OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	203109
Submission Date	November 30, 2011
Brand Name	Revatio®
Generic Name	Sildenafil citrate
Sponsor	Pfizer
Submission Type	Pediatric supplement
Therapeutic Class	Phosphodiesterase-5 (PDE5) Inhibitor
Marketed Formulation (Strength)	Oral tablet (20 mg), intravenous (10 mg/12.5 mL)
Indication & Dosing Regimen (Approved in Adults)	Pulmonary Arterial Hypertension (PAH), 20 mg tablet TID 10 mg i.v. bolus TID
Intended Population	Pediatric PAH 1 to < 17 years of age
Proposed Indication	Treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability (b) (4)
Proposed Formulation	Powder for Oral Suspension
Proposed Dosing Regimen	(b) (4)
OCP Division	Division of Clinical Pharmacology I
OND Division	Division of Cardiovascular and Renal Products
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1 EXECUTIVE SUMMARY

Sildenafil citrate (Revatio®), a phosphodiesterase 5 (PDE5) inhibitor, is approved in the United States for the treatment of pulmonary arterial hypertension (PAH) adults. The current submission (NDA 203139) is a pediatric supplement submission for the treatment of PAH in response to a pediatric written request originally issued in 2001.

The sponsor submitted seven studies for this pediatric clinical development program: two relative bioavailability studies in adults, a palatability study of the age-appropriate POS in adults, a 16-week dose-ranging safety and efficacy study with a 1-year open label clinical follow-up in pediatric PAH patients (1 to 17 years). Based on the results of these studies, the sponsor is seeking approval of sildenafil in children with PAH, 1 to < 17 years of age.

The following are the major findings:

1. The pediatric formulations (extemporaneous suspension and powder for oral suspension) have comparable pharmacokinetics to that of the approved intact tablets in adults.
2. The pharmacokinetics of sildenafil, after adjusting for weight in pediatrics, is similar to adults and is comparable across subgroups of age.
3. In the double-blind 16-week dose-ranging trial, sildenafil showed an exposure-dependent improvement in exercise capacity and hemodynamic parameters, with no substantial improvement with doses greater than medium dose level studied in the 16 week dose-ranging efficacy study.
4. An apparent dose-dependent increase in mortality was observed in the long term open-label extension. Further examination of data show some inconsistencies with the mortality finding, such as, a lower incidence proportion of death in the patients who received placebo in the double blind period, a lack of a dose-response relationship for mortality in the blinded phase of (~5 years) the long-term extension, and an inconsistent relationship between the predicted steady-state sildenafil exposures and mortality across the three dose groups. Based on the entirety of information, it is not fully clear whether the mortality is associated with the treatment.
5. Based upon the results of exercise capacity, hemodynamic response and the pharmacokinetics, the sponsor proposed dosing regimen is appropriate.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the clinical pharmacology and biopharmaceutics information provided in the current submission (NDA 203139), and recommends approval of Revatio® for treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability (b) (4)

Specifically the Office recommends:

1. Approval of the powder for oral suspension (POS) formulation pending overall recommendation by OSI.
2. Approval of Revatio® (b) (4)

2 CLINICAL PHARMACOLOGY SUMMARY

This pediatric clinical pharmacology program describes the effects of sildenafil in children with PAH aged 1 to <17 years, in terms of a dose relationship, and describes the pharmacokinetics of sildenafil in the same population.

In this NDA, two separate formulations were evaluated and compared to the currently marketed 20 mg sildenafil tablet. For the pivotal clinical trial, an extemporaneously prepared formulation was used for pediatric patients unable to take a tablet. An adult bioequivalence (BE) study was conducted in order to bridge the exposure information obtained from extemporaneously prepared formulation to the intact tablet. The to-be-marketed formulation is the powder for oral suspension (POS), in which an additional BE study was conducted in adults. The following were the major findings:

- No statistically significant difference in sildenafil $AUC_{0-\infty}$ systemic exposure between the intact tablet and the extemporaneously prepared suspension was observed. However, bioequivalence for C_{max} (85.2%, suspension vs. tablet) was not demonstrated, since the lower bound of the 90% CI is less than 80% (76.1%). This difference is not considered to be clinically relevant.
- For the POS formulation, the geometric mean ratio was 90.6% (suspension vs. tablet) for sildenafil $AUC_{0-\infty}$ and 94.9% for C_{max}. Inspection of the clinical and bioanalytical sites was requested for this study and a recommendation from the Office of Scientific Investigations (OSI) is pending.

For the pivotal trial, the selection of doses attempted to target a concentration required to inhibit PDE5 and mimic the sildenafil exposures established for adult PAH subjects by adjusting for weight. The pharmacokinetics of sildenafil, after adjusting for weight in pediatrics, is similar to adults and is comparable across subgroups of age and weight and the profile supports three times a day dosing. Based on the dosing regimen studied in A1481131 and A1481156, the steady-state exposures associated with the medium dose level in the pediatric patients correspond to that of approved 20 mg TID in adults.

Over the range of sildenafil doses studied, exposure-response relationships were observed with exercise capacity and pulmonary hemodynamics. Sildenafil administered three times a day improves both efficacy measurements in a dose related fashion in children aged 1 to 17 years.

With regard to the primary endpoint, percent change from baseline in VO_{2peak} at 16 weeks, a trend in the dose-response relationship was observed for the subset population who was able to perform exercise testing (approximately 115/235 randomized, ~49%). For the primary analysis, the sildenafil combined treatment group yielded a 7.7 (95% CI: -0.19, 15.6; p-value = 0.056) improvement in percent change from baseline compared to placebo. An Emax exposure-response relationship was observed with % change in VO_{2peak} at 16 weeks and predicted average sildenafil steady state concentration (C_{ss}). A near maximum effect of 9.1% change in VO_{2peak} is achieved at concentrations corresponding to medium and high doses (C_{ss} >80 ng/mL).

For absolute change from baseline in PVRI at 16 weeks, a trend in the dose-response relationship was observed for the pediatric population (analysis included 208/235 randomized, ~88.5%). The hemodynamic effect for the low dose was not significantly different compared to placebo,

while the medium and high dose groups exhibited greater increase compared to placebo (18% and 27%, respectively). An Emax exposure-response relationship was observed with % change in PVRI at 16 weeks and predicted average sildenafil steady state concentration. A near maximum effect of -30.5% change from baseline is achieved at concentrations corresponding to the medium dose level (EC50 ~ 62 ng/mL).

The improvement in exercise capacity and hemodynamics (percent change from baseline) was comparable between adults and pediatrics, for the maximum effective dose (i.e., 20 mg TID for adults, medium and high doses for pediatrics).

With respect to safety, a total of 35 deaths were reported in the long-term extension study. Five of the 35 deaths were in the low dose group (5/55; 9%), 10 were in the medium dose group (10/74; 14%), and 20 were in the high dose group (20/100; 20%) according to the randomized sildenafil treatment in Study A1481131 and the long-term extension Study A1481156. The hazard ratio for mortality in the high dose group compared to the low dose group was 3.5 (95% CI: 1.29 to 9.51), while the hazard ratio for mortality in the medium dose group compared with the low dose group was 1.85 (95% CI: 0.63 to 5.44).

It should be noted that there are several inconsistencies associated with the mortality findings:

- Subjects who received placebo in the pivotal study and then went on to receive sildenafil in the long-term extension had better survival than those who received sildenafil from the start of the trial, suggesting that a 16 weeks delay in the start of sildenafil treatment is beneficial for survival. There is no physiologically plausible explanation as to why delay in treatment by 16 weeks would confer a long-term survival advantage.
- Evaluation of the mortality dose-response information during 5 years of the blinded-phase (start of Study A1481131 to June 2008, i.e, completion of 16 week double blind phase by the last subject) and 3 years of the open-label phase reveals a disproportionate number of subjects died in the open-label phase of the study (n=11 subjects during blinded period vs. n=24 subjects after). Importantly, the dose-response relationship for mortality is not evident during the controlled, blinded-phase of the trial, which lasted 5 years (3.6%, 5.4% and 5.0% mortality rate in the low, medium and high dose cohorts, respectively).
- Exposure-response analysis indicates an exposure-dependent increase in mortality in the low and medium dose group but trends in the opposite direction for the high dose group. In the high dose group, the incidence proportion of death in patients with predicted steady-state exposure greater than median concentration of 129 ng/mL was ~0.15 compared to ~0.32 below the median.
- The 3-year survival rates obtained in this trial (87%, 88% and 80% for low, medium and high doses, respectively) are higher than reported in children with PAH prior to the availability of targeted PAH therapies (29-52%)[1].
- Baseline imbalances in specific covariates influenced the treatment comparisons with the survival data. Baseline etiology, pulmonary vascular resistance index and right atrial pressure were found to be most prognostic for survival. Accounting for these baseline risk factors, reduces the hazard ratio comparison between the dose groups.

Given the lack of controlled long term data in adults or for other approved PAH treatments, this

mortality signal is concerning and will play a significant role in understanding the benefit-risk relationship. On the other hand, it is not clear whether the dose-response relationship for the mortality finding is a true signal or if it is unique to sildenafil in pediatrics only.

Based on the above findings, the sponsor proposed regimen (b) (4) [redacted]

Table 1. The dosing recommendation in the proposed labeling

Population	Dose
Adult PAH (WHO Group I)	20 mg TID oral, 10 mg TID intravenous
(b) (4) [redacted]	[redacted]
[redacted]	[redacted]

- *Widlitz A and Barst RJ. Pulmonary hypertension in children. Eur Respir J 2003; 21(1): 155-76.*

3 QUESTION BASED REVIEW

An abbreviated version of the QBR is used for this review since key QBR elements have been addressed previously (NDA 21-845, 5/20/2005: Mishina and 4/10/2009: Jadhav).

3.1 GENERAL ATTRIBUTES OF THE DRUG

Sildenafil citrate, a phosphodiesterase type 5 (PDE5) inhibitor, was originally approved in 1998 for erectile dysfunction under the trade name Viagra® (NDA 20-895). The role of PDE5 and the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway in the pathology of pulmonary hypertension led to the initiation of a development program which explored the safety and efficacy of sildenafil citrate for the treatment of PAH. Under the trade name Revatio®, sildenafil citrate was subsequently approved for the treatment of PAH in the US in June 2005 (NDA 21-845). In the adult population, sildenafil demonstrated improvements in exercise ability, using the 6 minute walk distance (6MWD) test, and the approved dosage regimen for oral Revatio® is one 20 mg tablet administered 3 times daily (TID).

In May 2009, an efficacy supplement to NDA 21-845 to expand the current Revatio® indication of PAH (WHO Group I) to include a "delay to clinical worsening" claim was approved with the currently approved dose and dosing regimen. In November of 2009, an intravenous formulation was approved for use in the treatment of adult PAH patients who are currently prescribed oral Revatio® and who are temporarily unable to take oral medicine (NDA 22-473). The current application intends to seek approval of Revatio® for the treatment of PAH (WHO Group I) in pediatric patients to improve exercise ability (b) (4)

For clinical studies in the pediatric PAH population, the currently marketed tablet formulation was used. For those pediatric patients unable to take sildenafil tablets, an age appropriate oral suspension was made extemporaneously, by crushing sildenafil tablets in a mix of 2 commercially available vehicles (b) (4) or crushed and given with applesauce.

The proposed dosing regimen for Revatio® in the treatment of the PAH in children aged 1-17 years, is TID. Proposed doses are (b) (4) It is noted by the sponsor that higher than recommended doses should not be used in pediatric patients with PAH.

