Author's response to reviews

Title: Assessment of Measurement Properties of Peak VO2 in Children with Pulmonary Arterial Hypertension

Authors:

Joseph C Cappelleri (joseph.c.cappelleri@pfizer.com)
Lie-Ju Hwang (lie-ju.hwang@pfizer.com)
Jack Mardekian (jack.mardekian@pfizer.com)
Marko A Mychaskiw (marko.mychaskiw@pfizer.com)

Version: 2 Date: 24 March 2012

Author's response to reviews: see over
March 22, 2012

Dear Dr. Patel:

On behalf of my co-authors, I am pleased to enclose our manuscript, “Assessment of Measurement Properties of Peak VO$_2$ in Children with Pulmonary Arterial Hypertension” for consideration for publication in *BMC Pulmonary Medicine* (MS: 1462107003444067).

Our manuscript investigates the measurement properties of the peak oxygen consumption (VO$_2$, maximal exercise test) in pediatric patients with pulmonary arterial hypertension (PAH), in terms of its associations with other clinical endpoints and its reliability. The study found that the peak VO$_2$ has favorable measurement properties in pediatric patients with PAH. The peak VO$_2$ measurements exhibited good reliability and improvements that were associated with improvements in clinical endpoints, such as the WHO functional class and a physician global assessment of change.

We believe that this topic is of interest because the 6-minute walk test (a widely used, noninvasive technique to assess PAH severity and response to treatment in adults with PAH) may not be appropriate for children at all ages, and because our data were from the first large placebo-controlled trial to use and assess the peak VO$_2$ endpoint in the pediatric PAH population.

This research was supported by Pfizer Inc. I am an employee of Pfizer Inc as are my colleagues, Lie-Ju Hwang, Jack Mardekian and Marko A. Mychaskiw.

This manuscript has not been previously published and is not under consideration at another journal.

Please note that in 2010 we first submitted this manuscript and received reviewer comments but decided it would be best to temporary withdraw the manuscript from consideration until the primary clinical paper, upon which the manuscript stems from, gets officially published, which it now has (Barst et al. *Circulation* 2012). Dr. Simon Harold, assistant scientific editor for the BMC-series Journals, restated in 2011 that he and the journal remain quite happy to consider a resubmission provided that it is revised to address all of the outstanding issues from the previous round of review.

Following that encouragement, we are attaching the revised manuscript, along with the authors’ responses to those comments received (see below).

We hope you find our revised paper suitable for publication.

Sincerely,

Joseph C. Cappelleri
Joseph C. Cappelleri, PhD, MPH
Senior Director–Biostatistics
Pfizer Inc
445 Eastern Point Road (MS 8260-2502)
Groton, CT 06340, USA
Tel: +1 860 441-8033
E-mail: joseph.c.cappelleri@pfizer.com
Reviewer’s report (MS: 1462107003444067)

Title: Assessment of Measurement Properties of Peak VO2 in Children with Pulmonary Arterial Hypertension

Version: 1 Date: 20 November 2010

Reviewer: robert tulloh

Reviewer's report:

The authors are to be commended for attempting to tackle a problem which is important in paediatric pulmonary hypertension, namely the inability to assess 6MWT in younger patients.

MAJOR COMPULSORY REVISIONS:
1. The aims of this study are not clear. It seems to be suggested that the intention is to determine whether peak VO2 is a useful correlate with an improvement in functional class. However, it seems strange therefore that the data selects 50% of children who cannot perform VO2 because of developmental inability (not clearly classified) and 80% of children who did take part were in FC I or II in whom there would be little expectation of improvement.

