CMRO

Current Medical Research & Opinion Vol. 25, No. 10, 2009, 2479–2485

0300-7995
doi:10.1185/03007990903210066

Article 5173/421179

Original article

Tadalafil therapy and health-related quality of life in pulmonary arterial hypertension

Joanna Pepke-Zaba
Papworth Hospital, Cambridge, UK

Anthony Beardsworth
Eli Lilly & Co, Erl Wood, UK

Melanie Chan
Eli Lilly & Co, Toronto, Ontario, Canada

Mallik Angalakuditi
Eli Lilly & Co, Indianapolis, IN, USA

Address for correspondence:
Mallik Angalakuditi, BSPharm, PhD, Research Scientist, Global Health Outcomes, Eli Lilly & Co, Lilly Corporate Center, 520/03/132 DC 6134, Indianapolis, IN 46225, USA.
Tel.: +1 317 433 0401; Cell: +1 317 292 1313; Fax: +1 317 433 3835;
angalakuditi_mallik@lilly.com

Key words:
Adcirca – Hypertension, pulmonary – Patient outcomes assessment – Quality of life – Tadalafil

Accepted: 27 July 2009; published online: 4 September 2009

Abstract

Background:
Pulmonary arterial hypertension (PAH) is a rare, progressive lung disorder that impairs performance of daily activities and quality of life (QoL), leading to right heart failure and death. Treatment options include prostanoids, endothelin antagonists, and phosphodiesterase type 5 inhibitors (e.g., tadalafil). Currently there is no cure for PAH, but tadalafil has improved exercise capacity in these patients.

Objectives:
To explore the effect of tadalafil on health-related quality of life (HRQoL) measures.

Research design and methods:
The Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) clinical trial examined the efficacy and tolerability of tadalafil for the treatment of PAH. The impact of tadalafil on HRQoL and exercise capacity, as measured by 6-minute walk test (6MW test), was also examined. Change from baseline to last non-missing post-baseline was examined for the SF-36, EQ-5D, and 6MW test, along with the relationship between HRQoL and 6MW test performance.

Results:
Tadalafil 40 mg showed significant improvement over placebo for six of eight SF-36 domains, and EQ-5D index scores. Also, the tadalafil 40-mg group showed significant improvement over placebo on the 6MW test ($p < 0.001$), but no clear relationship was found between 6MW test performance and HRQoL.

Conclusion:
Results suggest that tadalafil 40 mg may significantly improve HRQoL and exercise capacity for PAH patients. Limitations of this study include its relatively short nature limited to 16 weeks and the relative heterogeneity of the study population.

Introduction

Pulmonary arterial hypertension (PAH) is a rare progressive lung disorder that is characterized by chronic elevation in pulmonary artery pressure and pulmonary vascular resistance[1]. The exact pathogenesis of PAH is unclear but pulmonary vasoconstriction, remodeling of the pulmonary vessel walls, and thrombosis consistently play a causal role in the disease[1–4]. Symptoms of PAH are nonspecific and include fatigue, dyspnea, chest pain, peripheral edema, and syncope. The disease is progressive, ultimately leading to right ventricular failure and death. With respect to demographics, the US-based REVEAL (The Registry to Evaluate Early And Long-Term PAH Disease Management) study has thus far shown, with 2977 individuals, that the mean age at diagnosis is 48 years, with 78–80% being female[5].

