

# Tadalafil for the Treatment of Pulmonary Arterial Hypertension

## A Double-Blind 52-Week Uncontrolled Extension Study

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### Objectives

The aim of this study was to evaluate the long-term safety and durability of efficacy of tadalafil for pulmonary arterial hypertension.

### Background

Tadalafil is an oral phosphodiesterase-5 inhibitor approved for PAH treatment. In the multicenter, placebo-controlled, randomized, 16-week PHIRST (Pulmonary Arterial Hypertension and Response to Tadalafil) study, tadalafil 40 mg improved exercise capacity and delayed clinical worsening.

### Methods

Eligible patients from PHIRST received once-daily tadalafil 20 mg (T20 mg) or 40 mg (T40 mg) (n = 357) in the double-blind, 52-week, uncontrolled extension study (PHIRST-2); 293 patients completed PHIRST-2. Durability of efficacy was explored using the 6-min walk distance (6MWD) test. Clinical worsening and changes in World Health Organization functional class were evaluated.

### Results

The safety profile of tadalafil in PHIRST-2 was similar to that in PHIRST, with typical phosphodiesterase-5 inhibitor adverse events. The 6MWDs achieved in PHIRST for the subset of patients receiving T20 mg and T40 mg in both PHIRST and PHIRST-2 ( $406 \pm 67$  m [n = 52] and  $413 \pm 81$  m [n = 59] at PHIRST-2 enrollment, respectively) were maintained at PHIRST-2 completion ( $415 \pm 80$  m [n = 51] and  $410 \pm 78$  m [n = 59], respectively). Numerically fewer patients who were on T40 mg in PHIRST and PHIRST-2 experienced World Health Organization functional class deterioration (6% [n = 5]) compared with those randomized to T20 mg (9% [n = 7]) across both studies. Post hoc analyses showed that background bosentan use and higher 6MWD at PHIRST baseline were associated with fewer clinical worsening events.

### Conclusions

Long-term treatment with tadalafil was well tolerated in patients with pulmonary arterial hypertension. In patients receiving either T20 mg or T40 mg, the improvements in 6MWD demonstrated in the 16-week PHIRST study appeared sustained for up to 52 additional weeks of treatment in PHIRST-2. (Pulmonary Arterial Hypertension and Response to Tadalafil Study; NCT00549302) (J Am Coll Cardiol 2012;60:768-74) © 2012 by the American College of Cardiology Foundation

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with steering committee activities for Eli Lilly & Company, Actelion, Pfizer, United Therapeutics, Bayer-Schering, and GlaxoSmithKline; has been a paid lecturer for Actelion, Pfizer, Bayer-Schering, and GlaxoSmithKline; and has done contract research for Eli Lilly & Company, Actelion, Pfizer, United Therapeutics, Bayer-Schering, and GlaxoSmithKline. Dr. Ghofrani has received honoraria from, acted as a consultant for, and/or been a steering committee member for Actelion, Bayer-Schering, Eli Lilly & Company, Ergonex, GlaxoSmithKline, Novartis, Pfizer, and United Therapeutics. Dr. Simonneau has received research support and/or acted as a consultant for Actelion, Bayer-Schering, GlaxoSmithKline, Pfizer, and United Therapeutics. Dr. Botros is an employee of and stockholder in Eli Lilly & Company. Ms. Chan is an employee of and stockholder in Eli Lilly & Company. Mr. Beardsworth is an employee of and stockholder in Eli Lilly & Company. Dr. Barst has received support for serving as a consultant and scientific advisor to Actelion, Bayer, Eli Lilly & Company, Gilead, Ikaria, Merck, Novartis, and Pfizer.

Manuscript received September 15, 2011; revised manuscript received April 24, 2012, accepted May 15, 2012.

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary circulation leading to early death (1,2). Regulatory approval of PAH therapies has been based primarily on improvements in exercise capacity in short-term, placebo-controlled trials (3). Few studies have prospectively evaluated the long-term safety and efficacy of these drugs.

