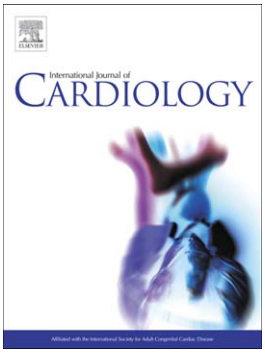

Tadalafil in Idiopathic or Heritable Pulmonary Arterial Hypertension (PAH) Compared to PAH Associated with Connective Tissue Disease

Nazzareno Galiè, Christopher P. Denton, Fabio Dardi, Alessandra Manes, Gaia Mazzanti, Baohui Li, Lucio Varanese, Anne Esler, Cathi Harmon, Massimiliano Palazzini

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Authors: Nazzareno Galiè[1], Christopher P. Denton[2], Fabio Dardi[3], Alessandra Manes[4], Gaia Mazzanti[5], Baohui Li[6], Lucio Varanese[7], Anne Esler[8], Cathi Harmon[9], Massimiliano Palazzini[10]

Corresponding Author:

Professor Nazzareno Galiè,

Department of Experimental, Diagnostic and Specialty Medicine (DIMES),

University of Bologna, via Massarenti 9,

40138-Bologna, Italy

Tel: +39 051 349 858

Fax: +39 051 344 859

Email: nazzareno.galie@unibo.it

Affiliations and Authorship

[1]Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. During the conduct of the study, Dr. Galiè reports grants and personal fees from Eli Lilly and Company, grants and personal fees from Actelion, grants and personal fees from GSK, grants and personal fees from Bayer, grants and personal fees from Pfizer.

[2]Centre for Rheumatology at the Royal Free and University College Medical School, Hampstead, London. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Outside the submitted work, Dr. Denton reports personal fees from Actelion Pharmaceuticals, personal fees from GSK, grants from Actelion Pharmaceuticals, personal fees from Bayer.

[3]Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Dr. Dardi has nothing to disclose.

[4]Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Dr. Manes has nothing to disclose.

[5]Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Dr. Mazzanti has nothing to disclose.

[6]Eli Lilly and Company, Indianapolis, IN, USA. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Dr. Li has nothing to disclose.

[7]Eli Lilly and Company, Indianapolis, IN, USA. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Dr. Varanese has nothing to disclose.

[8]inVentiv Clinical Solutions, LLC, Indianapolis, IN, USA. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Dr. Esler has nothing to disclose.

[9]Eli Lilly and Company, Indianapolis, IN, USA. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Mrs. Harmon has nothing to disclose.

[10]Department of Experimental, Diagnostic and Specialty Medicine (DIMES), University of Bologna, Bologna, Italy. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. Dr. Palazzini has nothing to disclose.

Keywords: Associated PAH, PHIRST, PHIRST-2, idiopathic, heritable

Abstract

Background

The primary objective of this post hoc analysis was to evaluate clinical outcomes of tadalafil in patients with pulmonary arterial hypertension (PAH) associated with connective tissue disease (CTD-PAH) compared with patients with idiopathic/heritable PAH (I/H-PAH) for primary and key secondary efficacy endpoints, and safety. This analysis included adult patients with CTD-PAH or I/H-PAH who participated in the PHIRST and PHIRST-2 studies.

Methods

Patients were randomized 1:1:1:1:1 to tadalafil (2.5, 10, 20, or 40 mg) or placebo in the PHIRST study and the majority of these patients were subsequently assigned 40 mg in PHIRST-2. Patients taking 20 mg in PHIRST without demonstrating clinical worsening continued on 20 mg in PHIRST-2. Outcomes analyzed included 6MWD, WHO-FC, and incidence and time to first occurrence of clinical worsening. Safety was assessed through evaluation of adverse events (AEs), clinical laboratory data, electrocardiograms, and physical examinations.

Results

Increased 6MWD in PHIRST was maintained in both CTD-PAH and I/H-PAH subgroups for 52 weeks. Patients with CTD-PAH tended to be older, were more likely female, had lower exercise capacity, were more likely to have clinical worsening, and experienced AEs more frequently than patients with I/H-PAH.

Conclusion

The effect of tadalafil treatment in patients enrolled in both PHIRST studies was detectable for both I/H-PAH and CTD-PAH subgroups. In general, subgroup differences were modest. Patients with CTD-PAH may perform less well than patients with I/H-PAH in safety and efficacy measures in all treatment groups, which is similar to other studies demonstrating a worse prognosis for patients with CTD-PAH.

