved | 126 (36.5) | 105 (30.5) | P = 0.014¶ |
| No change | 128 (37.1) | 113 (32.8) |  |
| Deteriorated | 91 (26.4) | 126 (36.6) |  |
| Combined ranking of 6MWD and Borg dyspnea score | — | — | P = 0.006¶ |
| WHO functional class, shift from baseline, n (%) | | | |
| Improved | 51 (14.7) | 37 (10.8) | P = 0.017¶ |
| No change | 256 (74) | 244 (70.9) |  |
| Deteriorated | 39 (11.3) | 63 (18.3) |  |
| Deaths (all causes), n (%) | | | |
| Deaths during study | 17 (4.9) | 18 (5.2) | HR, 1.00 (0.52 to 1.95); P = 0.992‡; P = 0.978† |
| Deaths at closure of study** | 38 (11.0) | 60 (17.4) | HR, 0.63 (0.42 to 0.95); P = 0.026‡; P = 0.032† |

Definition of abbreviations: 6MWD = 6-minute-walk distance; CI = confidence interval; HR = hazard ratio; LS = least squares; MMRM = mixed-model repeated measurement; NT-proBNP = N-terminal pro–brain natriuretic peptide; PAH = pulmonary arterial hypertension; WHO = World Health Organization.
*Hazard ratio, 95% CI, and P value were calculated with proportional hazard model with explanatory variables of treatment, background PAH therapy, and baseline 6MWD as a continuous variable.
†P value was obtained from log-rank test stratified by background PAH therapy and baseline 6MWD category.
‡LS mean, P value, estimated difference, and its 95% CI were from the MMRM with the change from baseline in 6MWD as the dependent variable, treatment, week, treatment-by-week interaction, and background PAH therapy as the fixed effects, and baseline 6MWD as the covariate. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.
§LS mean, P value, estimated difference, and its 95% CI were from the MMRM with the change from baseline in log-transformed data in NT-proBNP as the dependent variable, treatment, week, and treatment-by-week interaction as the fixed effects, and log-transformed baseline NT-proBNP as the covariate. An unstructured variance/covariance structure shared across treatment groups was used to model the within-subject errors.
¶P value was obtained from Fisher’s exact test.
†P value obtained from nonparametric analysis of covariance.
**Vital status was collected at the study closure for all subjects including subjects who rolled over to 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.

measurements appeared useful to document treatment-related benefits, and a prognostic score should be considered for future outcome studies to balance baseline risk profiles between the randomized treatment groups.

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Figure 4. (Continued). exact test. (C) Risk categorical change from baseline through Week 60. Percentages are calculated based on the number of participants at each visit within each treatment group. Low-risk criteria are defined as WHO functional class I or II, 6-minute-walk distance >440 m, or N-terminal pro–brain natriuretic peptide <300 pg/ml. Low-risk criteria met were only counted for subjects with all three measures. “Improved” indicates any increase in the number of low-risk criteria met; “no change” indicates the same number of low-risk criteria met; and “deteriorated” indicates any decrease in the number of low-risk criteria met. P values were obtained from Fisher’s exact test. PBO = placebo; TRE = oral treprostinil.
Table 3. Most Frequent Adverse Events

| Variable                  | Oral Treprostinil (n = 346) | Placebo (n = 344) |
|---------------------------|------------------------------|-------------------|
| Any event reported        | 342 (98.8)                   | 328 (95.3)        |
| Any event probably or possibly related to study drug | 334 (96.5)                   | 219 (63.7)        |
| Study drug-related serious adverse event     | 27 (7.8)                      | 18 (5.2)          |
| Study drug-related severe adverse event       | 78 (22.5)                     | 27 (7.8)          |
| Headache                    | 242 (69.9)                   | 102 (29.7)        |
| Diarrhea                    | 227 (65.6)                   | 68 (19.8)         |
| Flushing                    | 151 (43.6)                   | 26 (7.6)          |
| Nausea                      | 128 (37.0)                   | 58 (16.9)         |
| Vomiting                    | 111 (32.1)                   | 26 (7.6)          |
| Pain in jaw                 | 60 (17.3)                    | 8 (2.3)           |
| Dizziness                   | 52 (15.0)                    | 45 (13.1)         |
| Pain in extremity           | 48 (13.9)                    | 11 (3.2)          |
| Myalgia                     | 44 (12.7)                    | 23 (6.7)          |