The 16-week, double-blind, placebo-controlled PHIRST (Pulmonary Arterial Hypertension and Response to Tadalafil) study evaluated 4 doses of tadalafil (an oral, once-daily phosphodiesterase [PDE]-5 inhibitor) and demonstrated that the highest dose studied, 40 mg, significantly improved 6-min walk distance (6MWD) versus placebo ( $p < 0.01$ , pre-specified alpha value), with a safety profile consistent with its class (4). Tadalafil 40 mg (T40 mg) significantly improved time to clinical worsening and quality of life and is the approved dose for PAH treatment.

Data from the 52-week, double-blind, multicenter, long-term prospective extension study (PHIRST-2) are now reported. Because the results of PHIRST were not known when PHIRST-2 was performed (i.e., whether tadalafil 20 mg [T20 mg] or T40 mg would prove most effective), the

primary objective of PHIRST-2 was to evaluate the long-term safety and durability of efficacy of both the T20 mg and T40 mg.

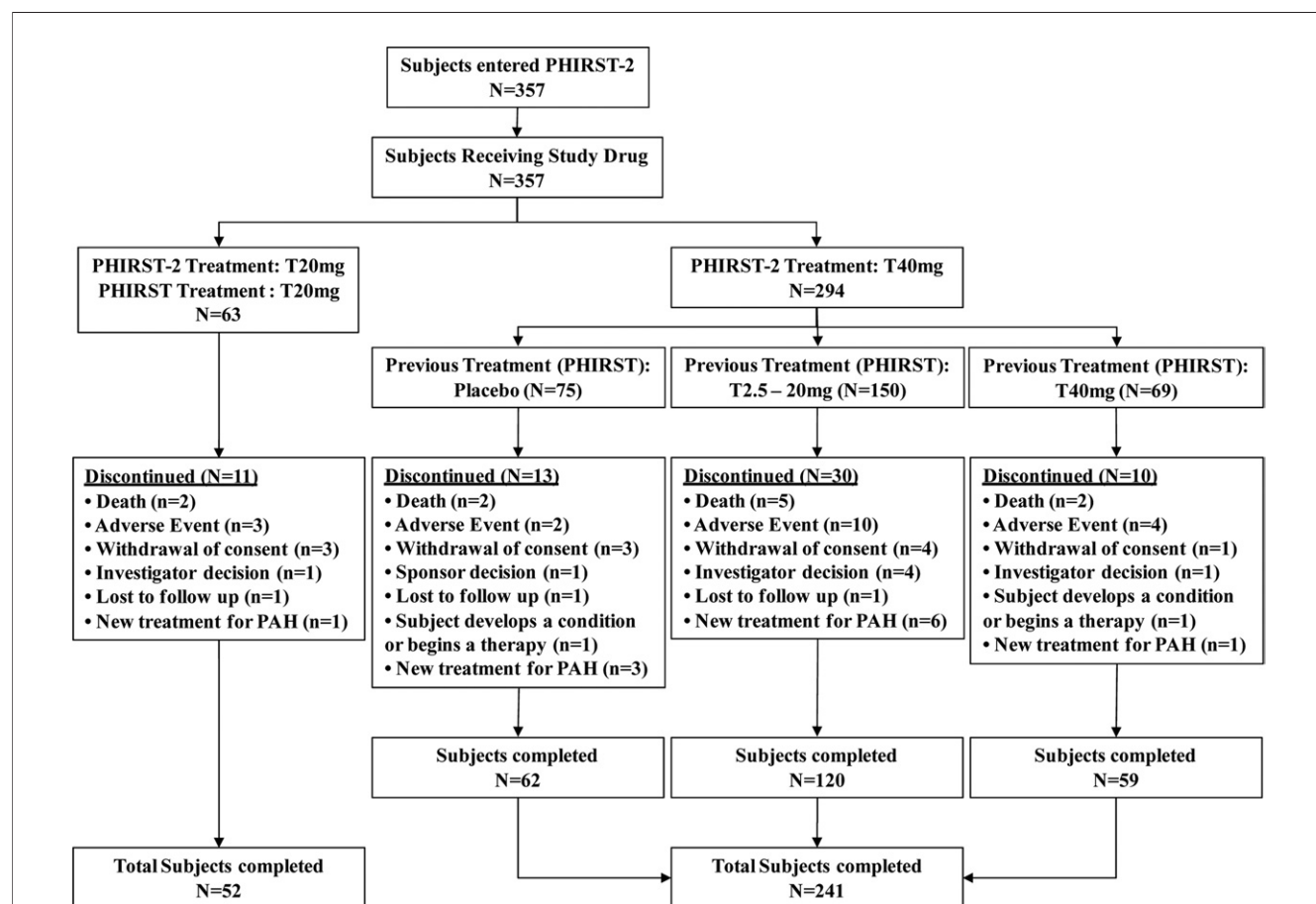
## Methods

**Study design and patient enrollment.** Eligible patients from PHIRST (4) were enrolled in PHIRST-2 and assigned to continue T20 mg (absent clinical worsening;  $n = 63$ ) or to receive T40 mg (all other patients;  $n = 294$ ) once daily for 52 weeks (Online Fig. 1).

During PHIRST-2, changes in conventional therapies, such as diuretic agents and digoxin, were allowed. However, patients were discontinued if they initiated prostacyclin analogs, PDE-5 inhibitors, and/or an endothelin receptor antagonist (patients receiving background bosentan at PHIRST enrollment continued on bosentan in PHIRST-2).

## Abbreviations and Acronyms

<b>AE</b>	= adverse event(s)
<b>PAH</b>	= pulmonary arterial hypertension
<b>PDE</b>	= phosphodiesterase
<b>6MWD</b>	= 6-min walk distance
<b>T20 mg</b>	= tadalafil 20 mg
<b>T40 mg</b>	= tadalafil 40 mg
<b>WHO-FC</b>	= World Health Organization functional class



