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RESEARCH**

APPLICATION NUMBER:

203109Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

ONDQA BIOPHARMACEUTICS PRODUCT QUALITY REVIEW

ADDENDUM

NDA Number	203-109 (0000)
Product/generic name of the actives, strength and dosage form	Revatio® (sildenafil citrate) 10 mg/mL Powder for Oral Suspension
Submission dates	Original NDA 11/30/2011 and the 2/29/2012 amendment (SDN 15) in response to 1/25/2012 IR letter And (SDN 21) submitted on 5/7/2012
Applicant	Pfizer Inc., New York, NY
Medical Division	Division of Cardiovascular and Renal Products
Type of Submission	Original NDA/505 b(1)
Primary CMC/Quality Reviewer	Mohan Sapru, Ph.D.
Biopharmaceutics Reviewer	Arzu Selen, Ph.D.

This is an addendum to the original Biopharmaceutics Review dated 4/25/2012 for sildenafil citrate 10 mg/mL powder for oral suspension.

During the teleconference with the Applicant on April 12, 2012, FDA agreed on the interim dissolution method and the acceptance criterion for the sildenafil citrate powder for oral suspension and requested submission of the following dissolution data using the pH 5 buffer medium by 5/7/2012 for completion of biopharmaceutics review of this NDA.

The information provided by Pfizer on 5/7/2012 (SDN#21) and our assessment are italicized.

- 1) Dissolution data using the product used in Study A1481293 (i.e. biobatch, lot number: 10-082576).

Pfizer provided the data as agreed.

This is acceptable (please see Appendix 1 for the dissolution profiles and data collected from the samples stored at 5°C and 25°C for approx. 27 months).

- 2) The Applicant would use the interim dissolution method and provide dissolution profile (multi point data) for further characterization of the product with viscosity values observed during stability testing. The Applicant would test products with viscosities covering the viscosity range observed in the stability studies such as the top, middle and bottom of the viscosity range (approximately (b) (4)) and also include product with viscosity value observed on Day 30 of the in-use stability testing (approximately (b) (4))

The Applicant did not provide all of the above described data, instead, the

Applicant included dissolution data for the two sets of samples (both from lot 10-082576) that were stored at 5°C or 25°C for approx. 27 months. At the 24-month stability testing, the viscosity of the samples stored at 5°C was (b) (4) (b) (4) for samples stored at 25°C (closer to the values observed on Day 30 of the in-use stability testing).

Although the submitted data do not include an assessment of dissolution testing at low viscosity values (such as around (b) (4)) that was discussed during the teleconference, the submission is providing information at the mid and the upper end of the range of typical viscosities reported during stability testing. The data show the effect of storage temperature on viscosity of the samples which as expected, is transient.

This approach is acceptable as it provides a baseline using the interim dissolution test method for the mid and upper range of viscosities observed for this product.

It was agreed with the Applicant that the final dissolution test method (to be submitted in 6 months from the action date), will also evaluate the effect of key multi-variate changes on the product (pH and viscosity). This approach will provide information on sensitivity and discriminatory nature of the proposed dissolution test for this product, using dissolution testing as a product quality tool.

It is noted that the Applicant refers to the teleconference as taking place on 4/15/2012 in their cover letter; this is incorrect, the teleconference took place on 4/12/2012 (please see meeting minutes written by ONDQA RPM Ms. Teshara Bouie).

RECOMMENDATION

Recommendation and Conclusion on Approvability

Following review of the additional information provided on 5/7/2012 and the original submission, the biopharmaceutics data and information provided for this NDA 203-109 for 10 mg/mL sildenafil citrate oral suspension (POS) is acceptable and the product is recommended for approval from the Biopharmaceutics perspective.

- The following dissolution method and dissolution acceptance criterion are acceptable on an interim basis as the final method will be developed and implemented within 14 months from the action date for this NDA.

Revatio® (sildenafil citrate) 10 mg/mL powder for oral suspension Interim Dissolution Method and Acceptance Criterion					
Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Acceptance criterion
USP No. 2 (paddle)	50 rpm	900 mL	37°C	pH 5.0 McIlvaine buffer	^(b) ₍₄₎ % at 20 min

SIGNATURES

Arzu Selen, Ph.D.
Biopharmaceutics Research Lead,
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Acting Supervisory Biopharmaceutics Lead,
Office of New Drug Quality Assessment

APPENDIX 1

Dissolution data collected with the interim dissolution method and the summary of the analytical method TM-1490A

Figure 1. Dissolution Profile using TM-1490A for Revatio POS, 10 mg/mL Lot 10082576 stored for 27 months at 5 °C