*Adverse events listed are those probably or possibly related to study drug that occurred in more than 10% of participants in either study group.
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References
1. Humbert M, Lau EM, Montani D, Jais S, Sitbon O, Simonneau G. Advances in therapeutic interventions for patients with pulmonary arterial hypertension. Circulation 2014;130:2189–2208.
2. Pulido T, Adzheriho I, Channick RN, Delcroix M, Galié N, Ghofrani HA, et al.; SERAPHIN Investigators. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013;369:809–818.
3. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galié N, et al.; GRIPHON Investigators. Selaxipag for the treatment of pulmonary arterial hypertension. N Engl J Med 2015;373:2522–2533.
4. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, et al.; Primary Pulmonary Hypertension Study Group. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996;334:296–301.
5. Jing ZC, Parikh K, Pulido T, Jerjes-Sanchez C, White RJ, Allen R, et al. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized, controlled trial. Circulation 2013;127:624–633.
6. Chakinala MM, Feldman JP, Rischard F, Mathier M, Broderick M, Leedom N, et al. Transition from parenteral to oral treprostinil in pulmonary arterial hypertension. J Heart Lung Transplant 2017;36;103–201.
7. White RJ, Sanchez Diaz CJ, Bohns Meyer GM, Pulido T, Sepulveda P, Wang KY, et al. Treatment with oral treprostinil is associated with improved survival in pulmonary arterial hypertension participants from the FREEDOM-EV Study [abstract]. Presented at the 13th PVRI Annual World Congress on PVD, January 31–February 3, 2019, Barcelona, Spain.
8. Tapson VF, Sanchez Diaz CJ, Bohns Meyer GM, Pulido T, Sepulveda P, Wang KY, et al. Treatment with oral treprostinil delays time to clinical worsening in patients with pulmonary arterial hypertension: results from FREEDOM-EV [abstract]. J Heart Lung Transplant 2019;38:S94–S95.
9. White RJ, Sanchez Diaz CJ, Bohns Meyer GM, Pulido T, Sepulveda P, Wang KY, et al. Risk scores and risk-based stratification of clinical worsening events in pulmonary arterial hypertension participants treated with oral treprostinil: FREEDOM-EV [abstract]. Am J Respir Crit Care Med 2019;199:A5587.
10. Simonneau G, Gatzaouli MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2013;62(Suppl):D34–D41.
11. Galié N, Barberà JA, Frost AE, Ghofrani HA, Hoeper MM, McLoughlin VV, et al.; AMBITION Investigators. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. N Engl J Med 2015;373:834–844.
12. Bouchy A, Weatherald J, Savale L, Jais X, Cottin V, Prevot G, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J 2017;50:170089–170089.
13. Hoeper MM, Pittrow D, Opitz C, Gibbs JSR, Rosenkranz S, Grünig E, et al. Risk assessment in pulmonary arterial hypertension. Eur Respir J 2018;51:1702606.
14. Benza RL, Gomberg-Maitland M, Elliott CG, Farber HW, Foreman AJ, Frost AE, et al. Predicting survival in patients with pulmonary arterial hypertension: the REVEAL risk score calculator 2.0 and comparison with ESC/ERS-based risk assessment strategies. Chest 2019;158:323–337.
15. Tapson VF, Jing ZC, Xu KF, Pan L, Feldman J, Kiely DG, et al.; FREEDOM-C2 Study Team. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background therapy.
endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): a randomized controlled trial. Chest 2013;144:952–958.

16. Tapson VF, Torres F, Kermeen F, Keogh AM, Allen RP, Frantz RP, et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): a randomized controlled trial. Chest 2012;142:1383–1390.

17. White RJ, Torres F, Allen R, Jerjes C, Pulido T, Yehle D, et al. Pharmacokinetics of oral treprostinil sustained release tablets during chronic administration to patients with pulmonary arterial hypertension. J Cardiovasc Pharmacol 2013;61:474–481.

18. Benza RL, Farber HW, Frost A, Ghofrani HA, Gómez-Sánchez MA, Langleben D, et al. REVEAL risk scores applied to riociguat-treated patients in PATENT-2: impact of changes in risk score on survival. J Heart Lung Transplant 2018;37:513–519.

19. Benza RL, Miller DP, Foreman AJ, Frost AE, Badesch DB, Benton WW, et al. Prognostic implications of serial risk score assessments in patients with pulmonary arterial hypertension: a Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) analysis. J Heart Lung Transplant 2015;34:356–361.

20. Weatherald J, Boucly A, Sahay S, Humbert M, Sitbon O. The low-risk profile in pulmonary arterial hypertension: time for a paradigm shift to goal-oriented clinical trial endpoints? Am J Respir Crit Care Med 2015;197:860–868.

21. Galié N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015;46:903–975.

22. Benza RL, Miller DP, Gomberg-Maitland M, Frantz RP, Foreman AJ, Coffey CS, et al. Predicting survival in pulmonary arterial hypertension: insights from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL). Circulation 2010;122:164–172.

23. Lajoie AC, Lauzieré G, Lega JC, Lacasse Y, Martin S, Simard S, et al. Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis. Lancet Respir Med 2016;4:291–305.

24. Hoeper MM, McLaughlin VV, Barberá JA, Frost AE, Ghofrani HA, Peacock AJ, et al. Initial combination therapy with ambrisentan and tadalafil and mortality in patients with pulmonary arterial hypertension: a secondary analysis of the results from the randomised, controlled AMBITION study. Lancet Respir Med 2016;4:894–901.