**Figure 1** Patient Flow

PAH = pulmonary arterial hypertension; PHIRST = Pulmonary Arterial Hypertension and Response to Tadalafil; T = tadalafil.

**Table 1** Baseline Characteristics for All Patients Who Entered PHIRST-2

Characteristic	T20 mg: T20 mg (n = 63)	Placebo: T40 mg (n = 75)	T2.5–20 mg: T40 mg (n = 150)	T40 mg: T40 mg (n = 69)
Age (yrs)	53 ± 16	54 ± 15	54 ± 15	53 ± 16
Female	48 (76%)	60 (80%)	117 (78%)	53 (77%)
Race				
White	48 (76%)	65 (87%)	122 (81%)	56 (81%)
Etiology				
Idiopathic/heritable	37 (59%)	49 (65%)	94 (63%)	43 (62%)
CTD	16 (25%)	15 (20%)	34 (23%)	13 (19%)
ASD	3 (5%)	8 (11%)	10 (7%)	8 (12%)
Anorexigen use	4 (6%)	2 (3%)	5 (3%)	4 (6%)
Corr-CHD	3 (5%)	1 (1%)	7 (5%)	1 (1%)
6MWD (m)*	398 ± 72	362 ± 100	369 ± 92	403 ± 84
n	63	73	145	69
WHO-FC*	63	75	150	69
I	5 (8%)	2 (3%)	5 (3%)	4 (6%)
II	42 (67%)	31 (41%)	67 (45%)	38 (55%)
III	16 (25%)	36 (48%)	66 (44%)	27 (39%)
IV	0 (0%)	6 (8%)	12 (8%)	0 (0%)
Bosentan use	37 (59%)	41 (55%)	77 (51%)	37 (54%)

Values are mean ± SD or as n (%). \*Reported at PHIRST-2 baseline.

ASD = pulmonary arterial hypertension associated with atrial septal defect; Corr-CHD = pulmonary arterial hypertension associated with corrective surgical repair of congenital heart disease ≥1 year before study enrollment; CTD = pulmonary arterial hypertension associated with connective tissue disease; PHIRST = Pulmonary Arterial Hypertension and Response to Tadalafil; 6MWD = 6-min walk distance; T40 mg = tadalafil 40 mg; T20 mg = tadalafil 20 mg; T2.5–20 mg = tadalafil 2.5 to 20 mg; WHO-FC = World Health Organization functional class.

Patients and investigators remained blinded to tadalafil doses; dose changes were not allowed in PHIRST-2.

The protocol was approved by local institutional review boards or independent ethics committees, and written informed consent (or assent when appropriate) was obtained from all patients.