1. Introduction

Pulmonary arterial hypertension (PAH) is a severe and chronic disease characterized by a progressive obstructive remodeling of the distal pulmonary arteries which results in increased pulmonary vascular resistance and pressure. PAH includes a heterogeneous group of clinical entities: idiopathic PAH (IPAH), heritable PAH (HPAH), drug and toxin induced PAH, and PAH associated with other conditions such as, connective tissue disease (CTD-PAH) [1].

When considering the entire adult PAH population, it has been estimated that up to 30% suffer from CTD-PAH [2], the second largest patient subgroup after IPAH. Patients with CTD-PAH have been included in many of the randomized controlled trials and adequately represent the subgroup as it occurs in the general PAH population. Previous studies suggest that CTD-PAH patients have a worse prognosis than other PAH subgroups and that patients with PAH associated with the scleroderma spectrum of diseases have a particularly poor outcome [3].

The **P**ulmonary Arterial **H**ypertens**I**on and **R**e**S**ponse to **T**adalafil (PHIRST) study was a 16-week, double-blind, placebo-controlled study evaluating 4 doses of tadalafil (an oral, once-daily phosphodiesterase [PDE]-5 inhibitor) [4]. Significant improvement as compared with placebo (PBO) was seen in the highest dose studied (40 mg), for six-minute walk distance (6MWD), time to clinical worsening (TTCW) and quality of life [4]. The approved dose of tadalafil for PAH treatment in adults is 40 mg [4]. After participating in the PHIRST trial,

eligible patients were enrolled in a 52-week, double-blind, multicenter, long-term prospective extension study (PHIRST-2) and received either tadalafil 20 mg (T20) or 40 mg (T40) [5]. The increased 6MWD observed in both T20 and T40 groups in PHIRST was also maintained during PHIRST-2 [5].

This study reports the result of a post hoc analysis of PHIRST and PHIRST-2 data in order to evaluate the effect of tadalafil treatment in the subset of patients with CTD-PAH as compared to the subset of patients with idiopathic/heritable PAH (I/H PAH).

2. Methods

2.1 Patients

Patient eligibility for the PHIRST and PHIRST-2 studies has been previously reported [4,5]. This post hoc analysis includes the subset of patients with CTD-PAH or I/H PAH who were randomized in the PHIRST study and transitioned to the PHIRST-2 extension study [5].

Both PHIRST study protocols were approved by local institutional review boards or independent ethics committees, and written informed consent (or assent when appropriate) was obtained from all patients. The PHIRST and PHIRST-2 studies were conducted in full compliance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation guidelines, or with the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the study subject.

The primary objective of this post hoc analysis was to evaluate some of the efficacy and safety endpoints of tadalafil in patients with CTD-PAH as compared with patients with I/H PAH. The detailed designs of both PHIRST and PHIRST-2 studies have previously been reported [4,5].

In the PHIRST study, patients with PAH were randomized 1:1:1:1:1 to tadalafil 2.5 mg (T2.5), tadalafil 10 mg (T10), tadalafil 20 mg (T20), tadalafil 40 mg (T40), or PBO for 16 weeks [4]. Thereafter, eligible patients from PHIRST were enrolled in PHIRST-2 and assigned to continue T20 or to receive T40 for 52 weeks. Patients who received tadalafil T20 in PHIRST without clinical worsening (CW) continued to receive T20 (T20/T20), patients who received T40 in PHIRST continued on T40 (T40/T40), and patients who previously received tadalafil T2.5, T10, or T20 (with CW) in PHIRST switched to T40 (T2.5-T20/T40). This analysis for the PHIRST study includes patients receiving PBO, T20, and T40; analysis for the PHIRST-2 study includes data for all patients who entered PHIRST-2.

Of note, patients were able to enter PHIRST while on background bosentan (125 mg twice daily) and continue on bosentan during PHIRST-2. Patients were discontinued from both studies if they began a new PAH-specific therapy such as prostanoids, other PDE-5 inhibitors and/or an endothelin receptor antagonist (ERA) [4,5].

2.2 Statistical methods

The PHIRST and PHIRST-2 studies were not powered to examine efficacy or safety differences within subgroups. Therefore, reported differences are descriptive and should be regarded as exploratory.

Within the etiology subgroups of I/H PAH and CTD-PAH, summaries are presented for patients randomized to PBO, T20 or T40 in PHIRST and all patients who continued in PHIRST-2.

The PHIRST baseline was defined as the pre-randomization period. PHIRST-2 baseline for 6MWD and World Health Organization Functional Class (WHO-FC) was determined using data obtained from the end of PHIRST. Other PHIRST-2 baseline demographics were established by the baseline demographic characteristics from the PHIRST screening visit.

Outcomes analyzed from the start of PHIRST through the end of PHIRST-2 included 6MWD, WHO-FC and incidence of, and time to first occurrence of CW. Continuous variables are presented as mean ± standard deviation (SD) and categorical variables are summarized as counts and percentages.