Currently there are three classes of pharmacologic therapy that have regulatory approval for the treatment of PAH in the United States and/or Europe: prostanoids (epoprostenol, treprostinil, iloprost); endothelin receptor antagonists (bosentan, ambrisentan, sitaxsentan); and phosphodiesterase type 5 inhibitors (sildenafil)[6]. With the advent of therapies and earlier diagnosis, the median survival time has been estimated to be 3.6 years to approximately 5 years, with estimated single-year survival rates of 84%, 67%, and 58% (at 1 year, 3 years, and 5 years, respectively)[7]. The primary, and regulatory recognized, endpoint utilized to assess the efficacy of the aforementioned therapies, with the exception of epoprostenol, has been the change in exercise capacity, measured by the 6-minute walk (6MW) test[8]. However, the validity and clinical significance of this endpoint is currently under review. A meta-analysis conducted by Macchia and colleagues[9] found that, while the various therapies do increase exercise capacity and reduce dyspnea for PAH patients, an increase in survival probability was not observed. However, a more recent meta-analysis by Galiè and colleagues[10] did demonstrate a reduction in all-cause mortality. Irrespective of this debate, there is increasing recognition that the current goals of therapy, in the absence of a cure, are to improve the ability to perform day-to-day activities, avoid hospitalization and invasive therapies, delay progression of the disease, and ultimately improve survival. A patient's quality of life is an important aspect of medical treatment. While clinicians routinely enquire about quality of life during the course of treatment, instruments such as the Short Form 36 (SF-36)[11] and the EQ-5D[12,13] have only recently been included in clinical trials[14], with results that have been variable and lacking in consistency[15–17]. A recent review of health-related quality of life (HRQoL) instruments conducted by Chen and colleagues[14] examined the variety of instruments that have been used to measure HRQoL in PAH, such as the SF-36[11], EQ-5D[12,13] and the Minnesota Living with Heart Failure Questionnaire[18].

Tadalafil is an orally administered, selective inhibitor of phosphodiesterase type 5, currently approved for the treatment of erectile dysfunction. Results from the Pulmonary Arterial Hypertension and Response to Tadalafil (PHIRST) study, a 16-week placebo-controlled clinical trial examining four different doses of tadalafil, were recently reported[19]. In addition to the traditional efficacy endpoints of the 6MW test, World Health Organization (WHO) functional class, clinical worsening, and Borg dyspnea score, the PHIRST study also assessed quality of life using the SF-36 and the EQ-5D. The HRQoL results and their relation to the 6MW test are presented here. The objective of this study was to evaluate HRQoL measures and their relation to the unencouraged 6MW test at baseline, 4, 8, 12, and 16 weeks.

Patients and methods

Study design

The present study was part of a randomized, double-blind, placebo-controlled, 16-week multicenter clinical trial that was conducted at 84 study sites in North America, Europe, and Japan between August 2005 and August 2007. Patients were stratified by PAH etiology, 6MW test performance, and bosentan use, and were randomly assigned to one of five treatment groups: tadalafil 2.5 mg, 10 mg, 20 mg, 40 mg, or placebo, taken once daily. Patients who were taking a maximum stable dose of 125 mg of bosentan twice daily for at least 12 weeks prior to their screening visit were allowed to enroll and continue taking bosentan in conjunction with the study medication. However, treatment with other targeted therapies for PAH such as epoprostenol, iloprost, treprostinil, sitaxsentan, ambrisentan and sildenafil was prohibited.

Subject selection

Patients were at least 12 years of age with symptomatic PAH that was idiopathic/familial or related to: collagen vascular disease; anorexigen use; HIV infection; congenital systemic-to-pulmonic shunts (i.e., an atrial septal defect with resting arterial oxygen saturation >88% on room air, or at least 1-year postsurgical repair of a ventricular septal defect and/or patent ductus arteriosus). Patients were excluded if they had a 6MW test distance <150 and >450 meters. The intent-to-treat (ITT) population consisted of 405 patients who were randomly assigned to one of the five treatment groups and who received at least one dose of the study medication.

The study was conducted in accordance with applicable laws and regulations, good clinical practices, and ethical principles that have their origin in the Declaration of Helsinki and are outlined in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The institutional review board at each investigative site reviewed and approved the study protocol. All patients or their authorized legal representatives provided written informed consent (and assent when appropriate).