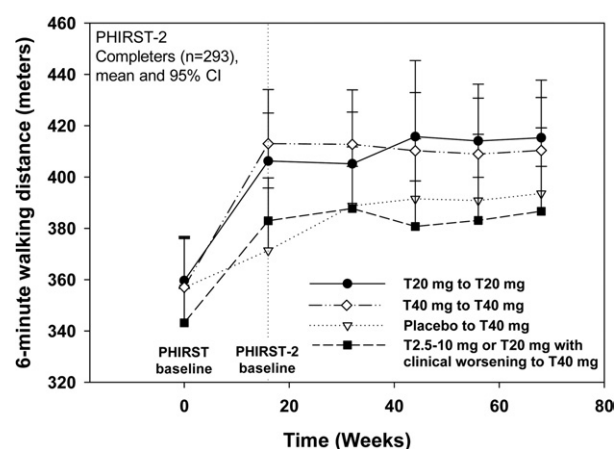
**Outcome measures.** Safety was evaluated in PHIRST-2 using adverse events (AEs), physical examinations, electrocardiograms, and clinical laboratory data. Treatment-emergent AEs were defined as events that first occurred or worsened in intensity after baseline (the run-in period before randomization in the 16-week PHIRST study).

Durability of efficacy was assessed by 6MWD tests across PHIRST and PHIRST-2 for all patients entering PHIRST-2 (n = 357). World Health Organization functional class (WHO-FC) and clinical worsening were reported only for patients who entered PHIRST-2 and received T20 mg or T40 mg in PHIRST (n = 161; lower doses were subtherapeutic in PHIRST and not used in PHIRST-2). Clinical worsening events were determined by the local investigator (not adjudicated).

**Statistical analysis.** Continuous variables are presented as mean ± SD and as numbers of observations. Categorical variables are summarized as counts and percents. Data for 6MWD were summarized using descriptive statistics and 95% confidence intervals (on the basis of *t* distribution).

Patients randomized to T20 mg or T40 mg in PHIRST were included in post hoc subgroup analyses; variables included change in WHO-FC and clinical worsening from PHIRST baseline to last observation in PHIRST or PHIRST-2. Clinical worsening over time and survival were

analyzed using Kaplan-Meier analysis. Clinical worsening was defined as death, lung or heart-lung transplantation, atrial septostomy, receiving any new long-term treatment for PAH, WHO-FC worsening, or hospitalization for



**Figure 2** 6-Min Walk Distance for Patients Who Completed PHIRST-2 (n = 293)

Data are presented for PHIRST (16 weeks) and PHIRST-2 (52 weeks). T20 mg to T20 mg: patients who received tadalafil 20 mg in both studies (n = 52). Placebo to T40 mg: patients who received placebo in PHIRST and switched to tadalafil 40 mg in PHIRST-2 (n = 62). T2.5–10 mg or T20 mg with clinical worsening to T40 mg: patients who previously received tadalafil 2.5 mg, tadalafil 10 mg, or T20 mg (with clinical worsening) in PHIRST and switched to T40 mg in PHIRST-2 (n = 120). T40 mg to T40 mg: patients who received T40 mg in PHIRST and continued to receive T40 mg in PHIRST-2 (n = 59). CI = confidence interval.

Table 2

**WHO-FC at PHIRST Baseline and at PHIRST-2 Endpoint Across Both PHIRST and the 52-Week PHIRST-2 Study (n = 161) for All Patients Who Received T20 mg (n = 82) or T40 mg (n = 79) in PHIRST**

	WHO-FC	T20 mg (n = 82)	T40 mg (n = 79)
Baseline at PHIRST	I	0 (0%)	2 (3%)
	II	28 (34%)	26 (33%)
	III	54 (66%)	51 (65%)
End point at PHIRST-2 (LOCF)	Missing	2 (2%)	0 (0%)
	I	6 (7%)	7 (9%)
	II	43 (52%)	43 (54%)
	III	28 (34%)	26 (33%)
	IV	3 (4%)	3 (4%)
Change from baseline to week 68	Missing	2 (2%)	0 (0%)
	Worsen	7 (9%)	5 (6%)
	No change	45 (55%)	47 (59%)
	Improved	28 (34%)	27 (34%)