3.2 GENERAL CLINICAL PHARMACOLOGY

3.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor submitted seven studies for this pediatric clinical development program. With regard to the new POS and extemporaneously prepared formulations, the following studies were performed:

- A relative bioavailability study of the age-appropriate powder for oral suspension (POS) to the marketed tablet (Study A1481293, performed in adults)

- A relative bioavailability study of the age-appropriate crushed tablet and interim extemporaneously prepared formulation to the marketed tablet (Study A1481275, performed in adults)
- A palatability study of the age-appropriate POS (Study A1481261, performed in adults)

The clinical trials that explored the efficacy and safety of Revatio® include the following:

- One 16-week dose-ranging safety and efficacy study with a 1-year open label clinical follow-up were conducted in pediatric PAH subjects :
    - Pivotal Study, A1481131: Phase 3, placebo controlled parallel group, dose ranging study. Subject's aged 1 to 17 years with body weight ≥8 kg, and with primary PAH, PAH secondary to congenital heart disease, or collagen vascular disease.
    - Study A1481156, long term extension study to A1481131: Same dosing as A1481131 with placebo subjects randomized to low, medium and high doses. Assessed the safety, tolerability and long-term efficacy of sildenafil for 1 year.
- Two dose-ranging studies were additionally performed but were terminated prematurely due to inadequate enrollment.
    - Study A1481134: Phase 2, placebo-controlled, study to assess IV sildenafil citrate in PAH patients with post-corrected Heart Surgery for CHD.
    - Study A1481157: Dose-ranging safety and PK study of IV sildenafil citrate for pulmonary hypertension of the newborn (PPHN).

3.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint in Study A1481131 was measured by determining peak volume of oxygen consumed during exercise (VO_{2peak}) using cardio-pulmonary exercise testing (CPET). VO_{2peak} is a well described measure of exercise capacity in both adults and children and reductions in VO_{2peak} are indicators of reduced exercise, an important measure of physical function in patients with PAH.[1]

In order to minimize diurnal variation, the Week 16/end-of-treatment CPET was performed at the same time of day as the baseline CPET and as close as possible to trough plasma levels of sildenafil. A Week 8 CPET test was performed as close as possible to peak plasma levels of sildenafil (i.e., 1 to 2 hours postdose). The primary efficacy endpoint was the percent change in VO_{2peak} normalized to body weight from baseline to Week 16 assessed by the CPET (cycle ergometry), evaluated in those subjects who were developmentally able to perform the CPET.

The FDA acknowledged that measuring this endpoint in the entire pediatric age range was not feasible. It was subsequently determined at the July 29, 2010 CRDAC meeting that the

hemodynamic measure pulmonary vascular resistance index (PVRI) was used to demonstrate efficacy and derive dosing information across the entire pediatric PAH age range.[2] Within the pivotal trial, hemodynamic measures were obtained as secondary endpoints and were collected from the entire population studied.

Hemodynamic status was assessed at baseline (prior to randomization) to determine eligibility, and at Week 16 (at trough plasma levels of sildenafil) using right heart catheterization. Centers were to ensure that the same method (Fick or Thermodilution method) was used at baseline and at Week 16.

Based on previous clinical experience in adults, a 16-week treatment period assured that a nearly full beneficial exercise effect would be observed for each dose level. Evaluation of the trough effect would help to determine whether the effect of sildenafil was well maintained during each dosing interval. The pre-specified primary efficacy endpoint was the mean response (defined as the percent change from baseline in VO_{2peak} at Week 16) in the 3 sildenafil treatment groups (low, medium and high dose) compared to that in the placebo group for the ITT population.

1. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation*. 2001;104:429–435

2. FDA CRDAC Meeting, July 29, 2010
http://www fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM225329.pdf

3.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Sildenafil citrate and its active metabolite, desmethylsildenafil, were identified and measured in plasma using a validated reversed-phase liquid chromatography and mass spectrometric method. Refer to Section 2.6 for further details regarding analytical methodology and performance. Exposure-response relationships for efficacy and safety were only determined with sildenafil.

3.2.4 Exposure-response

The exposure-response relationship was identified for improvement in exercise capacity and hemodynamics measures after 16 weeks of the sildenafil treatment. The sildenafil low group did not show improvement over placebo while the medium and high groups exhibited mean improvements over placebo for all endpoints. Importantly, a relationship was also observed between exposure and toxicity for adverse events and mortality.

3.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

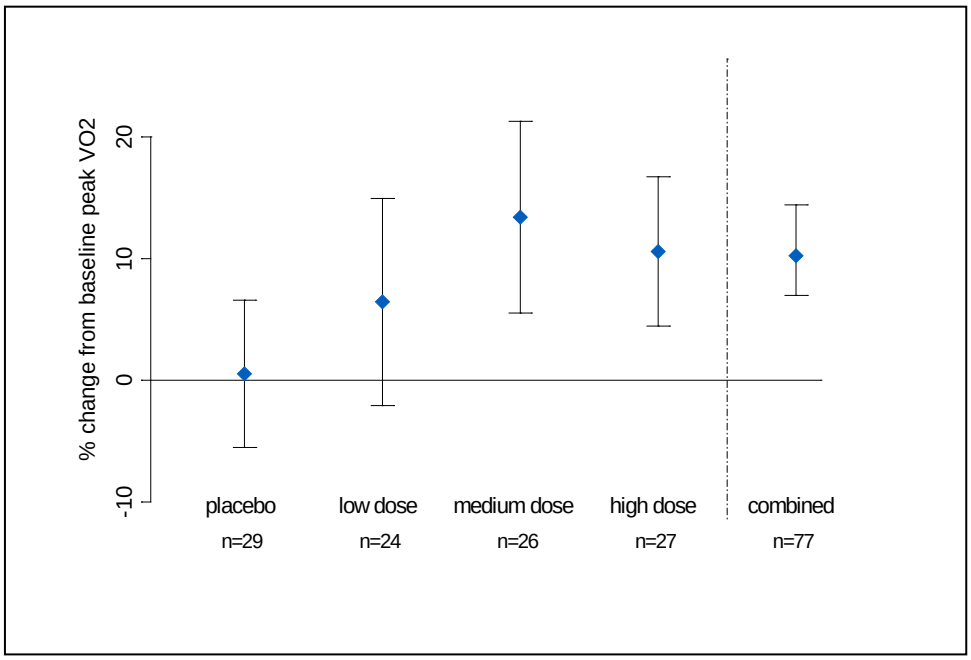
3.2.4.1.1 Exercise capacity (percent change from baseline in VO_{2peak} at 16 weeks)

With regard to the primary endpoint, percent change from baseline in VO_{2peak} at 16 weeks, a trend in the dose-response relationship was observed for the subset population who was able to perform exercise testing (approximately 115/235 randomized, ~49%). For the primary analysis, the sildenafil combined group yielded an improvement of 7.7% (95% CI: -0.19, 15.6; p-value = 0.056) from baseline compared to placebo. The low dose group had a modest increase compared to placebo, while the medium and high dose groups exhibited greater increase compared to placebo (11.3% and 8.0%, respectively). The dose-response relationship is depicted in Figure 1a.

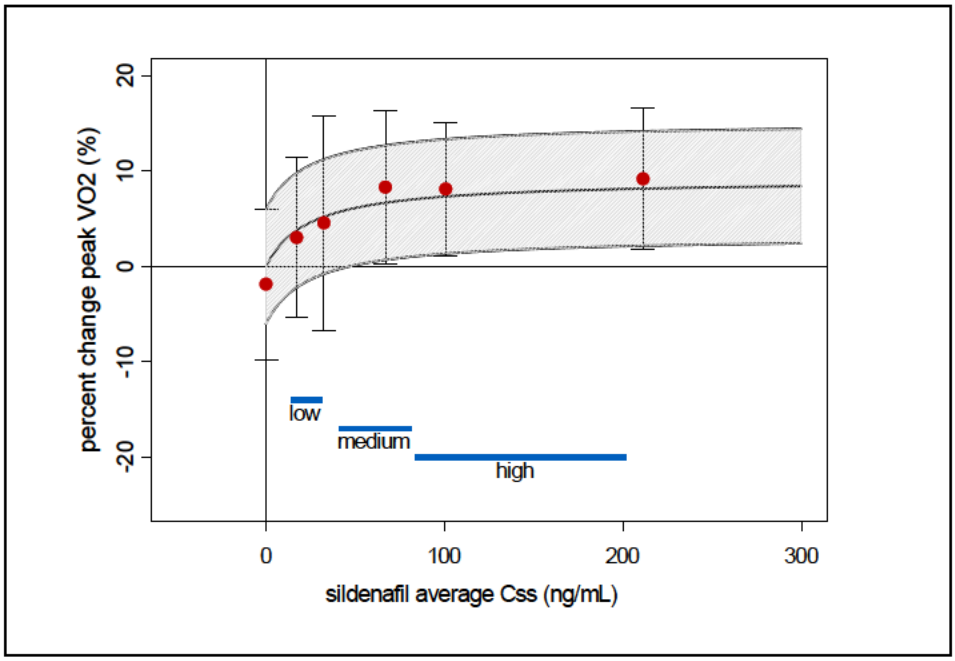
An Emax exposure-response relationship was observed with % change in VO_{2peak} at 16 weeks (Figure 1b) and predicted average sildenafil steady state concentration. A near maximum effect of 9.1% VO_{2peak} change in is achieved at concentrations corresponding to medium and high doses (EC_{50} ~ 24 ng/mL; EC_{90} ~ 100 ng/mL).

Figure 1. a) Dose-response and b) Exposure-response for changes in VO_{2peak} at 16 weeks from baseline (LOCF, ITT population in Study A1481131, mean ± 95% CI)

a) Dose-response



b) Exposure-response



Note: For exposure-response, solid symbols and bars represent the mean and 95% confidence interval of VO_{2peak} increase from baseline for each concentration quantile. The interquartile ranges for the low, medium and high doses are denoted by the horizontal lines. The solid line represents the mean prediction from the Emax relationship and its corresponding 95% confidence interval (shaded region).

A subset of the population supplied a Week 8 measurement of VO_{2peak}, performed at approximate peak sildenafil plasma concentrations (the week 16 measure of VO_{2peak} was taken at trough). For the ITT population, the mean percent change in VO_{2peak} for low, medium and high dose was 0.95, 8.33 and 10.04% change from baseline, respectively. Based on this information, the trend of increasing exercise effect of sildenafil can be observed as early as 8 weeks.

In the long-term extension trial, VO_{2peak} data were primarily collected to assess the maintenance of effects at 1 year. The data demonstrate that VO_{2peak} is maintained with 26/38 subjects (68.4%), 16/36 subjects (44.4%), and 20/40 subjects (50.0%), in the low, medium, and high dose groups, either showing no change or improvement in VO_{2peak} at Year 1 compared to baseline, respectively.

3.2.4.1.2 Pulmonary hemodynamics (percent change from baseline in VO_{2peak} at 16 weeks)

As a secondary endpoint, pulmonary hemodynamics including mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance index (PVRI) were measured in Trial A1481131. Specifically, PVRI was deemed an important measure of treatment response in children to demonstrate efficacy and derive dosing information across the entire pediatric PAH age range where VO_{2peak} is limited only to those children able to perform the test.

For absolute change from baseline in PVRI at 16 weeks, a dose-response relationship was observed for the pediatric population (analysis included 208/235 randomized, ~88.5%). The low dose group had a hemodynamic effect similar to that seen with placebo, while the medium and high dose groups exhibited greater increase compared to placebo (18% and 27%, respectively). The dose-response relationship is depicted in Figure 2a.

An Emax exposure-response relationship was observed with % change in PVRI at 16 weeks (Figure 2b) and predicted average sildenafil steady state concentration. The maximum effect of -30.5% is achieved at concentrations corresponding to the medium dose level (EC50 ~ 62 ng/mL).

For the primary statistical analysis, the log transformed PVRI (ratio to placebo) were analyzed for each dosing arm (Table 2).