Outcomes measures

The SF-36, a measure of self-reported health status, and the EQ-5D, a patient-reported HRQoL measure, were administered at baseline and weeks 8 and 16. Change from baseline to week 16, or last non-missing post-baseline, was the primary measure of interest for each questionnaire. The SF-36[11] consists of 36 items that represent eight health concepts/domains: physical functioning; role

limitations due to physical problems (Role-Physical); Bodily Pain; general health perceptions (General Health); Vitality; Social Functioning; role limitations due to emotional problems (Role-Emotional); and Mental Health. Each domain was scored by summing the individual items and then transforming the scores along a 100-point scale, with higher scores representing better functioning and health status. The SF-36 also includes a single item that assesses the patient's change in health from the previous year.

The EQ-5D[12,13] is divided into two parts. The first part consists of five questions that assess mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. The second part uses a visual analog scale (VAS) to identify patients' assessment of their own health on the day that they complete the questionnaire. Patients choose one of three options for each of the first five questions, coded as 1, 2, and 3, with a higher number reflecting an increasing degree of difficulty. The scores from the five questions form a five-digit code that describes the patient's health state. In this study, the EQ-5D index scores were constructed by applying US and UK general population-based preference weights to the health states defined by the responses obtained on the first five questions. The resulting index score reflects the general population's assessment of the HRQoL associated with the self-reported health state,[12,13] with higher scores reflecting better HRQoL.

Statistical analyses

Collection of data, organization and construction of the database, and all statistical analyses and outputs were performed and retained by the sponsor. All authors had access to the database and clinical study report and assume responsibility for the completeness and accuracy of the content of the manuscript.

Analysis of all of the efficacy variables included all randomized patients who received study medication (ITT analysis). The primary analysis for change from baseline to last non-missing post-baseline on the 6MW test was performed using a permutation test on rank stratified by randomization factors (i.e., PAH etiology, bosentan used, baseline walk distance) compared to placebo. For patients who died or had clinical worsening, the lowest rank was used. No change was assumed when assigning rank in patients who discontinued the study due to treatment-related adverse events. For all other patients, the change from baseline to last non-missing post-baseline observation was used to assign rank. The placebo-adjusted treatment difference was estimated using the ANCOVA model with type II sums of squares including terms for randomization factors. The significance level for the primary analysis was two-sided at an α-level of 0.01, and all subsequent analyses involving secondary measures (e.g., HRQoL measures) were tested at an α-level of 0.05. A complete description of the PHIRST clinical trial methodology and statistical analyses is reported elsewhere[19].

Change from baseline to week 16, or last non-missing post-baseline, for the SF-36 and EQ-5D measures (i.e., individual questions, index scores, and VAS) was tested using ANCOVA, controlling for baseline randomization factors. All comparisons were performed at a two-sided α-level of 0.05. No adjustment of significance values for multiple testing was performed. Missing values on the SF-36 and EQ-5D measures were not imputed.

The scores from the HRQoL measures (i.e., SF-36 domain scores, EQ-5D index scores, and EQ VAS) and 6MW test, for all doses combined, were used to estimate the linear relationship between HRQoL and 6MW distance (6MWD). The linear relationship between HRQoL and 6MWD was examined separately for the baseline, last non-missing post-baseline, and percent change (i.e., improvement) from baseline to last non-missing post-baseline scores.

Results

A total of 405 patients were randomly assigned to one of five treatment arms and received study medication. Demographic and baseline characteristics of the placebo and the tadalafil treatment groups (2.5, 10, 20, and 40-mg doses) in the PHIRST study have been previously reported[18]. The majority of patients were female, and had PAH that was idiopathic/familial with symptoms consistent with WHO functional class II and III. Baseline 6MWD ranged from 337 m to 352 m. A total of 53% of patients were receiving background bosentan therapy. Headache, myalgia, and flushing were the most common adverse events reported in the trial, and they were most often reported as being mild or moderate[18]. A complete description of the PHIRST clinical trial results are reported elsewhere[18]. Table 1 contains the baseline HRQoL scores for the placebo and tadalafil treatment groups (2.5, 10, 20, and 40-mg doses) in the PHIRST study.