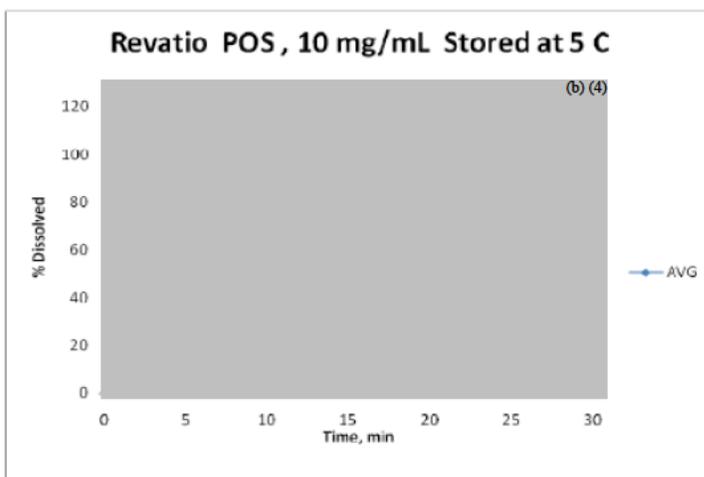
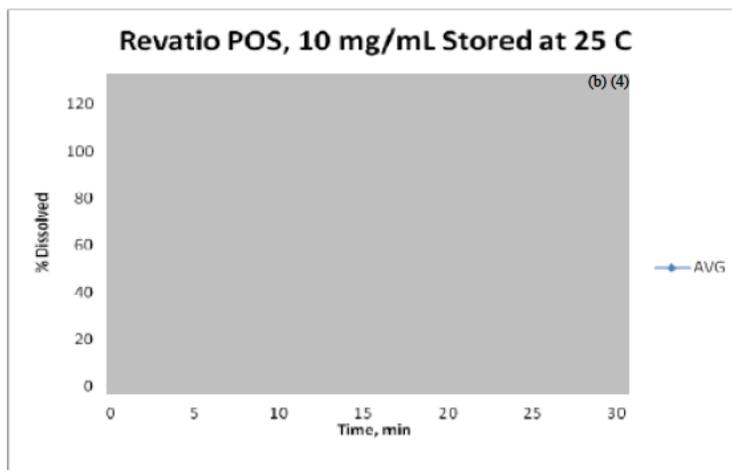


Figure 2. Dissolution Profile using TM-1490A for Revatio POS, 10 mg/mL Lot 10082576 stored for 27 months at 25°C



**Table 1. Dissolution Profile using TM-1490A for Revatio POS, 10 mg/mL
Lot 10082576 stored for 27 months at 5 °C**

Vessel	5 min (% dissolved)	10 min (% dissolved)	20 min (% dissolved)	30 min (% dissolved)
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Avg				
Max				
Min				
% RSD				

**Table 2. Dissolution Profile using TM-1490A for Revatio POS, 10 mg/mL
Lot 10082576 stored for 27 months at 25 °C**

Vessel	5 min (% dissolved)	10 min (% dissolved)	20 min (% dissolved)	30 min (% dissolved)
1	(b) (4)			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Avg				
Max				
Min				
% RSD				

Table 3. Validation Summary for TM-1490A

Specificity	Specificity of the method was demonstrated by injection of a solution of placebo containing excipient mixture for the sildenafil citrate POS dissolved in the dissolution medium. In addition, a degraded sample of sildenafil was examined to confirm specificity with respect to degradation product (b) (4). Absence of interference was demonstrated.
Linearity	Satisfactory linearity has been demonstrated for sildenafil. The correlation coefficient for the linearity was 0.9999 and the intercept was not greater than < 2% of the response at the nominal concentration. The response factor for all concentrations was within (b) (4) relative to the RF at the nominal sample concentration.
Rectilinearity	Satisfactory linearity in presence of excipients has been demonstrated for sildenafil. The correlation coefficient for the linearity was 0.9998 and the intercept was not greater than < 2% of the response at the nominal concentration. The response factor for all concentrations was within (b) (4) relative to the RF at the nominal sample concentration.
Accuracy/Recovery	Acceptable accuracy in the absence of excipients was demonstrated (at (b) (4) of nominal concentration). The recovery ranged from 101.6% to 103.0% for all concentrations. The relative standard deviation for the replicate preparations was less than 1.5%. Acceptable accuracy in the presence of excipients was demonstrated (at (b) (4) of nominal concentration). The recovery was between (b) (4) for all concentrations. The relative standard deviation for the replicate preparations was less than 1.5%.
System Precision	The system precision in the absence of excipients met the specification. The relative standard deviation for system precision was 0.24%. The system precision in the presence of excipients met the specification. The relative standard deviation for system precision was 0.48%.
Repeatability	Repeatability in the absence and the presence of excipients was demonstrated. The relative standard deviation for the nine replicate preparations (both in the presence and absence of excipients) was less than 1.5%.
Standard and Sample Solution Stability	Standard and sample solutions are stable up to 3 days. No new peaks were observed and potency values were between (b) (4) of their initial value.
(b) (4)	