LOCF = last observation carried forward; other abbreviations as in Table 1.

worsening PAH. Time to clinical worsening was defined as the first day of randomization in PHIRST to the first occurrence of any clinical worsening event in PHIRST or PHIRST-2. Patients were discontinued from the study if they died, underwent lung or heart-lung transplantation, or started new long-term PAH drugs. Patients were censored at study completion for any reason other than clinical worsening. Cox proportional hazards models were performed to identify factors associated with time to clinical

worsening events. Univariate and multivariate analysis for baseline (PHIRST) and post-baseline variables were performed; variables were preselected on the basis of clinical relevance, and analysis methods were specified before programming began.

## Results

Of 405 patients treated in PHIRST, the 341 patients who completed 16 weeks and the 23 patients who discontinued because of clinical worsening were eligible to enter PHIRST-2 (4). Of these, 7 declined to enter the extension (4); thus, 357 patients (88%) entered PHIRST-2 (Fig. 1). Of patients receiving T20 mg (n = 82) and T40 mg (n = 79) in PHIRST, 63 and 69 entered PHIRST-2, and 52 and 59 completed PHIRST-2, respectively.

**Baseline patient characteristics.** Table 1 summarizes baseline demographics for the PHIRST-2 subjects, using data obtained at the end of the PHIRST for 6MWD and WHO-FC baseline. Patients on T20 mg or T40 mg at the end of PHIRST had higher 6MWDs and lower WHO-FCs than those on lower doses or placebo (4). Baseline demographic characteristics from the PHIRST screening visit were used for PHIRST-2 demographics.

**6-min walk distance.** For the 111 patients completing PHIRST-2, improvements in 6MWD observed at the end of PHIRST appeared to be maintained at week 52 of PHIRST-2 (total 68 weeks) (Fig. 2). In contrast, patients

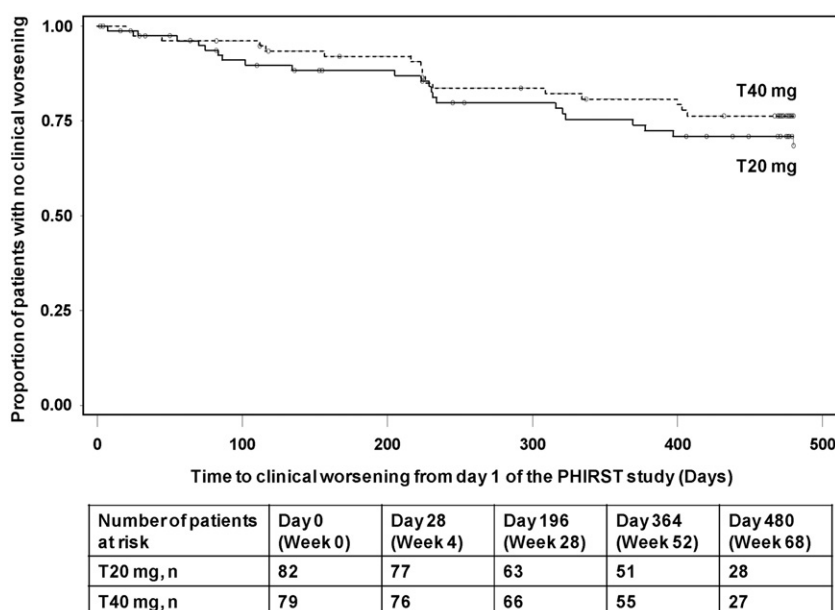


Figure 3 Time to Clinical Worsening

Kaplan-Meier estimates across PHIRST and PHIRST-2 (n = 161) for all patients who received tadalafil 20 mg (T20 mg) (n = 82) or tadalafil 40 mg (T40 mg) (n = 79) in PHIRST. Deterioration of World Health Organization functional class was the most frequent cause of clinical worsening. Factors significantly associated with time to clinical worsening (univariate analysis) were pulmonary arterial hypertension duration, baseline 6-min walk distance, bosentan use, and duration of bosentan use at PHIRST baseline.



previously receiving lower doses of tadalafil or placebo in PHIRST did not improve to similar levels in PHIRST.