The mean change in distance walked in 6 minutes was greater for all tadalafil doses than for placebo and increased by dose. The prespecified value of statistical significance ($p < 0.01$) was achieved only in the tadalafil 40-mg dose group, with a placebo-adjusted improvement in 6MWD of 32 m: $p = 0.402$, $p = 0.05$, $p = 0.03$, and $p < 0.001$ for the 2.5, 10, 20, and 40-mg tadalafil doses, respectively.

The tadalafil 40-mg treatment group showed significant improvement over placebo in the Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, and Social Functioning domains of the SF-36. The changes in domain scores in subjects on tadalafil were

Table 1. Mean baseline scores on the HRQoL measures.

Measure	Placebo ($n=82$)	Tadalafil			
		2.5 mg ($n=82$)	10 mg ($n=80$)	20 mg ($n=82$)	40 mg ($n=79$)
SF-36*					
Physical Functioning	38.4	38.4	35.7	38.5	41.3
Role-Physical	40.8	41.9	42.2	42.5	43.5
Bodily Pain	59.0	60.9	66.4	60.4	60.3
General Health	46.6	39.7	40.7	39.7	38.2
Vitality	44.2	41.4	44.8	43.4	44.8
Social Functioning	64.5	60.8	67.6	62.7	63.5
Role-Emotional	64.7	62.3	64.3	70.9	63.4
Mental Health	66.6	63.3	70.1	67.3	65.7
EQ-5D†					
US Index Score	0.75	0.71	0.75	0.74	0.74
UK Index Score	0.66	0.61	0.66	0.65	0.65
EQ VAS	56.3	55.9	57.3	58.6	59.7

*Higher scores reflect better functioning and health status.
†Higher scores reflect better HRQoL.

apparent at week 8. Figures 1A and 1B display the mean change from baseline to last non-missing post-baseline for the eight domains of the SF-36, for each of the four tadalafil treatment groups and the placebo group. For the 40-mg treatment group, the effect-size (i.e., mean change divided by the standard deviation) was 0.38 for Physical Functioning; 0.52 for Role-Physical; 0.44 for Bodily Pain; 0.49 for General Health; 0.34 for Vitality; 0.36 for Social Functioning; 0.15 for Role-Emotional; and 0.27 for Mental Health.

All of the tadalafil treatment groups had statistically significant improvements at 16 weeks in both the US and UK population-based EQ-5D index scores compared to placebo, with the largest improvement seen with the tadalafil 40-mg group. Only the tadalafil 40-mg treatment group displayed a significant change from baseline to week 16 on the EQ-5D current health state score (EQ VAS) compared to placebo. The changes in EQ-5D index scores and EQ VAS scores in subjects on tadalafil were apparent at week 8. Figures 2A and 2B display the mean change from baseline to last non-missing post-baseline on the US and UK population-based EQ-5D index scores and the EQ VAS (respectively), for the four tadalafil treatment groups and the placebo group. For the 40-mg treatment group, the effect-size on the EQ VAS was 0.35.

At baseline, the 6MWD showed the strongest correlation with the Physical Functioning domain of the SF-36, while for percentage change from baseline, the strongest correlation was with the General Health domain of the SF-36. However, the correlations between 6MWD and the SF-36 and EQ-5D were generally poor. Table 2 presents the coefficients of correlation between each of the SF-36 domains and 6MWD for all subjects combined, at baseline, last non-missing post-baseline, and percent change from baseline to last non-missing post-baseline.

Conclusion

The study findings presented suggest that tadalafil may improve HRQoL and exercise capacity for patients with PAH. Tadalafil improved aspects of HRQoL beyond those clearly related to physical activity. At 16 weeks, tadalafil 40 mg demonstrated significant improvements in the EQ-5D and EQ VAS scores and in six out of eight domains of the SF-36. The relative heterogeneity of the study population, particularly the large proportion of subjects on background bosentan therapy, reflects the clinical patient population and may have influenced the results. However, an exploratory analysis in patients with and without concomitant bosentan that revealed similar improvements in the measures of HRQoL indicates that the results may be generalizable to broader patient populations.