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/s/

ARZU SELEN
05/16/2012

ANGELICA DORANTES
05/16/2012

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) [REDACTED]
Proposed Formulation	Powder for Oral Suspension
Proposed Dosing Regimen	[REDACTED] (b) (4)
OCP Division	Division of Clinical Pharmacology I
OND Division	Division of Cardiovascular and Renal Products
OCP and PM Reviewer	Satjit Brar, Pharm.D., Ph.D.
Clinical Pharmacology Team Leader	Rajanikanth Madabushi, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.

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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 E_{max} 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)

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)	(b) (4)
(b) (4)	(b) (4)

- *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?

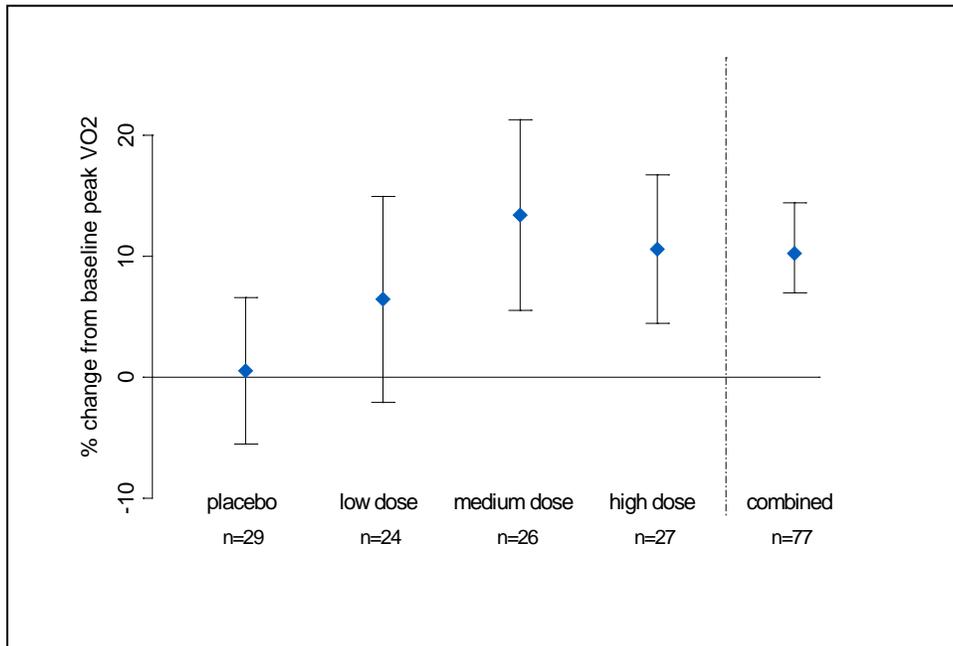
3.2.4.1.1 Exercise capacity (percent change from baseline in VO_{2peak} at 16 weeks)

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.

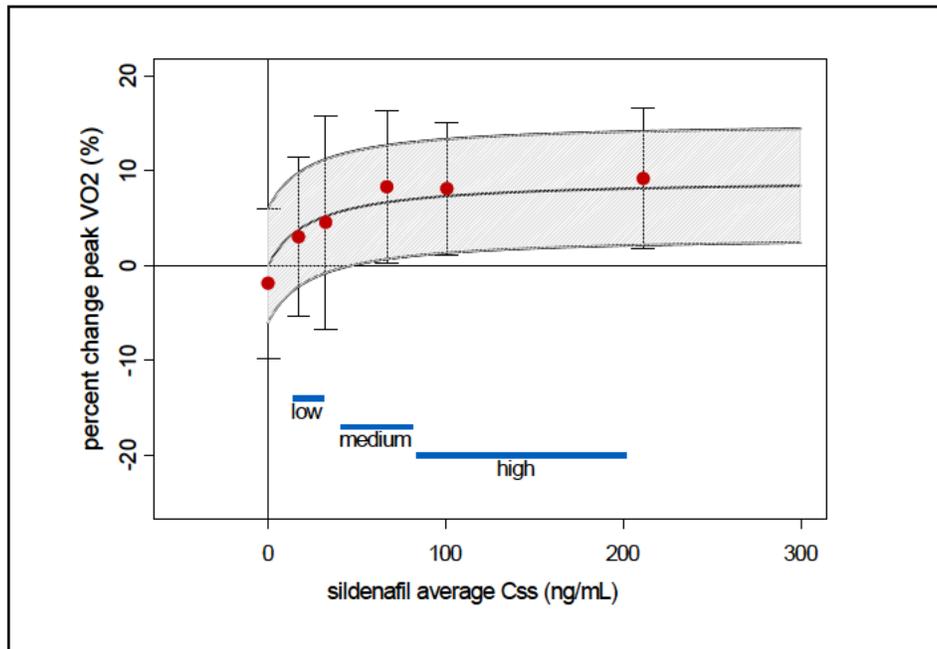
An Emax exposure-response relationship was observed with % change in VO_{2peak} at 16 weeks (Figure 1b) and predicted average sildenafil steady state concentration. A near maximum effect of 9.1% VO_{2peak} change in is achieved at concentrations corresponding to medium and high doses ($EC_{50} \sim 24$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