**WHO-FC.** After 68 weeks, for all patients who received T20 mg or T40 mg in PHIRST, 9% and 6% had worsened WHO-FCs, respectively, while 34% (for both doses) had improved WHO-FCs compared with PHIRST baseline (Table 2).

**Clinical worsening.** Across both studies, the incidence of clinical worsening at week 68 for all patients who received T20 mg or T40 mg in PHIRST was 27% and 22%, respectively (Fig. 3), with deterioration of WHO-FC the most frequent cause. Univariate analysis identified PAH duration (before PHIRST enrollment), baseline 6MWD, bosentan use, and duration of bosentan use at PHIRST baseline as factors that were significantly associated with time to clinical worsening across both studies (Table 3).

Multivariate analysis identified race, PAH etiology, duration of bosentan use, age, baseline WHO-FC, and 6MWD at PHIRST baseline as risk factors for clinical worsening (Table 3). Patients with connective tissue disease–associated PAH had 35% clinical worsening at week 68, compared with 24% of patients with idiopathic PAH or familial PAH and 8% of patients with other etiologies. Of patients receiving bosentan, 18% had clinical worsening at week 68 throughout both PHIRST and PHIRST-2, compared with 31% of those not receiving bosentan. Of patients in PHIRST-2 with baseline 6MWDs  $\leq 359$  m (the median PHIRST baseline 6MWD), 35% had clinical worsening at week 68, compared with 14% with baseline 6MWDs  $> 359$  m.

**Safety.** Of the 357 patients who entered and received study treatment in PHIRST-2, 92% experienced at least 1 treatment-emergent AE by the end of PHIRST-2; 49% of events were classified by the investigator as possibly related to the study drug. The most common AE was headache (Table 4), occurring in 14% to 16% of patients receiving T20 mg or T40 mg, which was lower than the 32% to 42% rate seen in PHIRST. Most AEs were mild to moderate in intensity and did not result in study discontinuation.

Thirty patients (8%) discontinued because of treatment-emergent AEs, and 91 patients (25.5%) had serious AEs (including 11 deaths). The majority of serious events were due to PAH-related conditions.

**Deaths and survival.** Three deaths occurred in PHIRST and 11 in PHIRST-2. Overall survival for all 405 patients treated in PHIRST was 97% at week 68. Assuming that all discontinued patients ( $n = 112$ ) had died (worst case), overall survival was 72%.

Across PHIRST and PHIRST-2, 3 deaths occurred among the 82 patients randomized to T20 mg in PHIRST (including 7 with clinical worsening on T20 mg who received T40 mg in PHIRST-2). Two deaths occurred among the 79 patients randomized to T40 mg. Kaplan-Meier survival estimates at 68 weeks for the T20 mg and T40 mg doses were 95% (95% confidence interval: 86% to 99%) and 97% (95% confidence interval: 89% to 99%), respectively (Fig. 4). Assuming that all discontinued patients died, survival was 66% and 75%, respectively.

Table 3

Univariate and Multivariate Analyses for Baseline and Post-Baseline Factors Associated With Time to Clinical Worsening Across PHIRST and PHIRST-2 ( $n = 161$ )