Discussion

The results of the present study show that tadalafil improves both HRQoL and exercise capacity for PAH patients. These improvements are most robust for tadalafil 40 mg. In addition to being the only dose to achieve the prespecified level of significance ($p<0.01$) compared to placebo in the change in 6MWD, tadalafil 40 mg also demonstrated significant improvements in all aspects of the EQ-5D and in six out of the eight domains of the SF-36.

The baseline data reflect the considerable impact PAH has both on exercise capacity and HRQoL and are consistent with those previously reported[15]. While the domains related to physical activity are most impacted, it should be noted that all aspects of quality of life, including General

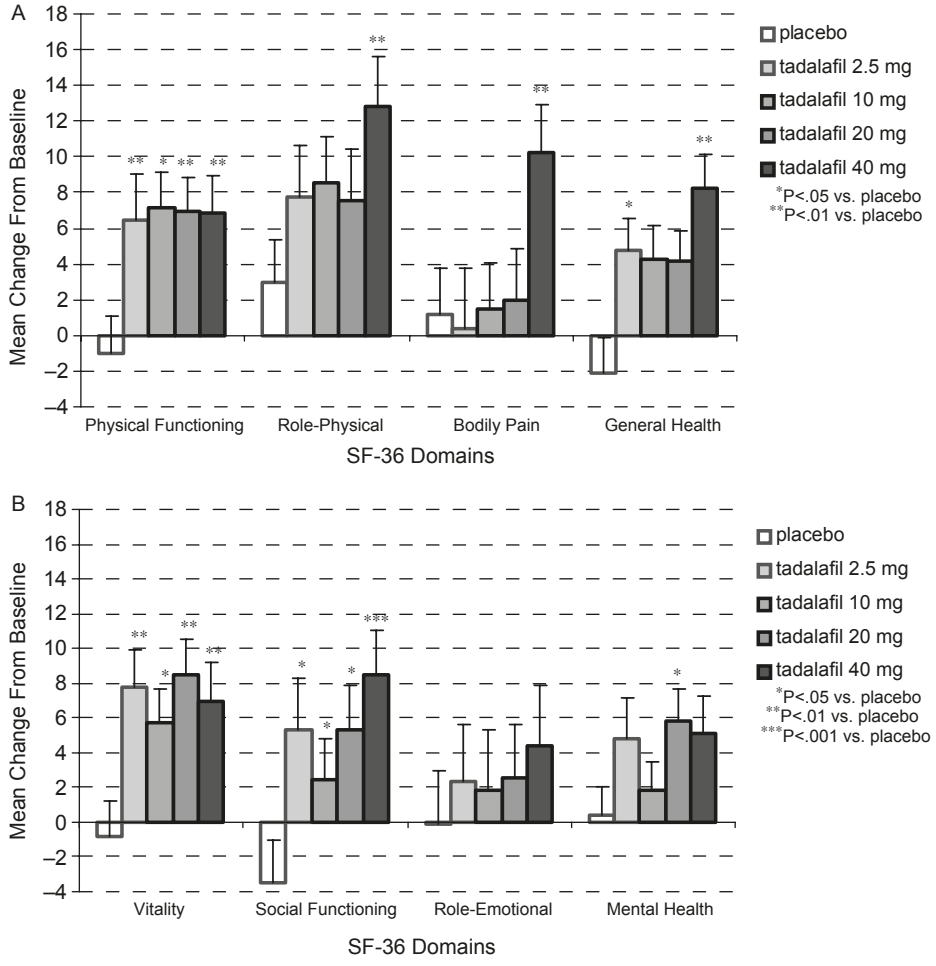

Figure 1. Change from baseline to last non-missing post-baseline on the SF-36. Figure 1A shows the mean changes in Physical Functioning, Role-Physical, Bodily Pain, and General Health. Figure 1B shows the mean changes in Vitality, Social Functioning, Role-Emotional, and Mental Health.

Health, Bodily Pain, Social Functioning, and Role-Emotional, are affected.