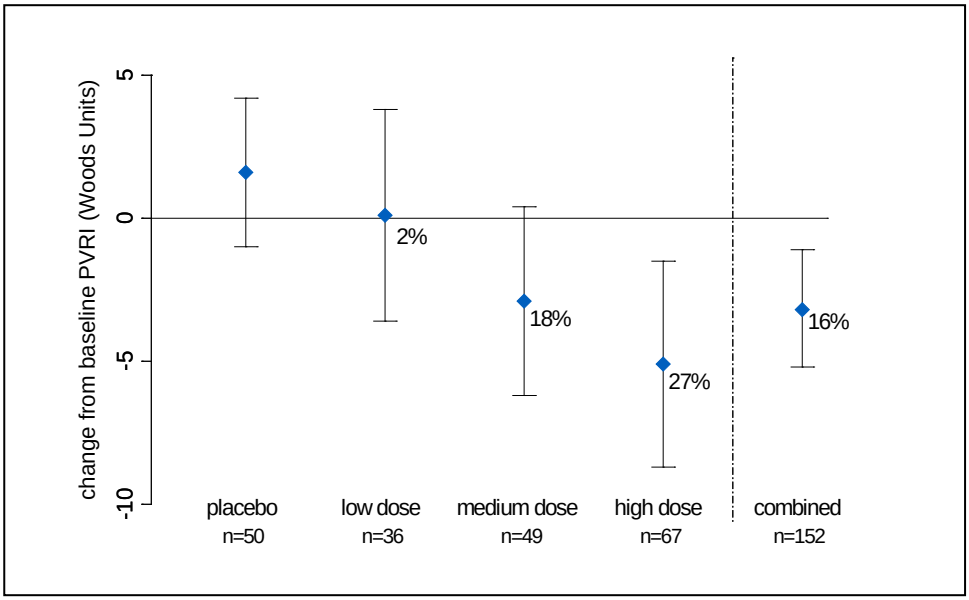
Table 2. Pulmonary Hemodynamics (PVRI) Treatment Comparison to Placebo (n=52)

Treatment group	Number of Subjects	Comparison to Placebo (95% CI)
Low Dose	37	0.98 (0.80, 1.20)
Medium Dose	51	0.82 (0.68, 0.98)
High Dose	68	0.73 (0.61, 0.86)
Combined Doses	156	0.84 (0.72, 0.970)*

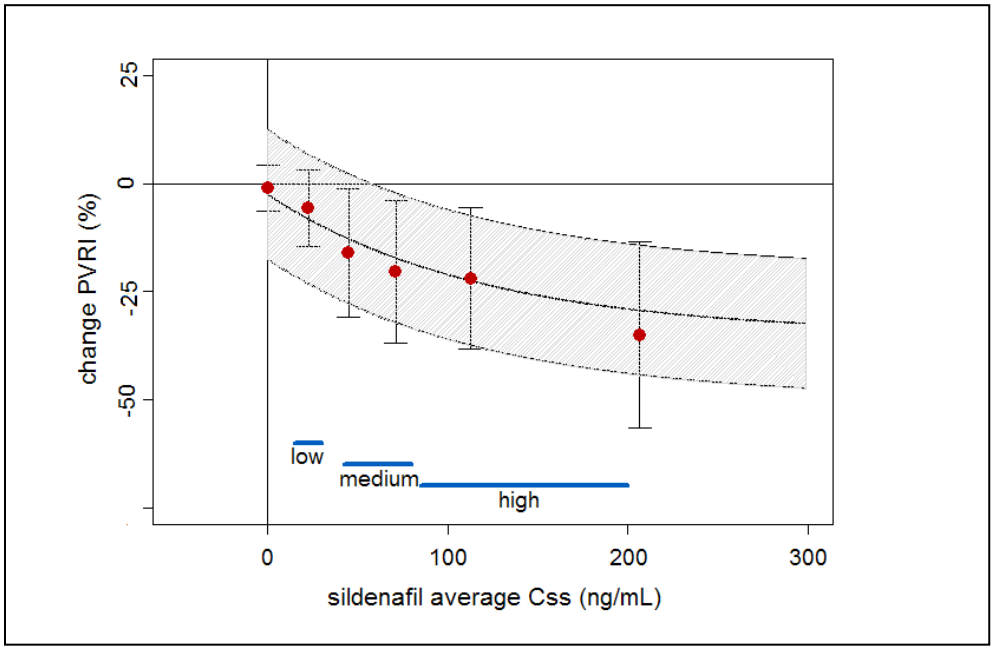
*p-value = 0.041

Figure 2. a) Dose-response and b) Exposure-response for changes in PVRI at 16 weeks from baseline (LOCF, ITT population in Study A1481131, mean ± 95% CI)

a) Dose-response



b) Exposure-response

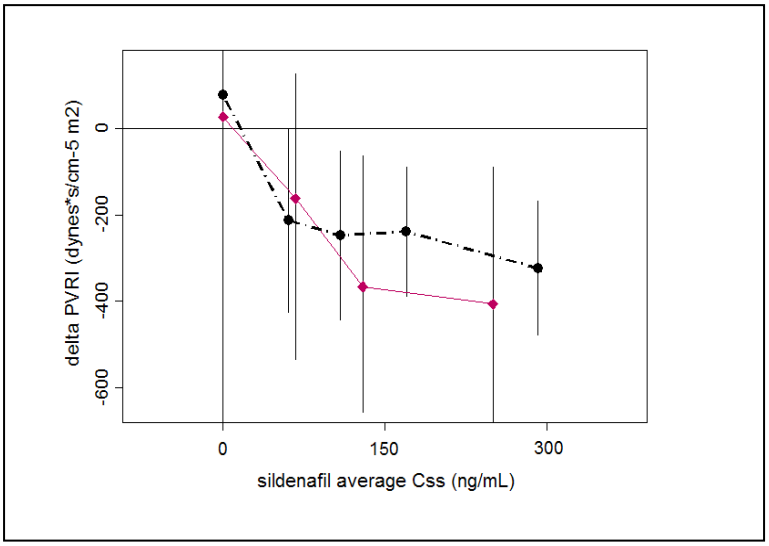


Note: For dose-response the percentages next to the point estimate are placebo-corrected. For the exposure-response, solid symbols and bars represent the mean and 95% confidence interval of PVRI decrease from baseline for each concentration quantile. The interquartile ranges for the low, medium and high doses are denoted by the horizontal lines. The solid line represents the mean prediction from the Emax relationship and its corresponding 95% confidence interval (shaded region).

Dose-response was also observed for mPAP, but the primary analysis deemed to be not significant upon comparison of the placebo group to the pooled doses (p-value = 0.172)

The analyses from the pharmacometric reviewer suggest that the concentration-response relationship of sildenafil for change in PVRI is consistent across the entire studied pediatrics and adults. Pooling exposure-response data in Study A1481140 (adults) and Study A1481131 (peds), shows similarity of the relationship between the populations (Figure 3).

Figure 3. Pooled exposure-response for changes in PVRI from baseline to the last treatment (based on the observed trough concentrations of active arms)



Baseline PVRI (dyne • s/cm^5 m^2)

Pediatrics – Study A1481131 (solid line)
range: 1222-1742

Adults – Study A1481140 (dashed line)
range: 1479-1810

Note: For the exposure-response, solid symbols and bars represent the mean and 95% confidence interval of PVRI decrease from baseline for each concentration quantile. The solid line represents the pediatric data while the dashed line represents the adult data.

3.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

The safety data evaluated from this submission is derived from studies A1481131 (16 weeks duration) and the long-term extension study A1481156 (in which all subjects had the potential to have been in the study for at least 3 years from the start of study A1481131). Of major note, a dose-response relationship (randomized dose) on mortality was observed in the long-term extension.

3.2.4.2.1 Trial A1481131

In the randomized phase of pivotal trial A1481131, treatment with sildenafil at daily doses of 10 mg to 20 mg in children weighing 8 to 20 kg and doses of 10 mg to 80 mg in children weighing >20 kg was well tolerated. The safety/tolerability profile of sildenafil as treatment of pulmonary hypertension in pediatrics is consistent with the experience of treating adults. Adverse events reported more frequently than placebo (>2%) included pyrexia, upper respiratory tract infection (URTI), nausea, vomiting and bronchitis. A dose response relationship was observed for pyrexia and vomiting. Table 3 summarizes the percentage of patients that experiences the safety event, by dose group. There were no on treatment deaths in the pivotal trial (double blinded phase of 16 weeks). The shaded rows signify the adverse event that showed a dose-response.

Table 3. Dose-response for safety of sildenafil in pediatrics during randomized portion of A1481131

Event	Placebo N=60	Low N=42	Medium N=55	High N=77	Sildenafil All N=174
TEAE (all causality)	67%	69%	80%	70%	73%
TEAE (treatment related)	23%	26%	24%	28%	26%
Pyrexia	1.7%	***7.1%***	***14.5%***	***24.7%***	11.5%
URTI	6.7%	11.9%	16.4%	11.7%	12.1%
Nausea	0%	0%	7.3%	5.2%	4.6%
Vomiting	6.7%	***7.1%***	***9.1%***	***14.3%***	10.9%
Bronchitis	1.7%	4.8%	9.1%	3.9%	5.7%

Compared to adults, the overall incidence of all-causality adverse events for all sildenafil-treated groups combined was lower (72.4% in Study A1481131, compared to 89.9% in Study A1481140 (adult study)). Similarly, serious adverse event reporting rates were lower in Study A1481131 compared with Study A1481140 (3.3% placebo vs. 9.9% sildenafil in children compared with 17% placebo vs. 15% sildenafil in adults). The adverse event profile sildenafil in children was consistent with those expected in the PAH disease population and with patients receiving PDE5 inhibitors.

3.2.4.2.2 Trial A1481156 – Survival Analysis

The DMC convened on July, 26 2011 to review the current safety data provided in this submission. At the time of the DMC meeting, a total of 35 deaths had been reported. Of these, 26 had been reported as being on-treatment and 9 as off-treatment deaths (ranging from 9 to 406 days post-treatment). Five (5) of the 35 deaths were in the low dose group (5/55; 9%), 10 were in the medium dose group (10/74; 14%), and 20 were in the high dose group (20/100; 20%) according to the randomized sildenafil treatment in Study A1481131 and the long-term extension Study A1481156. Patients that were randomized to placebo in Study A1481131 were further randomized to low, medium or high dose in the long-term extension study. The hazard ratio for mortality in the high dose group compared with the low dose group was 3.5 (95% CI: 1.29 to 9.51), while the hazard ratio for mortality in the medium dose group compared with the low dose group was 1.85 (95% CI: 0.63 to 5.44). The number of deaths is reported in the Table 4 below.

Table 4. Dose-response for mortality in pediatrics during the long-term extension Study A1481156

Randomized Dose for 1131	Randomized Dose for 1131/1156	Total Deaths	%
Low	Placebo/low	5/55	9%
Medium	Placebo/medium	10/74	13.5%
High	Placebo/high	20/100	20%

*Total deaths refer to deaths stratified by initial randomized dose in addition to the dose randomized to in the extension trial. Those patients randomized to the placebo arm in A1481131 were randomized to low, medium or high dose in the long-term trial.

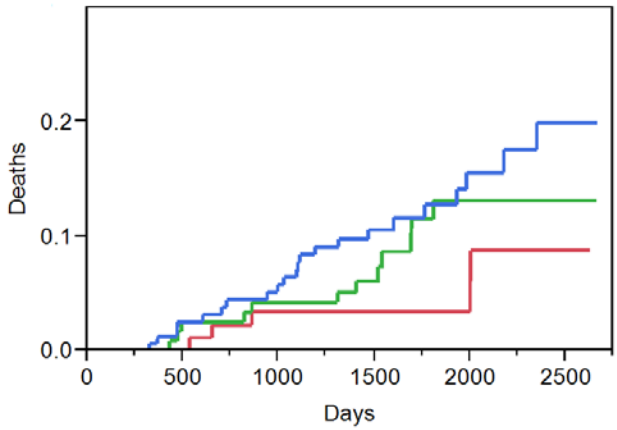
Evaluation of the individual stratified dosing cohorts also revealed an imbalance in deaths across dosing groups, in a dose-response manner. Results on Table 5 also show that subjects who initially received placebo in A1481131 and further randomized to sildenafil in the long-term extension, had better survival compared to those who received sildenafil from the start. This suggests a 16 week delay in treatment would confer long-term survival benefit (which there is no physiologically conceivable explanation). The sponsor reports that majority of deaths are due to the PAH disease worsening and, ultimately, right heart failure.