Variable	Hazard Ratio	p Value
Univariate analysis		
Baseline variables		
Age (yrs)	1.014	0.1734
PAH duration (yrs)	0.908	0.0488
Baseline weight (kg)	1.013	0.0937
Baseline 6MWD (m)	0.992	$<0.0001$
Baseline 6MWD ( $>$ median vs. $\leq$ median as reference)	0.331	0.0014
Duration of bosentan used (yrs)	0.657	0.0106
Bosentan use (yes vs. no as reference)	0.530	0.0491
WHO-FC (III or IV vs. I or II as reference)	1.121	0.7354
Sex (female vs. male as reference)	0.648	0.1995
PAH etiology		0.0513
Idiopathic	Reference	Reference
Connective tissue disease vs. idiopathic	1.656	0.1412
Other causes vs. idiopathic	0.290	0.0923
Race		0.3120
W/AI/AN	Reference	Reference
A vs. W/AI/AN	0.219	0.1348
B/NH/PI vs. W/AI/AN	0.799	0.7117
Post-baseline variables		
Dose (continuous)	0.986	0.3635
Dose (T40 mg vs. T20 mg)	0.751	0.3635
End point of 6MWD	0.991	$<0.0001$
Change from baseline to end point in 6MWD	0.993	0.0024
6MWD (time-dependent variable)	0.993	$<0.0001$
Change from baseline in 6MWD (time-dependent variable)	0.997	0.0712
Multivariate analysis		
All baseline and post-baseline variables		
Race		
W/AI or AN	Reference	Reference
A vs. W/AI/AN	0.137	0.0496
B/NH/PI vs. W/AI/AN	0.650	0.2379
PAH etiology		
Idiopathic	Reference	Reference
Connective tissue disease vs. idiopathic	2.102	0.0004
Other causes vs. idiopathic	0.512	0.0766
Duration of bosentan used (yrs)	0.709	0.0002
Age (yrs)	0.981	0.0060
WHO-FC (III or IV vs. I or II as reference)	0.597	0.0108
6MWD (time-dependent variable)	0.993	$<0.0001$

A = Asian; AI = American Indian; AN = Alaska Native; B = Black or African American; NH = Native Hawaiian; PAH = pulmonary arterial hypertension; PI = Pacific Islander; W = white; other abbreviations as in Table 1.

## Discussion

The 52-week PHIRST-2 study is the first to assess long-term safety and explore long-term efficacy of tadalafil in PAH; it is also the only study to evaluate the long-term safety and efficacy of a PDE-5 inhibitor at its approved dose (5). The long-term extension study of the only other PDE-5 inhibitor approved for PAH (sildenafil) evaluated a dose 4-fold higher than the approved dose (6).

**Table 4** Most Frequent TEAEs Occurring in >10% of Patients Who Entered PHIRST-2

TEAE	T20 mg: T20 mg (n = 63)	Placebo: T40 mg (n = 75)	T2.5–20 mg: T40 mg (n = 150)	T40 mg: T40 mg (n = 69)	Total (n = 357)
Headache	9 (14%)	21 (28%)	38 (25%)	11 (16%)	79 (22%)
Diarrhea	7 (11%)	7 (9%)	21 (14%)	11 (16%)	46 (13%)
Back pain	3 (5%)	12 (16%)	19 (13%)	7 (10%)	41 (12%)
Peripheral edema	6 (10%)	7 (9%)	22 (15%)	6 (9%)	41 (12%)
Upper respiratory tract infection	7 (11%)	9 (12%)	15 (10%)	10 (15%)	41 (12%)
Dizziness	4 (6%)	9 (12%)	24 (16%)	3 (4%)	40 (11%)
Palpitations	5 (8%)	5 (7%)	21 (14%)	7 (10%)	38 (11%)
Nasopharyngitis	5 (8%)	10 (13%)	13 (9%)	9 (13%)	37 (10%)
Dyspnea	5 (8%)	6 (8%)	15 (10%)	10 (15%)	36 (10%)

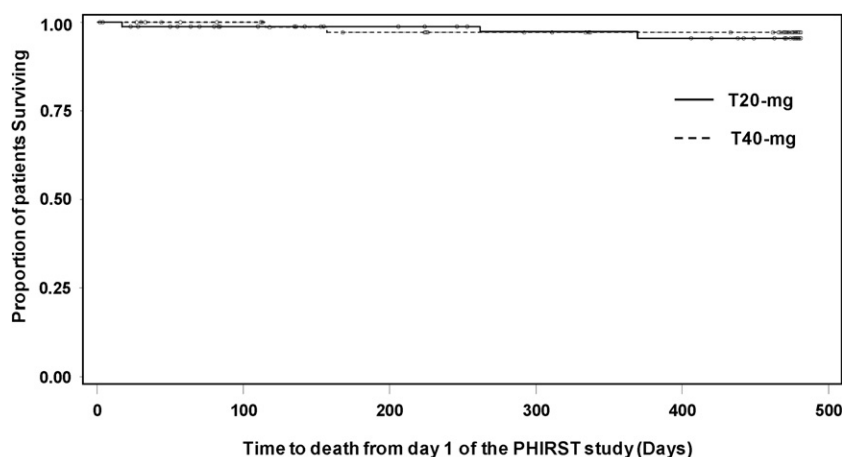
TEAE = treatment-emergent adverse event; other abbreviations as in Table 1.