At 16 weeks, tadalafil 40 mg demonstrated significant improvements in the Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, and Social Functioning domains of the SF-36 as well as all aspects of the EQ-5D. The effect-size of the SF-36 domains ranged from 0.15 to 0.52 standard deviation units, and was 0.35 for the EQ VAS. It is generally agreed that an effect size of between 0.3 and 0.5 can be considered as moderate, with effect sizes in excess of 0.5 being large. Thus, tadalafil improved aspects of HRQoL beyond those clearly related to physical activity and the magnitude of these improvements would appear to be of clinical significance based on the effect-size. This contrasts somewhat with the data reported for sildenafil, a short-acting inhibitor of phosphodiesterase type 5. Pepke-Zaba and colleagues[15] reported that sildenafil, at the approved dose of 20 mg given three times a day, showed significant improvements in only two of the eight domains of the SF-36: Physical Functioning and General Health. Similar results were seen at both 40 mg and 80 mg t.i.d., and when data were pooled for all sildenafil doses, significant improvement in the Vitality domain was also noticed.

Although patients in the tadalafil 40-mg treatment group showed significant improvement in exercise capacity and HRQoL, the authors were unable to demonstrate a strong relationship between the 6MWD and patient-reported responses on either the SF-36 or the EQ-5D. Both instruments are generic HRQoL measures, but even the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), which is a PAH disease-specific measurement[20–22], does not strongly correlate with 6MWD. However, McKenna and colleagues[20] did find strong correlations between the CAMPHOR subscales, namely the symptom and functioning subscales, and the EQ-5D index scores and EQ VAS scores. Gomberg-Maitland and colleagues[21] found similar strong correlations between these CAMPHOR subscales and the SF-36 domains.