To examine changes in 6MWD over time, mean 6MWD at each visit in PHIRST and PHIRST-2 was plotted by treatment group within each etiology subgroup. The proportion of the relationship between TTCW in PHIRST or PHIRST-2 and etiology was examined using Cox proportional hazard models for those patients who received T20 or T40 in PHIRST. In addition, Kaplan-Meier

estimates of the proportion of patients experiencing CW and remaining at risk at each PHIRST-2 visit were displayed graphically.

Adverse events (AEs) reported in PHIRST-2 were summarized as the number and percentage in each treatment group reporting the specific category of event; baseline for the definition of treatment-emergent adverse events (TEAEs) was the run-in period prior to randomization in PHIRST.

2.3 Outcome measures

Durability of efficacy was assessed by measuring 6MWD. WHO-FC and CW events were collected in both studies. WHO-FC was determined by the local investigator. Clinical worsening events were reported by investigators as any occurrence of death, lung or heart-lung transplantation, atrial septostomy, the start of any new chronic treatment for PAH, worsening WHO-FC, or worsening PAH requiring hospitalization.

Safety was assessed for both studies through evaluation of AEs, clinical laboratory data, electrocardiograms, and physical examinations. Treatment-emergent adverse events were those events that first ensued or increased in intensity after baseline (the run-in period before randomization in the 16-week PHIRST study).

3. Results

While multiple tadalafil doses were studied in PHIRST, this subgroup analysis only includes data from patients with I/H-PAH (n=150) on PBO (n=54), T20 (n=50) and T40 (n=46), and patients with CTD-PAH (n=56) on PBO (n=16), T20 (n=21) and T40 (n=19).

In PHIRST-2, 4 treatment groups were analyzed for the I/H-PAH (n=223) and CTD-PAH (n=78) subgroups, respectively: T20/T20 (n=37, n=16), T40/T40 (n=43, n=13), T2.5-T20/T40 (n=94, n=34), and PBO/T40 (n=49, n=15).

3.1 Baseline Demographics

Baseline demographics of patients with CTD-PAH and I/H-PAH enrolled in the PHIRST and PHIRST-2 studies are reported in Table 1. Patients with CTD-PAH were more likely to be female, and had a mean age that was slightly higher than patients with I/H-PAH in all treatment groups summarized.

Table 1: Baseline Demographic, Clinical and Exercise Characteristics, and Percent of Bosentan use in I/H-PAH and CTD-PAH Patients Enrolled in the PHIRST and PHIRST-2 Studies.

Characteristic	PHIRST (baseline)[a]						PHIRST-2 (baseline)							
	I/H-PAH (N=150)			CTD-PAH (N=56)			I/H-PAH (N=223)				CTD-PAH (N=78)			
	PBO (n=54)	T20 (n=50)	T40 (n=46)	PBO (n=16)	T20 (n=21)	T40 (n=19)	T20/T20 (n=37)	PBO/T40 (n=49)	T2.5-T20/T40 (n=94)	T40/T40 (n=43)	T20/T20 (n=16)	PBO/T40 (n-15)	T2.5-T20/T40 (n=34)	T40/T40 (n=13)
Age (years), mean (SD)	57 (15)	54 (15)	54 (15)	59 (13)	55 (15)	56 (14)	55 (15)	56 (15)	55 (16)	53 (15)	55 (13)	60 (14)	58 (13)	61 (14)
Sex, n (% female)	40 (74)	36 (72)	30 (65)	15 (94)	18 (86)	16 (84)	28 (76)	37 (76)	68 (72)	29 (67)	13 (81)	14 (93)	32 (94)	11 (85)
6MWD (meters), mean (SD)	337 (87)	346 (73)	362 (79)	347 (79)	317 (85)	327 (79)	405 (73)	370 (98)[b]	377 (91)[c]	408 (77)	375 (73)	321 (110)	333 (99)	380 (108)
WHO-FC, n (%):														
Class I	0	0	1(2)	0	0	1 (5)	2 (5)	1 (2)	3 (3)	2 (5)	2 (12)	0	2 (6)	1 (8)
Class II	17 (31)	13 (26)	16 (35)	5 (31)	9 (43)	5 (26)	24 (65)	24 (49)	45 (48)	24 (56)	11 (69)	5 (33)	8 (24)	6 (46)
Class III	35 (65)	37 (74)	29 (63)	11 (69)	12 (57)	13 (68)	11(30)	21 (43)	37 (39)	17 (40)	3 (19)	7 (47)	21 (62)	6 (46)
Class IV	2 (4)	0	0	0	0	0	0	3 (6)	9 (10)	0	0	3 (20)	3 (9)[d]	0
Bosentan use, n (% yes)	31 (57)	25 (50)	22 (48)	8 (50)	12 (57)	11 (58)	21 (57)	29 (59)	43 (46)	21 (49)	9 (56)	7 (47)	23 (68)	8 (62)