In the 16-week PHIRST trial, only T40 mg, the approved PAH dose, significantly improved exercise capacity, clinical worsening, and quality of life (4). We now demonstrate that this dose was generally well tolerated through up to 68 weeks of dosing, with a safety profile similar to that previously described through 16 weeks (4). Although caution must be exercised in interpreting AE rates because of the absence of a placebo control, the lower incidence of headache in PHIRST-2 compared with PHIRST among patients continuing tadalafil suggests that headache associated with tadalafil waned over time (Table 4).

Important and unique to this study, post hoc univariate and multivariate analyses found that PHIRST baseline PAH duration and etiology, 6MWD, bosentan use and duration of use, race, age, and WHO-FC were risk factors for clinical wors-

ening. These observations are critical in interpreting the findings from this and other trials and call for a need to reevaluate trial design when add-on therapy is being assessed (7,8).

Two additional characteristics in this study were unique. First, unlike other long-term studies, the addition of PAH-specific therapy other than bosentan was not permitted in PHIRST-2 (54% of patients in PHIRST-2 were receiving background bosentan at PHIRST enrollment). Despite this, the 161 patients on T20 mg and T40 mg in PHIRST-2 had estimated survival of 95% and 97%, respectively, which is comparable with estimates from other long-term studies in which additional PAH drugs were allowed (9–12). These results must be exercised with caution, because survival status was not available for patients who discontinued PHIRST or PHIRST-2 for other reasons (n = 22).



Number of patients at risk	Day 0 (Week 0)	Day 28 (Week 4)	Day 196 (Week 28)	Day 364 (Week 52)	Day 480 (Week 68)
T20 mg, n	82	78	65	58	30
T40 mg, n	79	77	66	60	31

**Figure 4** Survival Across Both PHIRST and PHIRST-2 (N = 161) for All Patients Who Received T20-mg (n = 82) or T40-mg (n = 79) in PHIRST

Kaplan-Meier estimated survival across both PHIRST and PHIRST-2 (n = 161) for all patients who received tadalafil 20 mg (T20-mg) (n = 82) or tadalafil 40 mg (T40-mg) (n = 79) in PHIRST. Of the 161 patients who received either T20-mg or T40-mg in PHIRST, 5 patients died across both PHIRST and PHIRST-2. Survival estimates at 68 weeks were 95% for T20-mg and 97% for T40-mg.

Second, patients who were initially randomized to placebo, tadalafil 2.5 mg, or tadalafil 10 mg (or T20 mg with clinical worsening) in PHIRST had lower 6MWDs throughout PHIRST-2 than patients taking randomized T20 mg or T40 mg, consistent with the hypothesis that a delay in the initiation of an effective drug or dose may result in less long-term efficacy.

**Study limitations.** Without a placebo control, these results should be interpreted with caution. Nevertheless, the long-term efficacy data suggest an acceptable safety profile for tadalafil at these doses. Also, given the progressive nature of PAH, the fact that 6MWDs remained improved in PHIRST-2 compared to PHIRST baseline suggests that tadalafil provided long-term maintenance of exercise capacity.

Not all eligible patients entered this extension study. Patients who received T40 mg in PHIRST and had clinical worsening were not allowed to enter PHIRST-2. Furthermore, survival outcome data were not available for patients who prematurely discontinued PHIRST or PHIRST-2. Finally, extrapolation of trial results to community practice should be undertaken with caution.

## Conclusions

These data demonstrate that the long-term safety profile of tadalafil appears similar to that in the 16-week PHIRST study and that treatment for up to 68 weeks appears safe and well tolerated. For patients receiving T20 mg and T40 mg, the short-term improvements in exercise capacity observed in PHIRST appeared to be maintained for an additional 52 weeks in PHIRST-2.

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**Key Words:** PDE-5 ■ pulmonary arterial hypertension ■ tadalafil.

## APPENDIX

For a supplemental figure, please see the online version of this article.