Table 5. Dose-response for mortality in pediatrics during the long-term extension Study A1481156

Dose for 1131	Dose for 1156	Total Deaths	%
Low	Low	5/42	12%
Medium	Medium	9/55	16.4%
High	High	17/77	22.1%
Placebo	Low	0/13	0%
Placebo	Medium	1/19	5.3%
Placebo	High	3/23	13%

At 3 years, 48/55 (87%), 65/74 (88%), and 80/100 (80%) subjects were known to be alive in the low, medium, and high dose groups, respectively (assumes all subjects where survival status was unknown had died). Evaluation of the event rate / year also shows a dose-response relation with patients randomized to a high, medium, and low dose at an event rate ~5%, 3.5% and 1.9%, respectively (table in Figure 4).

Figure 4. Failure plot for death in the long term extension trial A1481156 (based on randomized dose of active arms)



Treatment	Total N	Event rate / year (95%CI)
High	20/100	4.9% (3.8 – 5.7%)
Medium	10/74	3.5% (2.1 – 4.8%)
Low	5/55	1.9 (0.4 – 3.4%)

*the red, green, and blue line represents the probability of deaths over time for the randomized low, medium and high dose groups, respectively.

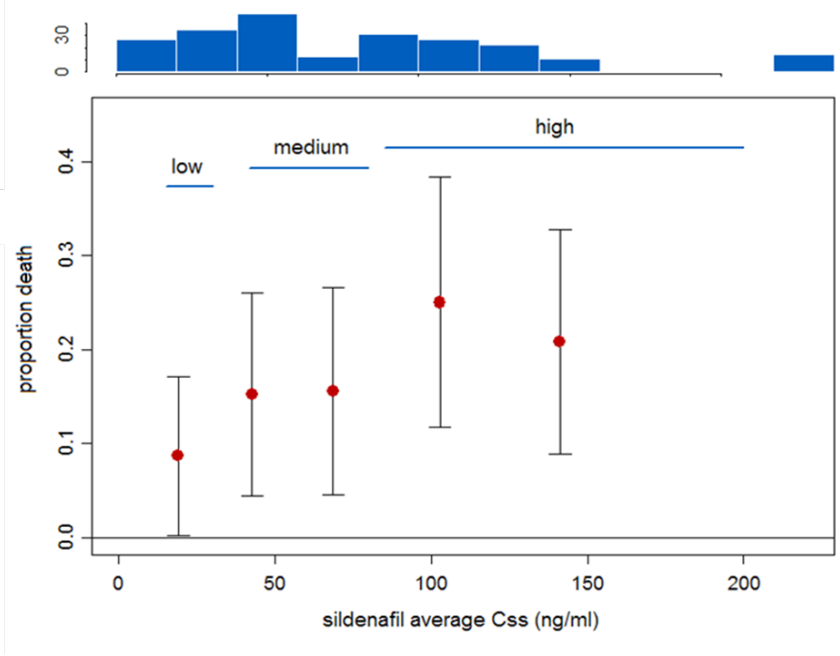
In comparison to historical control, the survival rates obtained in this trial are higher than reported in children with PAH prior to the availability of targeted PAH therapies. Survival at three years was 87%, 88% and 80% for low, medium and high doses, respectively. Prior to available therapies, the estimated survival for pediatric patients with PAH ranged from 29-52%.[3] Recent registry information for pediatric patients with PAH estimates a 3 year survival at 83%.[4]

To further explore the influence on sildenafil exposure on mortality, exposure-response analysis was performed using predicted concentrations from the population PK (POPPK) model. It should be noted, the POPPK prediction assumes compliance to the treatment by all patients. Predicted average steady state concentrations (for the randomized dose) were binned into quantiles and the proportion of deaths were determined for each bin. Figure 5 depicts a positive exposure-response relation increase with the proportion of deaths (i.e., increase in exposure yielding increase proportion of deaths). The bins within the high dose exposure group are different with the bin at corresponding to the highest concentration having a numerically lower proportion of deaths. Upon further scrutiny of the subjects who were randomized to high dose, the exposure-response relationship is directed in the opposite direction, with higher exposure yielding a lower proportion of deaths (Figure 6). This phenomenon was not observed in the low and medium dose groups. Of note, this exposure-response phenomenon for the high dose group was also seen using mg/kg dose as an exposure metric. These findings were consistent when the analyses were performed with the predicted steady-state concentration for the modal doses.

[3] Widlitz A and Barst RJ. Pulmonary hypertension in children. Eur Respir J 2003; 21(1): 155-76.

[4] Hislop A, Moledina S, Foster H, et al. Long-term efficacy of bosentan in treatment of pulmonary arterial hypertension in children. Eur Resp J 2011; 38: 70-77.

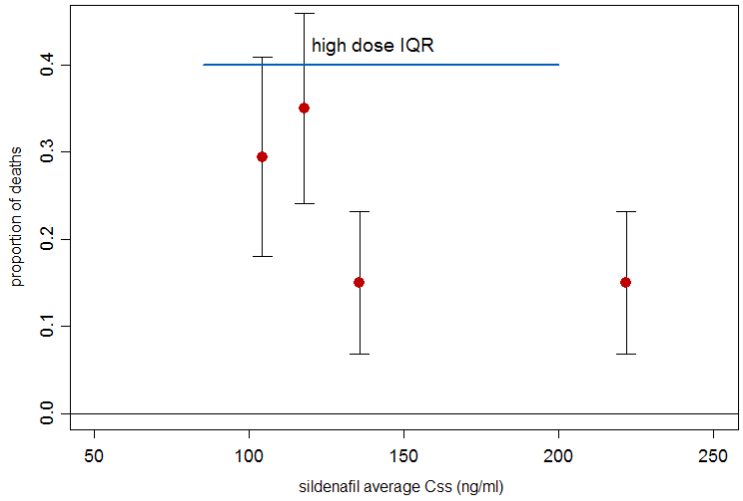
Figure 5. Exposure-response for death in the long term extension trial A1481156 (based on population predicted average steady state concentrations)



Bin	N	Median conc (ng/mL)	Proportion of deaths
1	46	19.0	0.09
2	46	42.6	0.15
3	45	68.6	0.16
4	44	102.8	0.25
5	48	141.2	0.21

Note: For the exposure-response, solid symbols and bars represent the mean and 95% confidence interval of the proportion of deaths for each concentration quantile. The interquartile ranges for the low, medium and high doses are denoted by the horizontal lines. The histogram above represents the distribution of sildenafil average steady state concentration across the population analyzed.

Figure 6. Exposure-response for death in the long term extension trial A1481156 for the patients randomized to the high dose group



Bin	N	Median conc (ng/mL)	Proportion of deaths
1	17	104.2	0.29
2	20	117.8	0.35
3	20	135.6	0.15
4	20	221.9	0.15

The dose-response relationship with mortality presented thus far pertains to the assigned randomized dose at the beginning of the randomized phase and the long-term extension. During the long-term extension, titrations were allowed, potentially confounding the mortality dose-response relationship (Table 6).

Table 6. Dose titrations by dosing group in long term extension trial

	Low Dose (N=55)	**Medium Dose (N=74)**	**High Dose (N=100)**
At least one titration	28% (51)	11 (15%)	13 (13%)
1 up titration	20 (36%)	8 (11%)	8 (8%)
2 up titrations	8 (15%)	3 (4%)	5 (5%)
Dose increases due to weight increase	18 (33%)	36 (49%)	39 (39%)

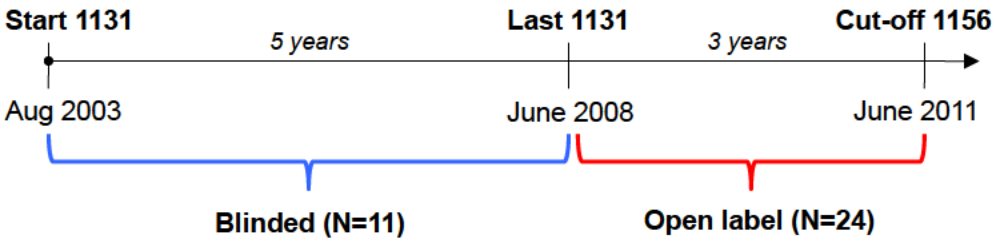
To account for the titration, modal dose (the dose that the patient was on for majority of the trial) was assessed for a dose response relationship with mortality (Table 7). According to the assessment via modal dose (last column), ***the low and medium doses are similar in proportion of deaths while the high dose shows higher mortality.***

Table 7. Shift table for Randomized and Modal Dose Groups, N (deaths)

	Randomized Dose			
Modal Dose	Low	Medium	High	Total
Low	41 (4)	**0**	**0**	41 (4, 10%)
Medium	**1**	64 (9)	**2**	67 (9, 13%)
High	**4**	**3 (1)**	86 (19)	93 (20, 22%)
Off-treatment	**9 (1)**	**7**	**12 (1)**	28 (2, 7%)
Total	55 (5, 9%)	74 (10, 14%)	100 (20, 20%)	229 (35)

Upon evaluation of the mortality dose-response information during the blinded phase (between August 2003 and June 2008) and open-label phase (August 2008 and June 2011), a disproportionate number of subjects died in the open-label phase of the study (n=11 subjects in the blinded period vs. n=24 subjects after un-blinding). To prevent treatment un-blinding in A1481131, double-blind was maintained in A1481156 until the last subject had completed A1481131. The Study A1481131 database was locked (June 2008). Since that time A1481156 had continued as an open-label study. Figure 7 depicts the time frame of the start of the randomized trial, the time of un-blinding and the cut-off date for the safety analysis by the Data Monitoring Committee (DMC) in June 2011.

Figure 7. Mortality dose-response pre- and post-blinding of trial A1481156



Dose group	ALL	Blinded (%)	Open-label (%)
Low	5/55 (9%)	2/55 (3.6%)	3/55 (5.4%)
Medium	10/74 (13.5%)	4/74 (5.4%)	6/74 (8.1%)
High	20/100 (20%)	5/100 (5%)	15/100 (15%)

Based on the assessment of the number of deaths before and after blinding of the long-term extension trial, the following interpretations can be made:

1) More than twice the number of deaths occurred after 5 years since the start of the randomized trial A1481131.

2) The dose-response relationship for mortality is not evident during the well-controlled, blinded phase of the trial, which lasted 5 years.

3) The dose-response relationship for mortality is observed only after unblinding (i.e., high dose having more deaths than medium and low dose groups)

4) The overall mortality dose-response relationship is driven by the open-label portion of the trial.

3.2.4.3 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The dose and dosing regimen proposed by the sponsor in pediatrics is consistent with the known relationship between dose-concentration-response in adults. The doses of sildenafil used in adult and pediatric studies were over a similar range. The exposures of the medium and high sildenafil doses in the pediatric study approximate to the exposures of sildenafil 20 mg TID and 40 mg TID, respectively, in the adult study. The clearance in heavier children (>40 kg) is similar to adults. In lighter children, the change in plasma clearance was less than proportional to changes in body weight.

As shown in Table 8, the studied dose that produces a maximum effect yields a similar improvement in exercise capacity and similar reduction in PVRI in pediatric subjects 1 to < 17

years of age and adults. This assessment is based on the comparison of the currently approved dose in adults (20 mg TID) and the pooled effect of medium and high doses in pediatric population.

Table 8. Comparison of Exercise Capacity and Pulmonary Vascular Resistance Index Effect in pediatric (medium and high doses pooled) and adult (20 mg TID) populations

	Placebo corrected % change from baseline	95% CI
Exercise capacity*		
Adults (A1481140)	13.10	(5.2, 21.3)
Pediatrics (A1481131)	9.65	(1.3, 18.0)
PVRI		
Adults (A1481140)	21.20	(10.5, 29.9)
Pediatrics (A1481131)	22.80	(10.1, 34.1)

A major finding in this dosing assessment is the dose-response relation on mortality in the pediatric long-term extension trial. This phenomenon was not observed in the adult trials and casts a negative benefit/risk profile for dosing sildenafil in pediatric population. The current proposed regimen (b) (4)

3.2.5 What are the pharmacokinetic characteristics of sildenafil in children with PAH 1 to < 17 years of age

The doses administered in trial A1481131 were dependent on body weight (see Table 9 below). The 3 target plasma sildenafil concentrations (47, 140, and 373 ng/mL) were selected such that the unbound sildenafil concentrations would be expected to be similar to sildenafil concentrations that produced approximately 53%, 77%, and 90% inhibition of PDE5 activity in the in vitro assay. Sildenafil dose levels were then selected based on body weight such that these approximate target plasma concentrations would be achieved at steady-state.