Abbreviations: I/H-PAH - idiopathic/heritable pulmonary arterial hypertension; CTD-PAH - pulmonary arterial hypertension associated with connective tissue disease; N - total number of patients included in analysis; n - total number of patients in each treatment arm analyzed

6MWD - 6 minute walk distance; T20/T20 - tadalafil 20 mg in PHIRST and PHIRST-2; PBO/T40 - placebo in PHIRST, tadalafil 40 mg in PHIRST-2; T2.5-20/T40 - tadalafil 2.5 mg to 20 mg in PHIRST, tadalafil 40 mg in PHIRST-2;T40/T40 - tadalafil 40 mg in PHIRST and PHIRST-2; SD - standard deviation; WHO-FC - World Health Organization Functional Class

[a]2.5 and 10 mg data not shown; [b]2 patients missing baseline value; [c]4 patients missing baseline value; [d]Numbers do not add up to 100 due to rounding

3.2 Exercise Characteristics (6MWD)

Consistent with the overall efficacy results previously reported for PHIRST [4], the greatest increases in 6MWD from baseline during PHIRST were seen in the T20 and T40 treatment arms in both the CTD-PAH and I/H-PAH subgroups. In the PBO group there was no improvement in 6MWD in patients with CTD-PAH, while patients with I/H-PAH showed modest improvement (Figure 1).

The increase seen in 6MWD at the end of PHIRST was maintained in both the CTD-PAH and I/H-PAH subgroups for 52 weeks. While improvements in 6MWD were seen in both subgroups, patients receiving PBO or lower doses of tadalafil in PHIRST and switched to T40 in PHIRST-2 had lower 6MWD at the end of PHIRST-2 than those patients who started and stayed on T20 or T40 throughout both studies (Figure 1).

3.3 WHO-FC

In the PHIRST study, a higher percentage of patients with CTD-PAH worsened in WHO-FC status than patients with I/H-PAH in the PBO, T20 and T40 treatment arms (Table 2).

For patients who were on T40 in both PHIRST and PHIRST-2, 7% with I/H-PAH and 15% with CTD-PAH had worsened WHO-FC. Improved WHO-FC was seen in 10% of those patients with I/H-PAH and 15% with CTD-PAH (Table 2).

For both etiologies, there were numerically higher proportions of patients with worsened WHO-FC in the T20 group than the T40 group in the PHIRST study and in the T20/20 group than the T40/40 group in PHIRST-2 (Table 2).

Table 2: Change in WHO-FC by Treatment Group and Etiology for PHIRST and PHIRST-2 Studies

Condition	Change from baseline to Week 16 (PHIRST)						Change from baseline to endpoint (PHIRST-2)							
	I/H PAH (N=150)			CTD-PAH (N=56)			I/H PAH (N=223[a])				CTD-PAH (N=78[b])			
	PBO n=53	T20 n=50	T40 n=46	PBO n=16	T20 n=19	T40 n=18	T20/T20 n=37	PBO/T40 n=48	T2.5-T20/T40 n=90	T40/T40 n=41	T20/T20 n=15	PBO/T40 n=14	T2.5-T20/T40 n=34	T40/T40 n=13
Worsened, n (%)	5 (9)	4 (8)	1 (2)	4 (25)	2 (11)	1 (6)	8 (22)	2 (4)	8 (9)	3 (7)	3 (20)	2 (14)	2 (6)	2 (15)
No change, n (%)	35 (66)	28 (56)	35 (76)	10 (62)	9 (47)	13 (72)	23 (62)	36 (75)	64 (71)	34 (83)	12 (80)	10 (71)	26 (77)	9 (69)
Improved, n (%)	13 (25)	18 (36)	10 (22)	2(12)[c]	8 (42)	4 (22)	6 (16)	10 (21)	18 (20)	4 (10)	0 (0)	2 (14)	6 (18)	2 (15)

Abbreviations: I/H-PAH - idiopathic/heritable pulmonary arterial hypertension; CTD-PAH - pulmonary arterial hypertension associated with connective tissue disease; N - total number of patients included in analysis; n - total number of patients in each treatment arm analyzed

[a]Data was only available for 216 patients at endpoint; [b]Data was only available for 76 patients at endpoint; [c]Please note the percentages do not add up to 100% due to rounding.