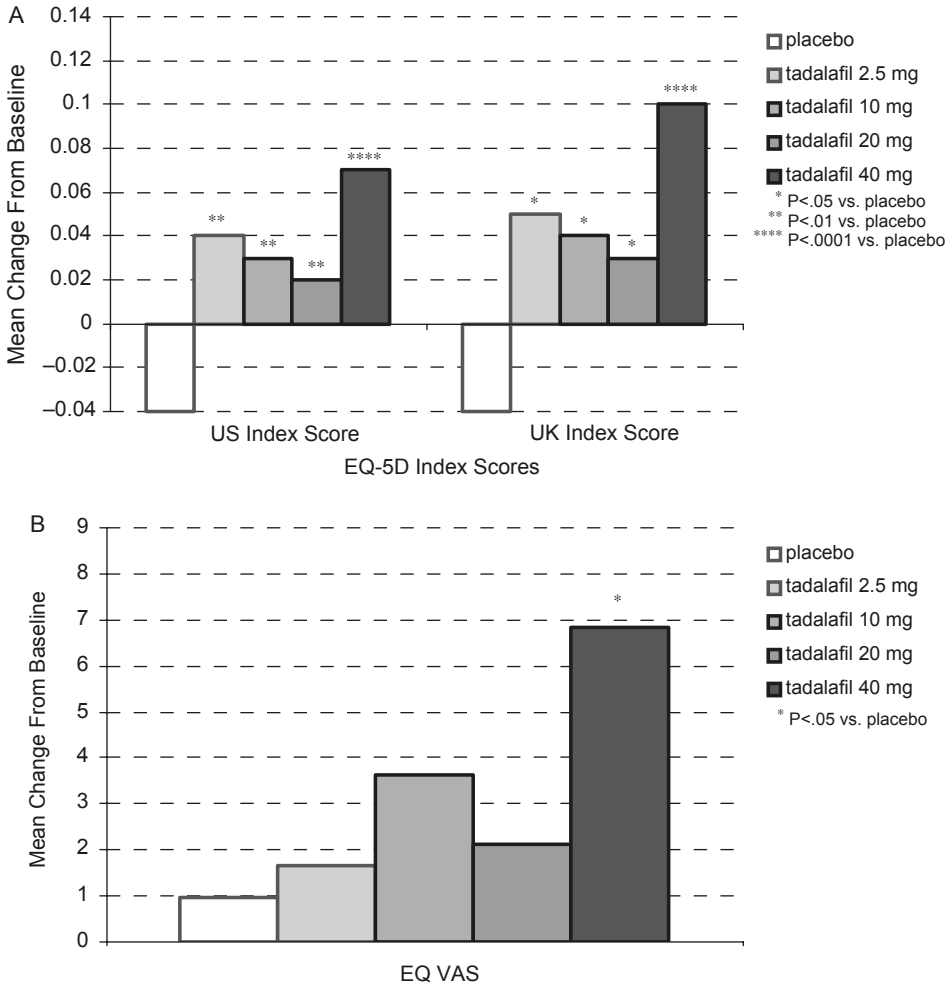

Figure 2. Change from baseline to last non-missing post-baseline on the EQ-5D. Figure 2A shows the mean changes in the EQ-5D Index scores (US Index and UK Index), and Figure 2B shows the mean changes in the EQ VAS scores.

Table 2. Correlations between 6MWD and scores on the SF-36 and EQ-5D.

Measure	6MWD								
	Baseline			Last non-missing post-baseline			% Change from baseline to last non-missing post-baseline		
	r	*n*	*p*-value	*r*	*n*	*p*-value	*r*	*n*	*p*-value
SF-36									
Physical Functioning	0.35	399	<0.0001	0.55	382	<0.0001	0.22	371	<0.0001
Role-Physical	0.22	397	<0.0001	0.43	382	<0.0001	0.14	349	0.0078
Bodily Pain	0.06	397	0.2105	0.27	382	<0.0001	0.16	372	0.0018
General Health	0.11	397	0.0321	0.29	382	<0.0001	0.30	373	<0.0001
Vitality	0.24	398	<0.0001	0.37	382	<0.0001	0.20	370	0.0001
Social Functioning	0.17	394	0.0009	0.31	380	<0.0001	0.18	362	0.0006
Role-Emotional	0.17	395	0.0006	0.30	382	<0.0001	0.14	364	0.0085
Mental Health	0.11	399	0.0238	0.21	382	<0.0001	0.13	376	0.0145
EQ-5D									
UK Index Score	0.25	394	<0.0001	0.37	377	<0.0001	–0.05	369	0.3192
EQ VAS	0.16	376	0.0022	0.28	378	<0.0001	0.02	352	0.7112

6MWD = 6-minute walk distance; *r* = correlation coefficient; *n* = number of patients.

The current goal of therapy, with the treatments available today, is to improve survival, ameliorate symptoms, and improve quality of life. While data exist for current therapies on their ability to delay clinical worsening and ameliorate symptoms, far less is known about the translation of these benefits into improvements in quality of life. Indeed, little work has been done to describe the complex relationship between the functional *disability* associated with PAH and an individual's HRQoL. This relationship is complicated further by variability in personal needs, the individual consequences of not meeting those needs, the degree of functional improvement required to meet those needs, as well as the broader aspects of an individual's environment that impact those needs. Clearly, the study results suggest that the SF-36 and EQ-5D are measuring broader aspects of an individual's HRQoL than just those affected by changes in exercise capacity. Indeed, this is also true of the disease-specific instrument, CAMPHOR, suggesting that these measures of HRQoL provide both complementary and additional information to that supplied by the more traditional outcome variables studied in PAH clinical trials.

Limitations of this study include its relatively short nature limited to 16 weeks, particularly bearing in mind the chronic nature of the disease under investigation. A further limitation may also be the relative heterogeneity of the study population, in particular the large proportion of subjects on background bosentan therapy. While this heterogeneity truly reflects the clinical patient population, it may have influenced the results. However, an exploratory analysis in patients with and without concomitant bosentan revealed similar improvements in the measures of HRQoL.

Despite these limitations, these data show that tadalafil 40 mg improves the exercise capacity, as measured by the 6MW test, of patients with PAH as well as the HRQoL across a broad spectrum of domains, as measured by the SF-36 and EQ-5D.

Transparency

Declaration of funding
This study was supported by Eli Lilly & Co.