An active metabolite of sildenafil, UK-103,320, has approximately one-half the potency of sildenafil as a PDE-5 inhibitor and is predicted to contribute approximately 20% to the pharmacological effect observed after oral dosing with sildenafil. In pediatrics, the PK is similar to adults and the ratio of the major circulating active metabolite (UK-103,320) to sildenafil at steady-state is 47%, which is consistent with the ratio of 54% seen in adults.

Table 9. Sildenafil doses (mg) given TID for the Pivotal trial in Pediatrics (Study A1481131)

BW Group (kg)	**Low Dose**	**Medium Dose**	**High Dose**
≥8 – 20	NA*	10	20
>20 – 45	10	20	40
>45	10	40	80

*low dose was predicted to be around 5 mg for the 8 to 20 kg subjects. Since the available lowest tablet strength was 10 mg, the same dose as that for the medium dose group, it was decided to exclude the low dose group for this weight group and randomize these patients to medium or high dose, or placebo. Proportionally more 8 to 20 kg subjects were randomized into the high dose group.

Table 10 and Table 11 display the pharmacokinetic parameters of sildenafil in children 1- 17 year of age, sub-grouped by body weight, following repeated dosing in trial A1481131.

Table 10. Summary of sildenafil clearance (CL/F) in children 1-<17 years of age following TID dosing in Trial A1481131

	Low Dose		**Medium Dose**		**High Dose**	
	Dose, *N*		Dose, *N*		Dose, *N*	
Weight Group (kg)	Geometric mean (L/h)	CV%	Geometric mean (L/h)	CV%	Geometric mean (L/h)	CV%
≥8 – 20	NA, NA		10 mg, *15*		20 mg, *33*	
	--	--	**29.4**	44.8	**23.3**	50.0
>20 – 45	10 mg, *30*		20 mg, *29*		40 mg, *29*	
	52.5	44.4	**48.2**	51.2	**42.5**	33.6
>45 – 122	10 mg, *10*		40 mg, *9*		80, *11*	
	87.1	50.2	**51.9**	28.4	**36.5**	34.2

Table 11. Summary of sildenafil exposure (predicted AUC) in children 1-<17 years of age following TID dosing in Trial A1481131

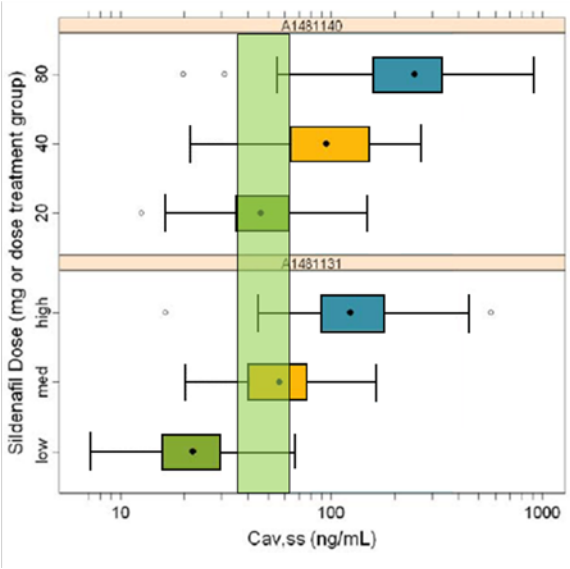
Weight Group (kg)	Low Dose		Medium Dose		High Dose	
	Dose, *N*		Dose, *N*		Dose, *N*	
	Geometric mean (ng*h/mL)	CV%	Geometric mean (ng*h/mL)	CV%	Geometric mean (ng*h/mL)	CV%
8 – 20	NA, NA		10 mg, *15*		20 mg, *33*	
	--	--	**339.6**	44.8	**857.8**	50.0
>20 – 45	10 mg, *30*		20 mg, *29*		40 mg, *29*	
	190.5	44.4	**425.4**	51.2	**941**	33.6
>45 – 122	10 mg, *10*		40 mg, *9*		80, *11*	
	114.8	50.2	**769.5**	28.4	**2193.6**	34.2

Based on results from adult PAH patients (Study A1481140) having received sildenafil orally, body weight (range 41 – 122 kg) and age did not affect apparent oral plasma clearance (CL/F), with the exception of the high dose group (systemic exposure is increased). This was also observed in adult studies at doses higher that 40 mg TID.

A population PK analysis was performed on the pediatric data from trial A1481131 and A1481140. The pediatric population, upon comparison of steady state concentrations with adults, showed an overall decreased exposure (see Figure 8) across the dose groups. The maximum apparent oral plasma clearance (CL/F) estimated in this combined analysis of 57.2 L/h is consistent with the previously reported value of 50.9 L/h obtained in adults. The CL/F in heavier children (>40 kg) is similar to adults. In lighter children, the change in CL/F was less than proportional to changes in body weight.

Sildenafil doses used in adult and pediatric studies were over a similar range, but exposures differed. The figure below shows how the estimated exposures for adult treatment groups in Study A1481140 (20 mg TID, 40 mg TID, 80 mg TID) compared to the treatment dose groups in children in Study A1481131 (low, medium and high treatment dose groups). The exposures of the medium sildenafil dose in pediatrics approximate to the exposures of sildenafil 20 mg TID in adults. The low dose group in the pediatric trial appears to produce an exposure below the intended concentration level (IC50 for PDE5~ 47 ng/mL).

Figure 8. Boxplot of predicted average steady state sildenafil concentrations for adults (Study A1481140: 20, 40 and 80 mg TID) and pediatrics >45 kg, >20 to <45kg and 8 to 20 kg weight groups that were randomized to a high (blue), medium (yellow) or low (green) dose.



* Black symbol represents median. Green shaded bar represents interquartile range of the steady state concentration for the approved adult dosing regimen of 20 mg TID.

3.3 INTRINSIC FACTORS

3.3.1 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

3.3.1.1 Pediatric patients

Pharmacokinetics, efficacy and safety of sildenafil have been established in subjects with PAH between 1 to <17 years of age. For pediatric patients >45 kg, the PK profile of sildenafil was generally comparable to adults, with the exception of the low dose. A systematic decrease of exposures is observed within each dosing group for patients <45 kg. Based on average steady state concentrations, dosing that would obtain exposures equivalent to the approved adult dose of 20 mg would include the following:

Table 12. Body weight stratified sildenafil doses (mg)

BW Group (kg)	**Recommended Dose equivalent to 20 mg in Adults**
	(b) (4)

The degree of exercise improvement and PVRI reduction amongst pediatrics and adults is similar (Table 8). Because sildenafil is well tolerated across the studied pediatric and adult population, the near maximum-effect starting dose selection strategy in pediatrics as in adults is reasonable.

3.3.1.2 Renal and Hepatic Impairment

No specific study has been conducted in pediatrics with renal or hepatic impairment. In adults, no dose adjustments are required for renal impairment (including severe impairment CLcr < 30 ml/min). Trial A1481131 included pediatric patients with a mean baseline CLcr of 110.4 ml/min (range: 33.6 – 266.7 ml/min). From the population analysis results, renal function did not have influence on sildenafil clearance. Based on this analysis, dose adjustment is not necessary for pediatric patients with renal impairment. This is consistent with the recommendation in adults that no initial dosage adjustment is necessary for patients with mild to moderate impairment in renal function.

With respect to adults with hepatic impairment, mild to moderate requires no dose adjustment. Adult patients with severe hepatic impairment have not been studied. Population analysis did not find baseline ALT (mean 18.5 U/L; range 7.3 – 55.9 U/L) or AST (mean 29.0 U/L; range 15.3 – 47.6 U/L) as a significant covariate for sildenafil clearance. These lab values are within normal range, therefore lack of significance in the covariate analysis is not unexpected.

3.4 EXTRINSIC FACTORS

Population PK analysis deemed beta blockers and CYP3A4 inhibitors as significant covariates, decreasing oral clearance by 34% and 30%, respectively. The increase in exposure resultant by decreases in oral clearance is not expected to be clinically relevant. It should be noted that the estimated effect of beta blockers on sildenafil comes from only one subject and thus the estimate should not be considered precise. These results are concordant to what is observed in adults.

3.5 GENERAL BIOPHARMACEUTICS

3.5.1 What is the relative bioavailability of sildenafil powder for oral suspension compared to sildenafil tablets?

There was no statistically significant difference in sildenafil $AUC_{0-\infty}$ and C_{max} systemic exposures between the intact tablet and the powder for oral suspension, the to-be-marketed formulation (Table 13). An OSI inspection of the clinical and bioanalytical site was requested for this pivotal BE study. The final recommendation of BE will depend on the overall recommendation by the OSI.

Table 13. The relative bioavailability of sildenafil suspension to sildenafil tablets in adult healthy volunteers

		Geometric Mean			Ratio	90% CI	
Parameter	N	Suspension (S)	N	Tablet (T)	S/T	Lower	Upper
$AUC_{0-\infty}$ (ng•h/mL)	42	166.6	42	184.0	90.6	85.5	95.9
C_{max} (ng/mL)	42	71.9	42	75.7	94.9	85.5	105.5

In the pivotal trial for pediatrics, the powder for oral suspension was not available. During the trial, an extemporaneously prepared suspension was given to pediatric patients that were unable to swallow the intact tablet. An adult relative BE study was conducted in order to bridge the exposure information obtained from extemporaneously prepared formulation to the intact tablet.

There was no statistically significant difference in sildenafil $AUC_{0-\infty}$ systemic exposure between the intact tablet and the extemporaneously prepared suspension. On the other hand, the sildenafil extemporaneously prepared suspension and tablet are not equivalent in terms of C_{max}, since the lower bound of the 90% CI is less than 80% (Table 14). The efficacy and safety results were consistent across the formulations and study groups. Considering the drug is well-tolerated and the beneficial effects of sildenafil is not considered to be C_{max} related, the minimal difference in C_{max} between the extemporaneously prepared suspension and tablet is not clinically relevant.

Table 14. The relative bioavailability of an extemporaneously prepared sildenafil suspension to sildenafil tablets in adult healthy volunteers

		Geometric Mean			Ratio	90% CI	
Parameter	N	Suspension (S)	N	Tablet (T)	S/T	Lower	Upper
$AUC_{0-\infty}$ (ng•h/mL)	18	207.9	18	199.5	104.2	97.3	111.6
C_{max} (ng/mL)	18	79.6	18	93.4	85.2	76.1	95.4

3.6 ANALYTICAL SECTION

3.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

A brief summary of the different bioanalytical methods used is shown in Table 15. Accepted validation indicates that accuracy and precision of the quality control samples met the FDA guidance "Bioanalytical Method Validation" recommendations. Acceptability of quality control sample performance during unknown plasma sample analysis is also indicated in Table 15.

Table 15. Summary of the bioanalytical methods used in the clinical studies

Report #	Type	Analyte(s)	Matrix	Calibration Range	Validation	Study Sample Performance
2100-530 (All Studies)	HPLC-MS/MS	Sildenafil and desmethylsildenafil	Plasma	1 – 500 ng/mL	Acceptable	Acceptable

3.6.2 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Total drug was measured for all moieties.

4 DRAFT LABELING RECOMMENDATIONS

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

2 DOSAGE AND ADMINISTRATION

(b) (4)

APPENDIX (CLINICAL PHARMACOLOGY – INDIVIDUAL STUDY REVIEW)

APPEARS THIS WAY ON ORIGINAL

Study# 1481293: Relative BE of Powder for Oral Suspension (POS) Formulation

Report #	A1481293
Investigator(s)	Pfizer, Inc.: Dr Laure Mendes da Costa
Study Site	Belgium (1), Center #1001
Study Period	1/17/2011 – 2/7/2011

Title

A Pivotal Randomized, Open-Label 3-Way Crossover Study to Demonstrate Bioequivalence of the Sildenafil Citrate Powder for Oral Suspension (10 mg/mL) and the Sildenafil Citrate 10 mg Immediate Release (IR) Tablet Relative to the Revatio 20 mg IR Tablet in Healthy Volunteers Under Fasting Conditions.