3.4 Clinical Worsening

Kaplan-Meier estimates of the proportion of patients experiencing CW at Week 16 of the PHIRST study demonstrated that CTD-PAH patients were more likely to experience CW (T40: n=2, 11%; PBO: n=4, 25%) compared to I/H-PAH patients (T40: n=2, 4%; PBO: n=8, 15%) (Figure 2).

In the 52-week PHIRST-2 study, 33% of patients with CTD-PAH and 14% of patients with I/H-PAH who had moved from PBO to T40 had experienced CW by Week 52. For patients who remained on T40, 46% of those with CTD-PAH had CW compared with 14% of those with I/H-PAH (data on file).

Combined data for patients with I/H-PAH taking T20 and T40 revealed a lower incidence of CW and a longer time to first event of CW than patients with CTD-PAH over 68 weeks (PHIRST and PHIRST-2 studies). The Kaplan-Meier

analyses of time to first event of CW in patients with I/H-PAH and CTD-PAH in the 68-week period are reported in Figure 3.

3.5 Safety

While AEs had a similar profile between groups in PHIRST, patients with CTD-PAH tended to have a higher frequency of AEs than patients with I/H-PAH.

In the PHIRST-2 study, patients with CTD-PAH had a similar frequency of at least one TEAE than patients with I/H-PAH (94% and 92% respectively), with headache being the most indicated AE. In addition, patients with CTD-PAH had a numerically higher rate of serious AEs (SAEs) including death, than patients with I/H-PAH (40% and 22% respectively) (data on file).

TEAEs occurring in >15% of patients on tadalafil in PHIRST and PHIRST-2 are shown in Table 3 and Table 4 respectively.

Table 3: TEAEs Occurring in Greater than 15 Percent of Tadalafil Patients by Etiology in the 16-week PHIRST Study

	PHIRST					
Adverse Event Preferred Term, n (%)	I/H PAH			CTD-PAH		
	PBO N=54	T20 N=50	T40 N=46	PBO N=16	T20 N=21	T40 N=19
Headache	6 (11)	11 (22)	16 (35)	2 (12)	6 (29)	10 (53)
Diarrhea	6 (11)	3 (6)	4 (9)	1 (6)	3 (14)	5 (26)
Nausea	4 (7)	3 (6)	3 (6)	0	5 (24)	4 (21)
Back pain	3 (6)	4 (8)	6 (13)	2 (12)	5 (24)	2 (10)
Myalgia	0	4 (8)	6 (13)	3 (19)	1 (5)	4 (21)
Dizziness	2 (4)	2 (4)	2 (4)	4 (25)	2 (10)	4 (21)
Vomiting	1 (2)	1 (2)	0	0	4 (19)	2 (10)
Dyspepsia	1 (2)	8 (16)	6 (13)	0	1 (5)	1 (5)
Pulmonary hypertension	3 (6)	7 (14)	3 (6)	4 (25)	0	3 (16)
Edema – peripheral	3 (6)	4 (8)	2 (4)	4 (25)	2 (10)	3 (16)
Nasal congestion	0	0	4 (9)	1 (6)	0	3 (16)
Flushing	0	4 (8)	7 (15)	1 (6)	0	1 (5)

Abbreviations: I/H-PAH - Idiopathic/heritable pulmonary arterial hypertension; CTD-PAH - pulmonary arterial hypertension associated with connective tissue disease; PBO - placebo; N=total randomized patients in treatment group; n=number of patients with adverse event preferred term

Table 4: TEAEs Occurring in Greater than 15 Percent of Tadalafil Patients by Etiology in the 52-week PHIRST-2 Study

Adverse Event Preferred Term, n (%)	PHIRST-2							
	I/H PAH				CTD-PAH			
	T20/T20 N=37	PBO/T40 N=49	T2.5-20/T40 N=94	T40/T40 N=43	T20/T20 N=16	PBO/T40 N=15	T2.5-20/T40 N=34	T40/T40 N=13
Headache	4 (11)	16 (33)	23 (25)	6 (14)	2 (13)	3 (20)	10 (29)	2 (15)
Back pain	2 (5)	9 (18)	9 (10)	7 (16)	0	3 (20)	7 (21)	0
Nasopharyngitis	5 (14)	9 (18)	8 (9)	5 (12)	0	0	1 (3)	0
Dyspnea	3 (8)	4 (8)	10 (11)	8 (19)	1 (6)	1 (7)	3 (9)	1 (8)
Edema – peripheral	3 (8)	2 (4)	12 (13)	5 (12)	2 (13)	4 (27)	7 (21)	1 (8)
Upper respiratory tract infection	4 (11)	1 (2)	9 (10)	7 (16)	0	4 (27)	2 (6)	3 (23)
Fatigue	1 (3)	1 (2)	7 (7)	6 (14)	0	2 (13)	1 (3)	3 (23)
Cough	5 (14)	2 (4)	2 (2)	4 (9)	0	5 (33)	4 (12)	2 (15)