   As stated at the end of the Introduction “The aim of this paper is to investigate the measurement properties of peak VO2 in terms of its associations with other clinical endpoints and its reliability. It was hypothesized that, as observed with other populations, percentage changes in peak VO2 in pediatric patients with PAH are reliable and are associated with changes in certain clinical endpoints.” Because the study was powered for the primary endpoint of peak VO2, the 106-patient subset was sufficient to test the hypothesis that sildenafil could improve exercise capacity as assessed by PVO2. More patients were enrolled in order to assess safety and additional efficacy endpoints (functional class, hemodynamics, patient/parent and physician global assessments). Inclusion of non-developmentally able patients reflects the clinical reality that some patients are simply unable to exercise. The fact that peak VO2 exhibited good reliability and improvements that were associated with improvements in other clinical endpoints, even when most of these patients were FC I or II and therefore had little room for improvements, supports the hypothesis. However, to clarify the generalizability of the results, the first sentence of the Discussion was modified to read “In general, the results indicate that the peak VO2 has favorable measurement properties in pediatric patients with PAH who are developmentally and physically able to perform exercise testing.”

2. The abstract gives no mention of the patients enrolled in this study

   The Methods subsection of the Abstract was modified to begin “Using data from the subpopulation of 106 patients who were developmentally and physically able to perform exercise testing, most of whom were World Health Organization Functional Class (WHO FC) I or II, reliability…”
3. There is no clarity with respect to the subgroup of diseases in this study. How many of the FC III or IV were APH with CHD, which are well known to behave very differently, and not to have the poor prognosis alluded to in the first introduction. Tabulated demographic and baseline data were added, and additional text was added to the Results section.

4. It is not clear that it is acceptable to take the mean of the screen and baseline assessment, since with small children there is likely to be a learning curve as to how the VO\textsubscript{2}, reporting and 6MWT are performed. Test-retest reliability was performed specifically to show that there were not any differences between screening and baseline assessments. As stated in the Results (paragraph 2) there were not any differences between the screening and baseline assessments. Thus the mean was taken.

5. Even though it is recognized that 6MWT cannot be performed in the younger patients, can VO\textsubscript{2} be undertaken reliably in those younger than for 6MWT. This must be the purpose of this paper and has not been addressed. Although PAH in children appears similar to PAH in adults (Barst Eur Respir J 2011;37:665-71), it is unclear what parameters best measure treatment response or disease progression in children (Haworth Curr Opin Pulm Med 16(suppl 1):S35-S41). 6MWD is not a maximal test in children, whereas cardiopulmonary exercise testing is a maximal test in adults and children. Because in adult PAH patients, peak VO\textsubscript{2} correlates with 6MWD (Miyamoto Am J Respir Crit Care Med 2000;161:487-92), peak VO\textsubscript{2} was chosen as the primary endpoint for the STARTS-1 study. Assessment of peak VO\textsubscript{2} in pediatric patients in STARTS-1 was limited to patients determined to be “developmentally able” (ie, >7 years of age, able to reach pedals, able to perform exercise per instructions) to exercise reliably (more details are specified in Circulation, in press). With this clinical rationale and substantive base, we sought to quantify the measurement properties of peak VO\textsubscript{2} in pediatric patients with PAH. In doing so, we found that these peak VO\textsubscript{2} measurements exhibited good reliability and improvements that were associated with improvements in other clinical endpoints.

6. Similarly, all the patients who completed the VO\textsubscript{2} might have been 17 years old, in which case 6MWT could be used satisfactorily. We have not been given this data to allow us to assess the information. Tabulated demographic and baseline data were added, and additional text was added to the first paragraph of the Results section.

7. It would be much more beneficial to consider only those patients in whom assessment was possible, rather than the tendency to magnify the numbers as stated in the introduction. As a result, we are not clear which of the 106 patients was in FC I, how many girls, how many had APH. It is recognized that this has been presented in this way, since the true numbers that could be reliably assessed with FC II to IV would be much less, but the paper would be clearer and more tidy.
Tabulated demographic and baseline data were added, and additional text was added to the first paragraph of the Results section.

MINOR REVISIONS
8. The background presents information not of relevance in this study. It is not about the causes of PAH, not about the therapies. It is about trying to determine an assessment tool. Hence the first two paragraphs should be severely shortened.
   Two sentences were cut.

9. I could not see a definition of SGA and PGA which are mentioned later
   Please see the Methods, paragraph 5 (pg. 7) and the List of Abbreviations (pg. 14).