Objectives

Primary objective(s):

- To demonstrate bioequivalence of a 20-mg dose of the sildenafil citrate pediatric POS formulation (10 mg/mL) to Revatio 1 x 20 mg IR oral tablet;
- To demonstrate bioequivalence of the 2 x 10 mg sildenafil citrate oral IR tablet relative to the intact Revatio 1 x 20 mg oral IR tablet; and
- To estimate the relative bioavailability of a 20-mg dose of the sildenafil citrate pediatric POS formulation (10 mg/mL) to the 2 x 10 mg sildenafil citrate oral IR tablet.

Secondary objective(s):

- To evaluate the safety and tolerability of a 20-mg dose of the sildenafil citrate pediatric POS formulation, the 2 x 10 mg sildenafil citrate IR oral tablet, and the Revatio 1 x 20 mg IR oral tablet in healthy volunteers.

Test Drug

All subjects received the following treatments:

- Treatment A: Revatio 1 x 20 mg IR oral tablet;
- Treatment B: 2 x 10 mg sildenafil citrate IR oral tablet; and
- Treatment C: 2 mL of the sildenafil citrate 10 mg/mL POS (provided as a powder in a bottle for constitution with water).

The following lot (and formulation identification) numbers were used:

Study Drug[a]	Dosage Form	Lot Number	Lot Size	Dosage Material Number
Sildenafil citrate 10 mg	Film-coated tablet	07-061004	(b) (4)	(b) (4)
Sildenafil citrate 10 mg/mL	Powder for oral suspension	10-082576		

Source: pg 20 of Clinical Study Report A1481293

Study Design

This study was a randomized, open-label, 3-treatment, 3-period, crossover, single-dose study in

healthy subjects. Forty-two (42) subjects were to be enrolled in the study. Following an 8-hour fast, subjects received study medication at approximately 0800 hours (±2 hours). Investigator site personnel administered study medication during each period with ambient temperature water to a total volume of 240 mL. In the case of Treatments A and B, subjects swallowed the study medication whole and did not chew the medication prior to swallowing. For Treatment C, subjects were given 2 mL of POS (10 mg/mL) by mouth via an oral syringe. In order to standardize the conditions on PK sampling days, all subjects refrained from eating food, and drinking beverages other than water during the first 4 hours after dosing.

Blood Sampling for Pharmacokinetics

During all study periods, blood samples (5 mL) to provide a minimum of 2 mL of plasma for PK analysis were collected into appropriately labeled tubes containing lithium heparin at the following times: predose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 14 hours postdose. Blood samples were centrifuged at approximately 1700×g for about 10 minutes at 4°C within 1 hour of collection. The plasma aliquot was stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C. Plasma samples were analyzed using a validated analytical method.

Bioanalytical Section

The analytical report for study A1481293 is summarized in Report 2100-530. Heparinized plasma samples were assayed by (b) (4) for sildenafil and desmethyl sildenafil using a previously validated method employing solid phase extraction followed by HPLC-MS/MS. The overall method imprecision values (CV) for the analysis of plasma quality control (QC) samples at concentrations of 3, 30, and 350 ng/ml were ≤6.3% for sildenafil and ≤ 5.3% for desmethylsildenafil. The mean inaccuracy (bias) of the assay ranged from +1.7 to +5.7% for sildenafil and -2.0 to +8.0 over the QC concentration range. The calibration range was 1 to 500 ng/mL for sildenafil, with an LLOQ of 1.0 ng/mL.

Pharmacokinetic and Safety Evaluations

PK parameters for sildenafil following single-dose administration were calculated for each subject for each treatment using noncompartmental analysis of plasma concentration-time data. Plasma concentrations below the LLOQ were set to 0 ng/mL for analysis. Actual PK sampling times were used in the derivation of PK parameters. The schedule of assessments is provided in the table below.

Protocol Activity	Screen	Periods 1 through 3														
		Day 0[b]	Day 1													
			Time Postdose (hours)													
			Predose	0	0.25	0.5	0.75	1	1.5	2	3	4	6	8	10	12	14
Informed consent	X																
Medical history	X	X															
Drug/alcohol/tobacco history	X	X															
Physical examination[a]	X	X															X[c]
Single 12-lead electrocardiogram	X																
Single supine and standing vital signs (blood pressure, pulse rate, and body temperature)	X[f]		X														X
Urine drug screen	X	X[d]															
Admission to CRU		X[e]															
Randomization			X[b]														
Study treatment				X													
Safety laboratory tests	X	X															X[c]
Pregnancy test[g]	X	X[d]															X
Follicle-stimulating hormone	X[h]																
Pharmacokinetic blood samples			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medication	X	X	----------X----------														X[c]
Baseline symptoms/AE monitoring	X	X	----------X----------														X
Discharge from CRU																	X[e]

Source: Section 16.1.1.
CRU = clinical research unit; AE = adverse event;
[a] A full physical examination including height and weight at screening and brief physical examinations on Day 0 of Period 1 and prior to discharge in Period 3 (only if previous finding or open/new AEs) were performed. The Screening physical examination could have been deferred to Day 0 of Period 1.
[b] Period 1 only.
[c] Prior to discharge from the CRU in Period 3 only, or upon study discontinuation/early termination.
[d] All periods requiring admission to the CRU.
[E] Subjects could have stayed at the CRU between periods.
[f] Assessed for orthostatic hypotension at screening.
[g] Females of childbearing potential only. During the main phase of the study, a pregnancy test could have been performed either on Day 0 or Day 1 prior to dosing.
[h] Post-menopausal females only, and amenorrheic for at least 2 years.

Source: pg 16 of Clinical Study Report A1481293

Subjects

A total of 42 healthy, adult subjects were randomized for the study, and all 42 subjects were treated and completed each study treatment.

Pharmacokinetic Results

The PK results for the study are provided in the table below.

Parameter (units)	Adjusted Geometric Means		Ratio (Test/Reference) of Adjusted Means[a]	90% CI for Ratio
	Test	Reference		
Sildenafil 20 mg (2 mL) POS (Test) versus REVATIO 20 mg IR Tablet (Reference)				
AUC_{inf} (ng*h/mL)	166.6	184.0	90.57	(85.54, 95.90)
AUC_{last} (ng*h/mL)	161.3	178.6	90.35	(85.17, 95.84)
C_{max} (ng/mL)	71.91	75.74	94.95	(85.48, 105.46)
Sildenafil 2 x 10 mg Tablets (Test) versus REVATIO 20 mg IR Tablet (Reference)				
AUC_{inf} (ng*h/mL)	184.9	184.0	100.52	(94.83, 106.55)
AUC_{last} (ng*h/mL)	178.3	178.6	99.82	(94.10, 105.89)
C_{max} (ng/mL)	76.12	75.74	100.50	(90.48, 111.63)
Sildenafil 20 mg (2 mL) POS (Test) versus Sildenafil 2 x 10 mg Tablets (Reference)				
AUC_{inf} (ng*h/mL)	166.6	184.9	90.10	(85.00, 95.50)
AUC_{last} (ng*h/mL)	161.3	178.3	90.51	(85.32, 96.01)
C_{max} (ng/mL)	71.91	76.12	94.47	(85.05, 104.93)

Source: Table 14.4.3.2., A1481293 CSR
CI = confidence interval; POS = powder for oral suspension.
[a] The ratios (and 90% CIs) were expressed as percentages.

Source: pg 43 of Clinical Study Report A1481293

As the 90% confidence intervals lay within the bioequivalence criteria (80 to 125%) for the AUCinf, AUClast, and Cmax ratios (test/reference) it may be concluded that the 20 mg dose (2 mL) of sildenafil citrate POS and sildenafil citrate 2 x 10 mg tablet met bioequivalence criteria relative to Revatio 20 mg IR tablet.

Conclusions (per Sponsor)
The data from Study A1481293 demonstrated the bioequivalence of sildenafil 20 mg POS with Revatio 20 mg IR tablet and sildenafil 2 x 10 mg tablets and the bioequivalence of sildenafil 2 x 10 mg tablets with REVATIO 20 mg IR tablet. Based on the results of Study, the POS formulation is considered equivalent to the approved REVATIO tablets.

Reviewers Comments

The bioanalytical validation and study design presented along with the results gathered by the sponsor are acceptable pending overall recommendation by OSI.

Study# 1481275: Relative BE of Crushed Tablet and Extemporaneously Prepared Suspension

Report #	A1481275
Investigator(s)	Pfizer, Inc.: Dr. Marie-Noella Ndongo
Study Site	Belgium (1), Center #1001
Study Period	9/16/2009 – 9/28/2009

Title

A Randomized, Open-Label 3-Way Crossover Study to Investigate the Relative Bioavailability and Bioequivalence of the Crushed Revatio® 20 mg Tablet Mixed With Apple Sauce, the Extemporaneously Prepared Suspension (EP), and the Intact Revatio® 20 mg Tablet in Healthy Volunteers Under Fasting Conditions.

Objectives

Primary objective(s):

- To estimate the relative bioavailability of 20 mg EP formulation to intact Revatio 1 x 20 mg oral tablet.
- To estimate relative bioavailability of the crushed Revatio 1 x 20 mg oral tablet mixed with apple sauce relative to the intact Revatio 1 x 20 mg oral tablet.
- To estimate the relative bioavailability of 20 mg EP formulation to the crushed Revatio 1 x 20 mg oral tablet mixed with apple sauce.

Secondary objective(s):

- To evaluate the safety and tolerability of 20 mg EP formulation, crushed Revatio 1 x 20 mg oral tablet mixed with apple sauce and the intact Revatio 1 x 20 mg oral tablet in healthy volunteers.

Test Drug

All subjects received the following treatments:

- Treatment A: Revatio 20 mg intact oral tablet;
- Treatment B: Revatio 20 mg crushed tablet mixed with apple sauce
- Treatment C: Revatio 20 mg EP formulation.

Commercially available Revatio 20 mg tablets (for Treatments A, B and C) and apple sauce (for Treatment B) were supplied by the CRU. (b) (4) were supplied by the sponsor in commercially available bottles, for extemporaneous preparation of oral suspension (for Treatment C) at the CRU. For Treatment B, Revatio tablets were crushed and mixed with apple sauce. For Treatment C, Revatio oral dosing suspensions were prepared in the CRU by 2 operators, one of whom was a qualified pharmacist, according to details given in a separate Extemporaneous Dispensing Record and were administered to the subjects in 2 mL syringes. Lot (and formulation identification) numbers were not supplied.

Study Design
This study was a randomized, open label, 3-treatment, 3-period, crossover, single-dose study in healthy, adult subjects. Eighteen (18) subjects were to be enrolled in the study. Study treatment was administered on the morning of Day 1 of each study period following a 10-hour overnight fast. Each subject received single dose of the following 3 treatments over 3 study periods (1 treatment per period) as per the assigned treatment sequence.

Blood Sampling for Pharmacokinetics
During all study periods, blood samples (5 mL) to provide a minimum of 2 mL of plasma for PK analysis were collected into appropriately labeled tubes containing lithium heparin at the following times: predose, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 14 hours postdose. Blood samples were centrifuged at approximately 1700×g for about 10 minutes at 4°C within 1 hour of collection. The plasma aliquot was stored in appropriately labeled screw-capped polypropylene tubes at approximately -20°C. Plasma samples were analyzed using a validated analytical method.

Bioanalytical Section
The analytical report for study A1481275 is summarized in Report 2100-530 and are the same as outlined in study A1481293 Heparinized plasma samples were assayed by (b) (4) (b) (4) for sildenafil and desmethyl sildenafil using a previously validated method employing solid phase extraction followed by HPLC-MS/MS. The overall method imprecision values (CV) for the analysis of plasma quality control (QC) samples at concentrations of 3, 30, and 350 ng/ml were ≤6.3% for sildenafil and ≤ 5.3% for desmethylsildenafil. The mean inaccuracy (bias) of the assay ranged from +1.7 to +5.7% for sildenafil and -2.0 to +8.0 over the QC concentration range. The calibration range was 1 to 500 ng/mL for sildenafil, with an LLOQ of 1.0 ng/mL.