Abbreviations: I/H-PAH - Idiopathic/heritable pulmonary arterial hypertension; CTD-PAH - pulmonary arterial hypertension associated with connective tissue disease; PBO - placebo; N=total randomized patients in treatment group; n=number of patients with adverse event preferred term

4. Discussion

This is the first analysis to compare the effects of tadalafil in the 2 largest subgroups of PAH (I/H-PAH and CTD-PAH) in studies where approximately 50% of the patient population was on background therapy with bosentan.

Patients with CTD-PAH tended to be older, were more likely to be female, had a lower exercise capacity, were more likely to have CW, and experienced AEs more frequently than patients with I/H-PAH.

The treatment effect on 6MWD observed with tadalafil was similar among the CTD-PAH and I/H-PAH groups in the PHIRST study. This is in contrast with

the smaller effect observed in patients with CTD-PAH as compared with patients with I/H-PAH in other randomized controlled studies in PAH [6]. This apparently larger effect of tadalafil in CTD-PAH as compared to other studies should be confirmed by specific studies to exclude an effect due to spontaneous variability.

Both patients with CTD-PAH and I/H-PAH who were on PBO or on lower doses (T2.5 and T10) of tadalafil in PHIRST and then transitioned to T40 in PHIRST-2 did not improve as well as those who started and stayed on T20 or T40 throughout both studies. This may suggest that patients with CTD-PAH and I/H-PAH could benefit from efficacious therapy as early as possible in the clinical course.

In both subgroups, the increase in exercise capacity at the end of the 16-week PHIRST study was maintained for 52 weeks, but improved more in patients randomized initially to T20 or T40 as compared with those randomized to PBO, T2.5, T10 or T20 with a worsening event. This may confirm the need to start the effective dose of tadalafil as soon as possible because a delay may result in a lower effect on exercise capacity. However, the PHIRST baseline values of 6MWD in patients receiving PBO or lower doses of tadalafil in PHIRST appear to be lower and this may have influenced their final absolute value at the end of PHIRST-2.

In PHIRST and PHIRST-2 studies, numerically higher proportions of patients with CTD-PAH worsened in WHO-FC as compared to patients with I/H-

PAH. This is consistent with the higher rate of progression of PAH in patients with CTD.

In the PHIRST study, TTCW events were numerically higher in the PBO group as compared to the T40 group in both I/H-PAH and CTD-PAH groups. In the PHIRST-2 analysis, TTCW events were numerically higher in CTD-PAH than in I/H-PAH across all treatment groups, except T2.5-T20/T40. The lack of a PBO group in the PHIRST-2 study does not allow us to analyze the relative reduction of TTCW events, if any, in the I/H-PAH and CTD-PAH groups. Over 68 weeks, TTCW was more delayed in patients with I/H-PAH than in patients with CTD-PAH.

These data support the worse prognosis of patients with CTD-PAH as compared with I/H-PAH and as observed in registry data [7,8].

The reasons for these findings may include the older age of patients with CTD-PAH, the presence of comorbidities, and/or a lower efficacy of PAH-approved treatments on the outcome of patients with CTD-PAH as observed in other studies [9].

During long-term treatment, patients with CTD-PAH had a numerically higher rate of SAEs, including death, than patients with I/H-PAH. The TEAE profile was similar for both subgroups. These data confirm the worse general clinical profile of patients with CTD-PAH as compared to those with I/H-PAH.

4.1 Study Limitations

Overall, this subgroup analysis indicates long-term treatment with tadalafil was well tolerated in patients with I/H-PAH and CTD-PAH. All differences in the baseline demographics and treatment effects are described numerically and cannot be substantiated by a statistical test as the PHIRST and PHIRST-2 studies were insufficiently powered to examine efficacy or safety within subgroups. Some patients participating in the PHIRST study did not elect to continue in the long-term extension period, and patients on T40 with CW were not eligible to transition to PHIRST-2. In addition, some patients discontinued early from the studies and therefore survival results are not available for these patients. The missing data of these patients may have influenced the study results.

Data from the PHIRST-2 study should be interpreted with caution given the lack of a PBO control and a slightly higher percentage (60%) of CTD-PAH patients on background bosentan compared to I/H-PAH patients (51%).