10. The results are presented incorrectly. This study is not about the efficacy of sildenafil, but about the correlation of VO2 with reported symptoms. Hence, the presentation of results starting with 234 patients randomized is incorrect.
    This information was moved from the Results section to the Methods section.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
The reviewer has received educational grants from all the companies involved in pulmonary hypertension medication including Pfizer, but holds no shares, financial stakes or positions within the companies. No patents are held or applied for. There are no recognised financial competing interests therefore in assessing this publication.
Reviewer's report (MS: 1462107003444067)

Title: Assessment of Measurement Properties of Peak VO2 in Children with Pulmonary Arterial Hypertension

Version: 1 Date: 13 November 2010

Reviewer: Ageliki Karatza

Reviewer's report:
RE: Assessment of measurement properties of Peak VO2 in children with pulmonary arterial hypertension, by Cappelleri JC et al.

this is a very well designed study assessing the reliability of Peak VO2 values and the responsiveness of measurement. The reliability of peak VO2 values (achieved with formal cardiopulmonary exercise testing) was tested with the ICC, Pearson correlation coefficient and was also strongly suggested by the Bland-Altman plot.

The percentage of change in VO2 values from baseline correlated well and showed responsiveness to a physician global assessment of change and with the change in the WHO FC.

Formal cardiopulmonary exercise testing using a cycle ergometer is more standardized than the 6-minute walk test and has a prognostic value regarding survival in adult patients with IPAH.

1. However, cardiopulmonary exercise testing is a lot more demanding test and has certain limitations in the pediatric population. The authors state that only 106 out of the 234 children initially randomized and treated with sildenafil or placebo underwent cardiopulmonary exercise testing. The test was performed at baseline and post treatment only in those who were developmentally able to participate and achieved functional capacity limits 10-28 mL/Kg/min at screening. It is not clear for the reader which was the age group that was evaluable, taking into account that the children that were enrolled aged 1-17 years. (ie, had the ability to co-operate and the appropriate height to function on the bicycle ergometer). I would suggest, that some demographic data and explanation regarding this issue should be added in the manuscript (MAJOR COMPULSORY REVISION).

Tabulated demographic and baseline data were added, and additional text was added to the first paragraph of the Results section.

2. The authors describe that 21 out of the 106 children who were tested were assigned to WHO FC III/IV at baseline. One might argue that cardiopulmonary exercise testing may have uninterpretable results in patients with severe exercise limitations (symptoms with minimal exercise). Therefore, the reliability of VO2 in children with I/II versus III/IV WHO FC should be emphasized in the results section (MAJOR COMPULSORY REVISION)
Rather than having uninterpretable results, patients with severe exercise limitations have more room for improvement. Indeed, theoretically, only FC II-IV patients can improve. Regardless (as noted in the response to comment #1 of Dr. Tulloh, above), to clarify the generalizability of the results, the first sentence of the Discussion was qualified to read “In general, the results indicate that the peak VO$_2$ has favorable measurement properties in pediatric patients with PAH who are developmentally and physically able to perform exercise testing.

3. The patients were randomized into low, medium and high sildenafil dose groups based on the maximum plasma concentrations of the medication. The authors might like to report the range of sildenafil dosage (in mg/Kg/day) (DISCRETIONARY REVISION).

Paragraph 3 of the Methods was modified as follows “...The 8-kg to 20-kg group was randomized 1:2:1 to sildenafil medium (10 mg) and high (20 mg) doses and placebo, respectively. The >20-kg to 45-kg group was randomized 1:1:1:1 to sildenafil low (10 mg), medium (20 mg), and high (40 mg) doses and placebo, respectively. The >45-kg group was randomized 1:1:1:1 to sildenafil low (10 mg), medium (40 mg), and high (80 mg) doses and placebo, respectively.

The question posed by the authors is well defined and the methods are appropriate and well described. However, the limitations of the work are suggested to be more clearly stated (comments 1+2)

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:** 'I declare that I have no competing interests'