Pharmacokinetic and Safety Evaluations
PK parameters for sildenafil following single-dose administration were calculated for each subject for each treatment using noncompartmental analysis of plasma concentration-time data. Plasma concentrations below the LLOQ were set to 0 ng/mL for analysis. Actual PK sampling times were used in the derivation of PK parameters. The schedule of assessments is provided in the table below.

Protocol Activity	Screen	Periods 1 through 3														
		Day 0[a]	Day 1													
			Time Postdose (Hours)													
			Predose	0	0.25	0.5	0.75	1	1.5	2	3	4	6	8	10	12	14
Informed Consent	X																
Medical History	X	X[a]															
Drug/Alcohol/ Tobacco History	X	X[a]															
Physical Examination[b]	X	X[a]															X[c]
Single 12-Lead ECG	X																
Single Supine and Standing Vital Signs (BP and pulse rate)	X[d]		X														X
Urine Drug Screen	X	X[e]															
FSH	X[f]																
Pregnancy Test[g]	X	X[e]															X[c]
Admission to CRU		X[h]															
Safety Laboratory Tests	X	X[i]															X[c]
Randomization			X[a]														
Study Treatment				X													
PK Blood Samples			X		X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/ Concomitant Medication		X	----------X----------														X[c]
Baseline Symptoms/ Adverse Event Monitoring		X	----------X----------														X
Discharge from CRU																	X[h]

Source: Appendix A1

ECG = Electrocardiogram; BP = Blood pressure; FSH = Follicle stimulating hormone; CRU = Clinical Research Unit; PK = Pharmacokinetic

[a] Period 1 only.

[b] Full physical examination at screening; brief physical examination on Day 0 of Period 1 and prior to discharge in Period 3. The screening physical examination could be deferred to Day 0 of Period 1.

[c] Prior to discharge from the CRU in Period 3 only, or upon study discontinuation.

[d] Orthostatic hypotension was to be assessed at screening.

[e] All periods requiring admission to the CRU.

[f] Postmenopausal females only.

[g] Females of childbearing potential only. During the main phase of the study, pregnancy test could be performed either on Day 0 or Day 1 prior to dosing.

[h] Subjects could be accommodated at the CRU between periods if successive doses were no more than 2 days apart; discharge from CRU could occur in the morning on Day 2.

[i] Blood and urine samples for safety laboratory tests (see) were to be obtained after admission, but prior to dosing. Safety laboratory tests had to have no clinically significant findings, as judged by the investigator, in order for a subject to be dosed on Day 1

Source: pg 12 of Clinical Study Report A1481275

Subjects

A total of 18 healthy, adult subjects were randomized for the study, and all 18 subjects were treated and completed each study treatment.

Pharmacokinetic Results

The PK results for the study are provided in the table below.

Parameter (units)	Test[a]	Reference[a]	Ratio (%)[b]	90% Confidence Interval	
				Lower	Upper
Revatio® 20 mg EP (Test) versus Revatio® 20 mg Intact Tablet (Reference)					
AUC_{inf} (ng*hr/mL)	207.86	199.53	104.17	97.25	111.58
AUC_{last} (ng*hr/mL)	200.56	193.93	103.42	96.77	110.52
C_{max} (ng/mL)	79.61	93.42	85.22	76.13	95.40
Revatio® 20 mg Crushed Tablet (Test) versus Revatio® 20 mg Intact Tablet (Reference)					
AUC_{inf} (ng*hr/mL)	202.01	199.53	101.24	94.22	108.79
AUC_{last} (ng*hr/mL)	195.28	193.93	100.69	94.23	107.61
C_{max} (ng/mL)	85.02	93.42	91.01	81.30	101.88
Revatio® 20 mg EP (Test) versus Revatio® 20 mg Crushed Tablet (Reference)					
AUC_{inf} (ng*hr/mL)	207.86	202.01	102.90	95.91	110.39
AUC_{last} (ng*hr/mL)	200.56	195.28	102.70	96.11	109.75
C_{max} (ng/mL)	79.61	85.02	93.64	83.64	104.82

Source: Table 13.5.3. EP = Extemporaneously prepared suspension
[a] Adjusted geometric mean values
[b] Ratio of adjusted geometric means
Parameters are defined in Table 2

Source: pg 28 of Clinical Study Report A1481275

Comparison between Revatio 20 mg EP formulation (Test) and Revatio 20 mg intact tablet (Reference), the Test/Reference ratios of the adjusted geometric means of AUClast and Cmax were 103.42% and 85.22%, respectively. The ratio of the adjusted geometric means of AUCinf was 104.17%. The associated CIs surrounding total exposure (area under the plasma concentration-time profile [AUC]) were all completely contained within the range of 80 – 125%; while the lower bounds of the CIs surrounding peak exposure (Cmax) was below 80% (90% CI: 76.13 – 95.40%).

Following a comparison between Revatio 20 mg crushed tablet (Test) and Revatio 20 mg intact tablet (Reference), the Test/Reference ratios of the adjusted geometric means of the primary endpoints, AUClast and Cmax were 100.69% and 91.01%, respectively. The ratio of the adjusted geometric means of AUCinf was 101.24%. The associated CIs were all completely contained within the range of 80 – 125%.

Following a comparison between Revatio 20 mg EP formulation (Test) and Revatio 20 mg crushed tablet (Reference), the Test/Reference ratios of the adjusted geometric means of the primary endpoints, AUClast and Cmax were 102.70% and 93.64%, respectively. The ratio of the adjusted geometric means of AUCinf was 102.90%. The associated CIs were all completely contained within the range of 80 – 125%.

Conclusions (per Sponsor)

- The relative bioavailability, as measured by the ratios of adjusted geometric means (90% CI) of a single dose of Revatio 20 mg EP AUClast and Cmax was 103.42% (96.77%, 110.52%) and 85.22% (76.13%, 95.40%), respectively compared to Revatio 20 mg intact tablet. AUC met standard bioequivalence criteria for the Revatio 20 mg EP formulation in comparison to Revatio 20 mg intact tablets, and Cmax marginally missed lower boundary of bioequivalence criteria with a lower 90% CI of 76%. This study was not powered for

bioequivalence. However, the slight decrease in Cmax is not clinically relevant and the EP formulation is considered acceptable for pediatric use.

- The relative bioavailability, as measured by the ratios of adjusted geometric means (90% CI) of a single dose of Revatio 20 mg EP AUClast and Cmax was 102.70% (96.11%, 109.75%) and 93.64% (83.64%, 104.82%), respectively compared to Revatio 20 mg crushed tablet. Both AUC and Cmax met standard bioequivalence criteria for the Revatio 20 mg EP formulation in comparison to Revatio 20 mg crushed tablet.

- The relative bioavailability, as measured by the ratios of adjusted geometric means (90% CI) of a single dose of Revatio 20 mg crushed tablet AUClast and Cmax was 100.69% (94.23%, 107.61%) and 91.01% (81.30%, 101.88%), respectively compared to Revatio 20 mg intact tablet. Both AUC and Cmax met standard bioequivalence criteria for the Revatio 20 mg crushed tablet in comparison to Revatio 20 mg intact tablet.

- Single oral doses of all 3 formulations of Revatio 20 mg (intact tablet, crushed tablet mixed with apple sauce, and EP formulation) were safe and well tolerated in this 3-treatment crossover study conducted in healthy adult subjects.

Reviewers Comments

The bioanalytical validation and study design presented along with the results gathered by the sponsor are acceptable. Lot numbers for the formulations were not supplied.

Study# 1481131: Safety and Efficacy

Report #	A1481131
Investigator(s)	Pfizer, Inc.: Multiple investigators at multiple centers
Study Site	Multiple centers: 32 centers: Brazil: 1 center; Canada: 1 center; Chile: 1 center; Colombia: 3 centers, Guatemala: 1 center; Hungary: 2 centers; India: 2 centers, Italy: 1 center; Japan: 1 center; Malaysia: 1 center; Mexico: 1 center; Poland 3 centers; Russia 1 center; Sweden: 1 center; Taiwan: 3 centers; and United States: 9 centers
Study Period	8/28/2003 – 6/5/2008

Title

A Randomized, Double-Blind, Placebo Controlled, Dose Ranging, Parallel Group Study of Oral Sildenafil in the Treatment of Children, Aged 1-17 Years, With Pulmonary Arterial Hypertension

Objectives

Primary objective(s):

- to assess the efficacy of 16 weeks of chronic treatment with oral sildenafil in pediatric subjects, aged 1 to 17 years, with PAH.

Secondary objective(s):

- to assess\ safety, tolerability, and pharmacokinetics of 16 weeks of chronic treatment with oral sildenafil in pediatric subjects, aged 1 to 17 years with PAH, and to assess the survival status of subjects who did not enter A1481156.

Test Drug

Subjects were stratified according to weight and developmental ability to perform the exercise capacity test. With the exception of the subjects weighing ≤20 kg, subjects were randomized 1:1:1:1 to sildenafil low, medium and high doses, and placebo, respectively. In subjects weighing from 8 to 20 kg, subjects were randomized 1:2:1 to sildenafil medium and high doses, and placebo, respectively.

Subjects were randomized to receive the following treatments:

Body Weight (kg)	Dose (mg)		
	Low	Medium	High
≥8-20	NA[a]	10[a]	20
>20-45	10	20	40
>45	10	40	80

TID=3 times daily; NA=not applicable

[a] Modeling of the plasma concentrations for each dose level showed that the low and medium doses were predicted to be similar for the 8 to 20 kg subjects (ie, subjects would receive the same dose because of the available tablet strengths); consequently there was no low dose for this weight group.

For subjects able to swallow tablets, 1 tablet of sildenafil (10, 20, 40 or 80 mg) or placebo was taken with water, at least 2 hours after food intake, and 2 hours prior to next food intake, TID ≥6 hours apart, for 16 weeks. For subjects unable to swallow tablets, tablets were crushed (care-

givers were provided with a tablet crusher and instructions) and mixed with a small (5 mL) spoonful of soft food, and the entire food portion was consumed immediately. Use of a tablet crusher was documented in the CRF.

The following lot (and formulation identification) numbers were used:

Study Drug	Dosage Form	Lot Number	FID/DMID Number (b) (4)
Sildenafil citrate film coated tablet	10 mg tablet	CF0250402 CF0050303 05-021177	
Sildenafil citrate film coated tablet	20 mg tablet	CF0200402 CF0440902 05-020981	
Sildenafil citrate film coated tablet	40 mg tablet	CF0300602 05-020980	
Sildenafil citrate film coated tablet	80 mg tablet	O5-020983 CF0230402 CF0080303	
Placebo for sildenafil citrate film coated 10 mg tablet	Placebo tablet	05-020973 CF0190302 CF0180302	
Placebo for sildenafil citrate film coated 20 mg tablet	Placebo tablet	05-021172 CF0320602	
Placebo for sildenafil citrate film coated 40 mg tablet	Placebo tablet	05-020975 CF0090302 CF0430902	
Placebo for sildenafil citrate film coated 80 mg tablet	Placebo tablet	05-020978 05-020977 CF0280502 CF0270502 CF0410802	

Source: Appendix A6
FID=formulation identification; DMID=dose material identification

Source: pg 51 of Clinical Study Report A1481131

Study Design

This was a randomized, double-blind, multi-center, placebo controlled parallel group, dose ranging study. The study included subjects, aged 1 to 17 years with body weight >8 kg, and with primary pulmonary hypertension (PH), or PAH secondary to congenital heart disease, or collagen vascular disease.

Subjects received 1 of 3 sildenafil doses (low, medium or high), or placebo. Actual doses administered were dependent on body weight. Subjects were stratified according to weight and developmental ability to perform the CPX test. Sildenafil low, medium or high doses, or placebo were administered TID, ≥6 hours apart, for 16 weeks. All subjects randomized to sildenafil, including subjects randomized to the sildenafil medium and high doses, initially received sildenafil 10 mg TID for 1 week. After 1 week, their sildenafil dose was increased to their randomized dose. Subjects in the placebo, low dose and medium (for subjects ≤20 kg) dose groups underwent dummy titrations.