5. Conclusion

In summary, the PHIRST study demonstrated that patients with I/H-PAH and CTD-PAH receiving 40 mg tadalafil experienced favorable results on exercise capacity. While subgroup differences overall were generally small in the PHIRST-2 study, patients with CTD-PAH tended to perform less well in clinical and safety measures in all treatment groups, consistent with a worse outcome for these patients. Since patients with CTD-PAH who transitioned from suboptimal doses in PHIRST to T40 in PHIRST-2 showed less improvement than those who remained on T20 and T40 during both trials, it suggests that earlier use of effective dosing is advantageous.

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Figures:

Figure 1

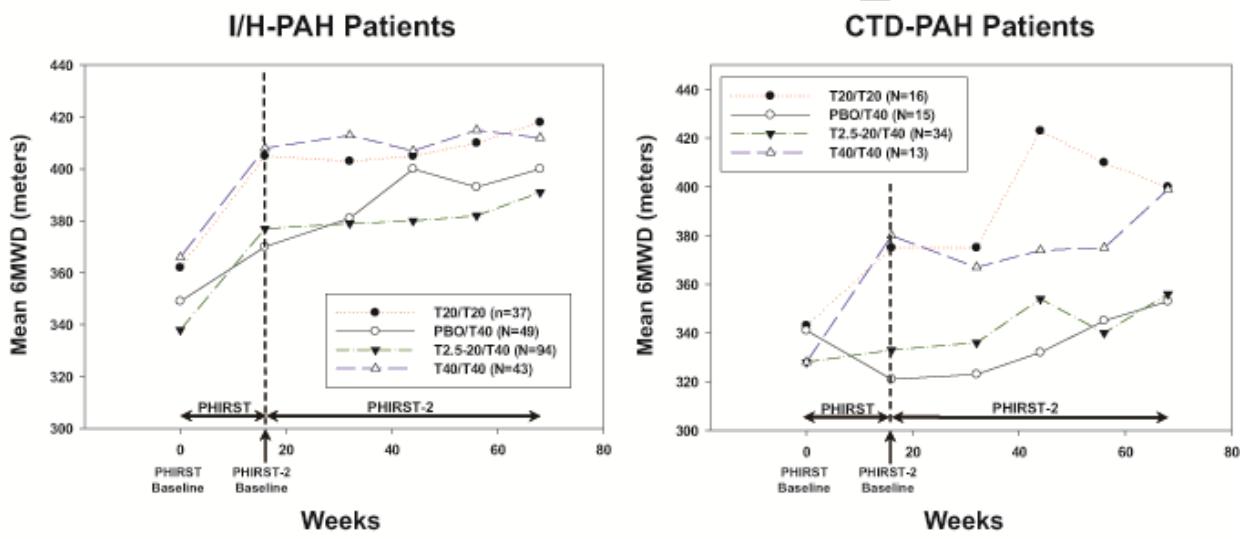
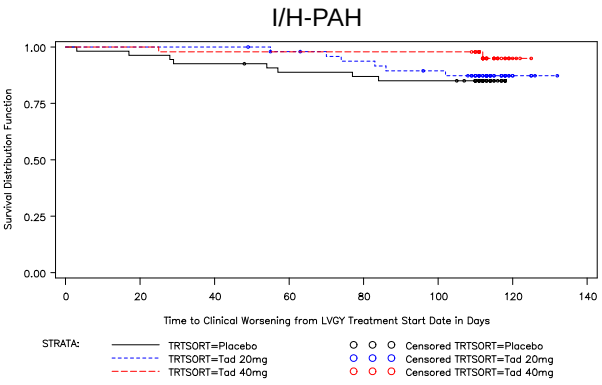
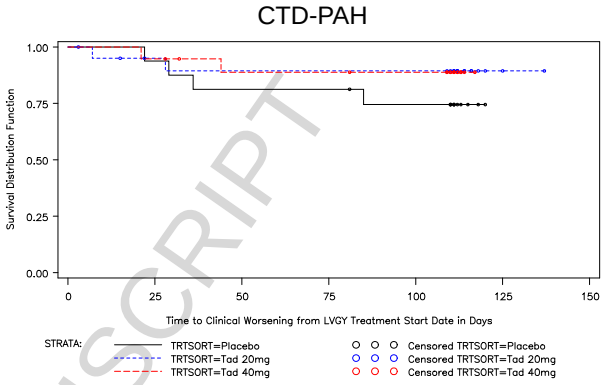