Declaration of financial/other relationships
A.B., M.C. and M.A. have disclosed that they are employed by, and own stock in, Lilly. J.P-Z. has disclosed that she has been a consultant for Lilly.

Some peer reviewers receive honoraria from CMRO for their review work. The peer reviewers of this paper have disclosed that they have no relevant financial relationships.

Acknowledgment
The authors thank Virginia Rosen, Victoria Porter, and Victoria Zarotsky of i3 Innovus, and Kathryn Gilmore of Lilly Medical Communications, for their assistance with the preparation of this manuscript.

References

1. Simonneau G, Galié N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol 2004;43:5-12S
2. Chin KM, Rubin LJ. Pulmonary arterial hypertension. J Am Coll Cardiol 2008;51:1527-38
3. Humbert M, Sitbon O, Simmoneau G. Treatment of pulmonary arterial hypertension. N Engl J Med 2004;351:1425-36
4. Farber HW, Loscalzo J. Pulmonary arterial hypertension. N Engl J Med 2004;351:1655-65
5. Frost AE, Badesch DB, Barst RJ, et al. A comparison of REVEAL registry demographic data with other/prior registries of pulmonary arterial hypertension (PAH). Chest Meeting Abstracts 2008;134:p134001
6. Badesch DB, Abman SH, Simmoneau G, et al. Medical therapy for pulmonary arterial hypertension. Updated ACCP Evidence-Based Clinical Practice Guidelines. Chest 2007;131:1917-28
7. Thenappan T, Shah SJ, Rich S, et al. A USA-based registry for pulmonary arterial hypertension: 1982-2006. Eur Respir J 2007;30:1103-10
8. Enright PL. The six-minute walk test. Respir Care 2003;48:783-85
9. Macchia A, Marchioli R, Marfisi R, et al. A meta-analysis of trials of pulmonary hypertension: a clinical condition looking for drugs and research methodology. Am Heart J 2007;153:1037-47
10. Galiè N, Manes A, Negro L, et al. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. Eur Heart J 2009;30:394-403
11. Ware JEJ, Kosinski M, Gandek B. SF-36® Health Survey: Manual & Interpretation Guide, 2nd edn. Lincoln, RI: Qualitymetric, Inc, 2000
12. Johnson JA, Coons SJ, Ergo A, et al. Valuation of EuroQOL (EQ-5D) health states in an adult US sample. Pharmacoeconomics 1998;13:421-33
13. Rabin R. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33:337-43
14. Chen H, Taichman DB, Doyle RL. Health-related quality of life and patient-reported outcomes in pulmonary arterial hypertension. Proc Am Thorac Soc 2008;5:623-30
15. Pepke-Zaba J, Gilbert C, Collings L, et al. Sildenafil improves health-related quality of life in patients with pulmonary arterial hypertension. Chest 2008;133:183-9
16. Galiè N, Olschewski H, Oudiz RJ, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. Circulation 2008;117:3010-19
17. Olschewski H, Simonneau G, Galié N, et al.; for the Aerosolized Iloprost Randomized Study Group. Inhaled iloprost for severe pulmonary hypertension. N Engl J Med 2002;347:322-9
18. Rector RS, Kubo SH, Cohn JN. Patients' self-assessment of their congestive heart failure. Heart Fail 1987;1:198-209
19. Galiè N, Brundage BH, Ghofrani HA, et al. Tadalafil for pulmonary arterial hypertension therapy. Circulation 2009 May 26 [Epub ahead of print]
20. McKenna SP, Doughty N, Meads DM, et al. The Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR): A measure of health-related quality of life and quality of life for patients with pulmonary hypertension. Qual Life Res 2006;15:103-15
21. Gomberg-Maitland M, Thenappan T, Rizvi K, et al. United States validation of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR). J Heart Lung Transplant 2008;27:124-30
22. Meads DM, McKenna SP, Doughty N, et al. The responsiveness and validity of the CAMPHOR Utility Index. Eur Respir J 2008;32:1513-19