The efficacy assessments included the CPX test (subjects who were developmentally able to perform the test), hemodynamic monitoring, symptom assessment, WHO functional class, change in background treatment, and quality of life measurements (subjects ≥5 years of age for who the questionnaire was available in their first language at all visits). Those subjects not developmentally able to perform a CPX test were included in the study for an evaluation of safety, hemodynamic monitoring, WHO functional class, quality of life measurements and growth and development. Subjects who completed the A1481131 study were eligible to enter the extension study A1481156. If subjects receiving sildenafil in this study (and their families) consented to participate in the extension study, they were maintained on their A1481131 sildenafil dose. However, those subjects who received placebo in A1481131 were stratified by weight and randomized to receive sildenafil as per 1 of the active treatment groups in A1481131.

Efficacy Measures
The primary efficacy endpoint was percent change in VO2 peak (normalized to body weight) from baseline at Week 16 assessed by CPET using bicycle ergometry, evaluated in those subjects who were developmentally able to perform CPET.

For the purpose of this study PVRI was defined as a secondary end-point. The following endpoints, which were assessed for the whole study population, were defined as change from baseline at Week 16, and were evaluated to assess efficacy in the total population: PVRI and mPAP. The following secondary endpoint, defined as percent change from baseline at Week 16, was also evaluated: time to VO2peak (for subjects able to perform the exercise test), WHO functional class, Cardiac Index, Child Health Questionnaire - Parent Form (CHQ-PF28), Pulmonary vascular resistance (PVR), Right atrial pressure (RAP); RER measurements were taken to determine whether maximal exercise capacity was achieved for each subject

Blood Sampling for Pharmacokinetics
Blood samples for were collected predose at baseline, and Weeks 4, 8 and 16, and additionally after the first dose of the day at Week 16 during the following sampling windows: 15 minutes to 3 hours, 3 to 6 hours and >6 to 8 hours.

Bioanalytical Section
The analytical report for study A1481131 is summarized in Report 2100-530 and are the same as outlined in study A1481293.

Pharmacokinetic and Safety Evaluations
PK parameters for sildenafil following single-dose administration were calculated for each subject for each treatment using population analysis of plasma concentration-time data. The schedule of assessments is provided in the table below.

Study Visit: Study dates are "ideal" dates, these specified dates had a ± window:	Screening (S_1) Up to 3 Weeks Pre-randomization Day -21 to -1	(T_1) Tx Baseline Day -2 to 1	(P_1) Phone Contact Day 7	(T_2) Tx Week 4 Day 28±3	(T_3) Tx Week 8 Day 56±4	(T_4) Tx Week 16 Day 112±4	Follow-up[a] 30-40 Days After T_4	For All Unscheduled Visits	Yearly survival status	End of Study
Observation/Procedure										
Obtain Informed Consent	X						X[b]			
Medical History	X									
Physical Examination	X[c]					X				
Height	X					X				
Head Circumference[d]		X				X				
Weight	X	X		X	X	X		X		
Hemodynamic Evaluation[e]		X				X				
Chest X-ray	X[f]									
ECG		X				X				
Study Medication		X[g]		X	X			X (if dose reduced)		
Safety Assessments										
Vital Signs (heart rate, blood pressure)	X	X		X	X	X	X	X		
Urine Pregnancy Test (dipstick)[h]	X	X				X				
Clinical Laboratory Tests - Complete Set[i]	X[h]	X[h]		X	X	X[h]				
Ocular Measures		X				X		If ocular AE		
Adverse Events		X	X	X	X	X	X	X		
Survival Status [j]									X	X
Outcome Assessments										
CPX test (Bicycle Ergometer)[k]	X	X			X[l]	X				
Questionnaires[m]		X			X	X				
WHO PH Functional Class		X		X	X	X				
Parent/Physician Global Assessment				X	X	X				
Other Assessments										
Digoxin Level[n]		X				X				
BNP, pro-BNP		X				X				
Plasma Sildenafil and UK 103320		X		X	X	X				
Concomitant Medication	X	X		X	X	X	X	X		

Source: pg 43 of Clinical Study Report A1481131

Subjects

A total of 324 pediatric subjects with PAH were screened and 235 subjects were randomized to 1 of 4 treatment groups. Of those subjects who started study treatment, 6 subjects discontinued: 2 subjects each in the sildenafil low, sildenafil high and placebo treatment groups. A total of 228 subjects completed the study, of which 220 subjects entered the extension study A1481156. The distribution of subjects across treatment groups was not even because no subjects with weight <20 kg were randomized to the sildenafil low treatment group, and the randomization allocation to sildenafil medium, high and placebo groups was 1:2:1 in this weight group.

Efficacy Results

A dose relationship was observed with most of the efficacy endpoints in the study. The sildenafil low group rarely showed much improvement over placebo while the medium and high groups exhibited mean improvements over placebo for all endpoints. The efficacy results for Peak VO2 are provided in the table below.

	Sildenafil				
Dose	Low	Medium	High	Combined	Placebo
Number of subjects[a]	24	26	27	77	29
Mean (SD) VO_2, mL/kg/minute					
Baseline[b]	17.37 (4.36)	18.03 (4.70)	17.43 (3.70)	17.61 (4.22)	20.02 (3.80)
Week 16	18.40 (5.61)	20.39 (6.16)	19.00 (3.59)	19.28 (5.21)	20.01 (4.44)
Change from baseline	1.03 (3.41)	2.36 (3.36)	1.57 (2.56)	1.67 (3.13)	-0.01 (3.34)
Percentage change from baseline	6.44 (20.16)	13.40 (19.50)	10.58 (15.51)	10.24 (18.39)	0.53 (15.91)
Mean difference versus placebo (SE)[c]	3.81 (5.00)	11.33 (4.84)	7.98 (4.85)	7.71 (3.98)	NA
95% Confidence interval[c]	-6.11, 13.73	1.72, 20.94	-1.64, 17.60	-0.19, 15.60	NA
P-value[c]	NA	NA	NA	0.056	NA

LOCF=last observation carried forward; ITT=intention-to-treat population; SE=standard error; SD=standard deviation; NA=not applicable

[a] ITT subset of developmentally able subjects

[b] Baseline was the average of all assessments on or before the first day of study treatment

[c] Analyses were performed using analysis of covariance with etiology, weight and baseline peak VO_2 as the covariates

Source: pg 10 of Clinical Study Report A1481131

In the primary analysis of peak VO2 the sildenafil combined group displayed a 7.71 (95% CI: -0.19, 15.60) improvement in percentage change from baseline, compared to placebo, but failed to achieve statistical significance, with a borderline p-value of 0.056.

The secondary hemodynamic endpoints (mPAP and PVRI) were supportive to the primary endpoint and demonstrated a dose response over the dose range. The sildenafil medium and high dose groups both showed improvements over placebo (mean reductions compared to placebo for mPAP were -3.5 and -7.3 mmHg, respectively, and for PVRI were -4.5 and -7.2 Wood units.m2, respectively), whilst the low dose group showed similar results to the placebo group (mean change compared to placebo for mPAP was 1.6 mmHg and PVRI was -0.6 Wood units.m2).

	Sildenafil				
Dose	Low	Medium	High	Combined	Placebo
Number of subjects	39	55	71	165	56
Mean (SD) mPAP, mmHg					
Baseline[a]	66.3 (22.2)	61.9 (18.1)	61.6 (23.9)	62.8 (21.7)	59.4 (21.6)
Week 16	67.1 (24.4)	57.9 (19.4)	54.2 (20.6)	58.5 (21.6)	59.0 (20.3)
Change from baseline	0.9 (12.3)	-3.9 (12.0)	-7.4 (15.4)	-4.3 (13.9)	-0.4 (15.9)
Mean difference versus placebo[b] (SE)	1.6 (3.1)	-3.5 (2.7)	-7.3 (2.6)	-3.1 (2.2)	NA
95% Confidence interval[b]	-4.5, 7.6	-8.9, 1.9	-12.4, -2.1	-7.5, 1.3	NA
P-value[b]	NA	NA	NA	0.172	NA

LOCF=last observation carried forward; ITT=intention-to-treat population; SE=standard error; SD=standard deviation; NA=not applicable

[a] Baseline was the last mPAP assessment from 21 days before study treatment to the first day of study treatment

[b] Analyses were performed using analysis of covariance with etiology, weight and ability to perform the cardiopulmonary exercise test as the covariates

	Sildenafil				
Dose	Low	Medium	High	Combined	Placebo
Number of subjects	36	49	67	152	50
Mean (SD) PVRI, Wood units/m^2					
Baseline[a]	23.5 (15.2)	19.0 (13.8)	20.9 (19.0)	20.9 (16.6)	16.1 (12.0)
Week 16	23.6 (16.0)	16.0 (11.0)	15.8 (13.5)	17.7 (13.7)	17.7 (13.8)
Change from baseline	0.1 (10.9)	-2.9 (11.5)	-5.1 (14.7)	-3.2 (13.0)	1.6 (9.2)
Mean difference versus placebo (SE)[b]	-0.6 (2.7)	-4.5 (2.4)	-7.2 (2.3)	-4.1 (2.0)	NA
95% Confidence interval[b]	-5.9, 4.7	-9.3, 0.3	-11.7, -2.7	-8.0, -0.2	NA
P-value[b]	NA	NA	NA	0.041	NA

LOCF=last observation carried forward; ITT=intention-to-treat population; SE=standard error; SD=standard deviation; NA=not applicable

[a] Baseline was the last PVRI assessment from 21 days before study treatment to the first day of study treatment

[b] Analyses were performed using analysis of covariance with etiology, weight and ability to perform the cardiopulmonary exercise test as the covariates

Safety Results

Treatment-emergent AEs were experienced by similar proportions ofsubjects in each treatment group (66.7 to 80.0%), with no direct relationship to the dose of sildenafil administered. The most frequently reported all causality treatment emergent AEs in the sildenafil treatment groups were headache, upper respiratory tract infection, pyrexia, vomiting and diarrhea. Upper respiratory tract infection, pyrexia and vomiting were experienced by more subjects in the sildenafil combined group than the placebo treatment group (11.5%, 11.5% and 10.9% compared to 6.7%, 1.7% and 6.7%, respectively). Vomiting and nausea were observed with increased incidence in the medium and high dose groups, although the overall incidences were low. The majority of AEs of headache were considered treatment-related; most AEs of pyrexia and diarrhea were not considered treatment-related. The proportion of AEs of vomiting which were considered treatment-related varied across the treatment groups (66.6%, 60.0% and 36.4% for the sildenafil low, medium and high treatment groups, respectively,

compared to 25.0% for the placebo group). No upper respiratory tract infections were considered treatment-related.

Treatment-emergent SAEs were experienced by 11 subjects: 1 subject each in the sildenafil low and medium groups (2.4% and 1.8%, respectively), 7 subjects (9.1%) in the sildenafil high group and 2 subjects (3.3%) in the placebo treatment group. Two SAEs were considered treatment-related, both occurred in the sildenafil high treatment group, however 1 SAE occurred while the subject was receiving sildenafil 10 mg prior to up titration. There were no treatment-emergent deaths; 2 subjects died before randomization (1 subject during preparation for catheterization and 1 subject while catheterized; both deaths were considered related to general anesthesia).

Conclusions (per Sponsor)

The analysis of the primary endpoint of peak VO2 suggested an improvement in the aerobic capacity in the sildenafil combined group after 16 weeks of treatment (the mean change in the peak VO2 compared to placebo was 7.71%; 95% CI: -0.19, 15.60; p=0.056): a dose response was observed with the lower dose group being similar to placebo. The low dose group had a similar mean percentage change from baseline to the placebo group (difference of 3.81%), while both the medium and high dose groups displayed greater increases compared to placebo (11.33% and 7.98%, respectively). Hemodynamic endpoints (mPAP and PVRI) and disease severity endpoints (WHO functional class for PAH, subject/parent and physician global assessments) displayed efficacy improvements with sildenafil compared to placebo: a dose response was observed with the low dose group being similar to placebo. Sildenafil was generally well tolerated with most AEs being of mild or moderate intensity. There were no treatment-emergent deaths and there were very few discontinuations from the study. Eleven subjects experienced 18 SAEs, of which 9 subjects were receiving sildenafil (16 SAEs).

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