Figure 2

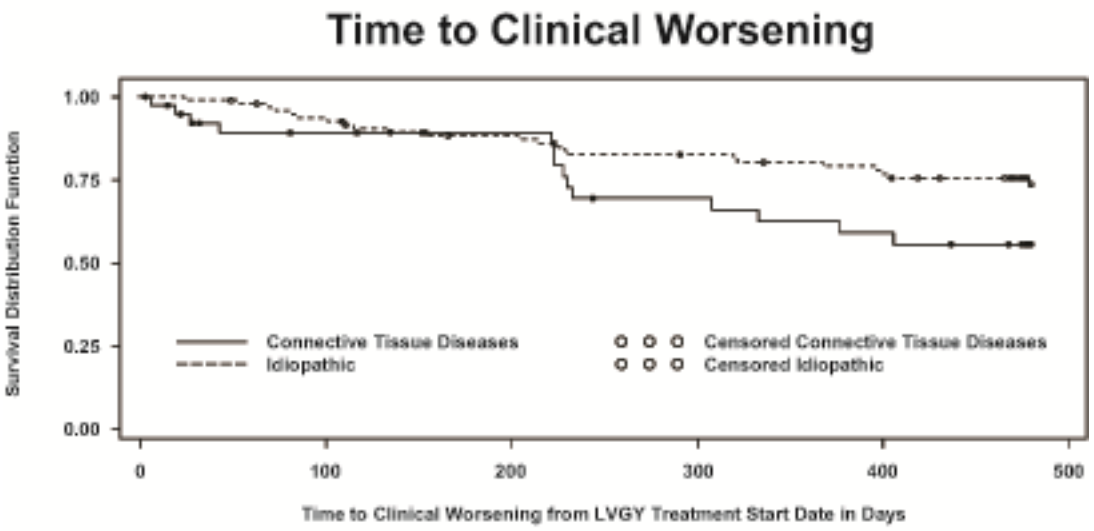




	Day 28 (4 weeks)		Day 56 (8 weeks)		Day 84 (12 weeks)		Day 112 (16 weeks)	
Treatment group	At risk	CW	At risk	CW	At risk	CW	At risk	CW
I/H-PAH (N=150)								
PBO, n (%)	51 (94)	3 (6)	48 (89)	5 (9)	45 (83)	8 (15)	20 (37)	8 (15)
20 mg, n (%)	50 (100)	0	47 (94)	1 (2)	43 (86)	4 (8)	28 (56)	6 (12)
40 mg, n (%)	45 (98)	1 (2)	45 (98)	1 (2)	45 (98)	1 (2)	33 (72)	2 (4)

	Day 28 (4 weeks)		Day 56 (8 weeks)		Day 84 (12 weeks)		Day 112 (16 weeks)	
Treatment group	At risk	CW	At risk	CW	At risk	CW	At risk	CW
CTD-PAH (N=56)								
PBO, n (%)	15 (94)	1 (6)	13 (81)	3 (19)	12 (75)	3 (19)	4 (25)	4 (25)
20 mg, n (%)	16 (76)	2 (10)	16 (76)	2 (10)	16 (76)	2 (10)	8 (38)	2 (10)
40 mg, n (%)	17 (89)	1 (5)	15 (79)	2 (11)	14 (74)	2 (11)	5 (26)	2 (11)

Figure 3



	Day 28 (4 weeks)		Day 196 (28 weeks)		Day 364 (52 weeks)		Day 480 (68 weeks)	
Treatment group	At risk	CW	At risk	CW	At risk	CW	At risk	CW
(N=96) I/H-PAH, n (%)	95 (99)	1 (1)	79 (82)	11 (11)	68 (71)	18 (19)	39 (41)	23 (24)
(N=40) CTD-PAH, n (%)	34 (85)	3 (8)	27 (68)	4 (10)	18 (45)	12 (30)	0 (0)	14 (35)

Figure Captions

(Figure 1)

6MWD for PAH patients by etiology.

(Figure 2)

Kaplan-Meier analysis of clinical worsening in PHIRST patients by etiology.

(Figure 3)

Kaplan-Meier analysis of time to clinical worsening of patients with I/H-PAH and patients with CTD-PAH treated with tadalafil 20 mg or 40 mg in the PHIRST and PHIRST-2 studies.

Figure Legends

(Figure 2)

Abbreviations: TTCW = time to clinical worsening; PBO = placebo; I/H-PAH = idiopathic/heritable pulmonary arterial hypertension; CTD-PAH = pulmonary arterial hypertension associated with connective tissue disease; CW = clinical worsening

N = total number of randomized subjects who have received study medication in the 3 treatment groups; n = number of subjects per category

(Figure 3)

Abbreviations: TTCW = time to clinical worsening; I/H-PAH = idiopathic/heritable pulmonary arterial hypertension; CTD-PAH = pulmonary arterial hypertension associated with connective tissue disease; CW = clinical worsening

The tadalafil 20 and 40 mg treatment groups were combined for each subgroup

N = total number of subjects in the tadalafil 20 and 40 mg treatment groups for the I/H=PAH and CTD-PAH subgroups; n = number of subjects per category