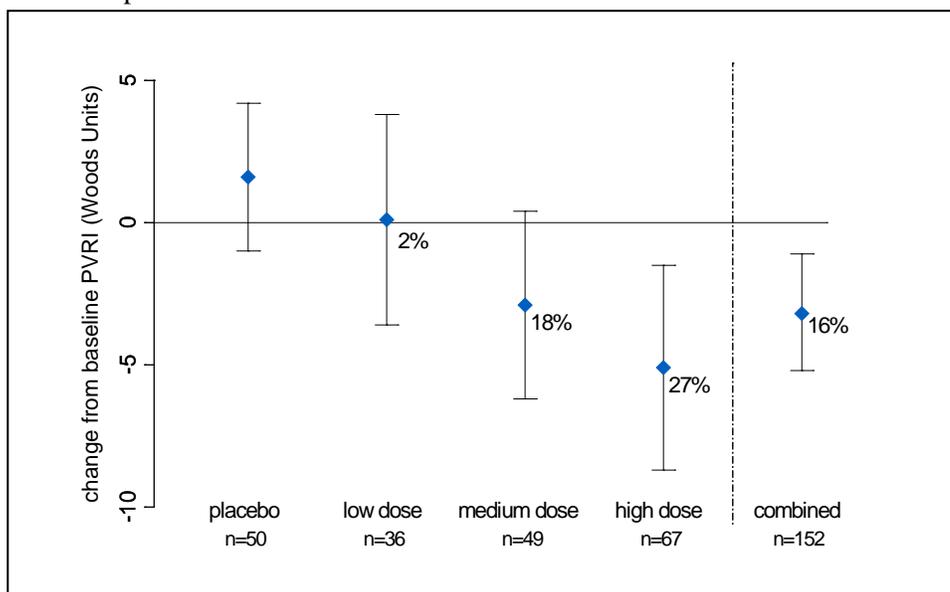
Table 2. Pulmonary Hemodynamics (PVRI) Treatment Comparison to Placebo (n=52)

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)*

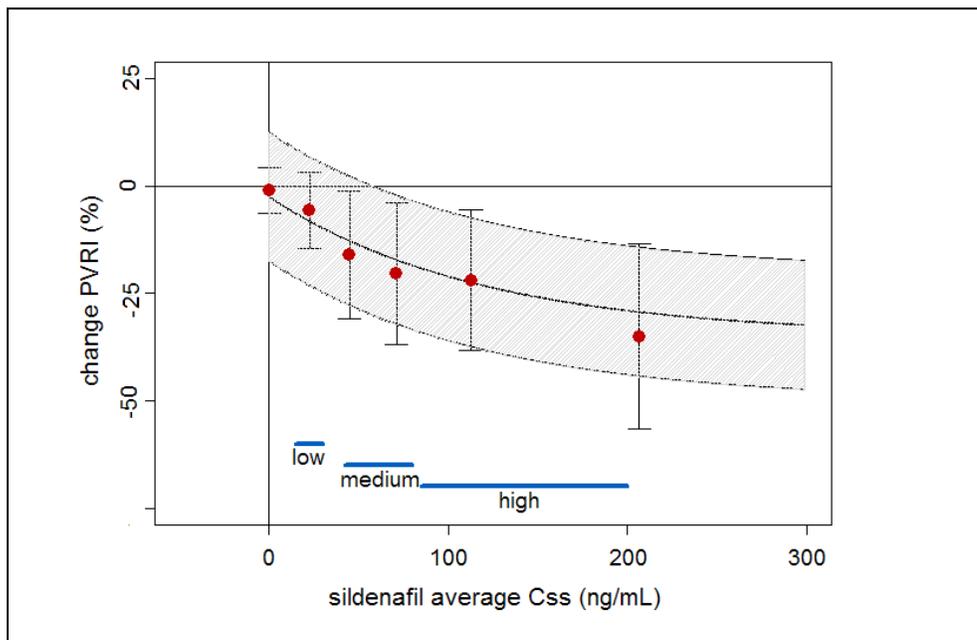
*p-value = 0.041

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

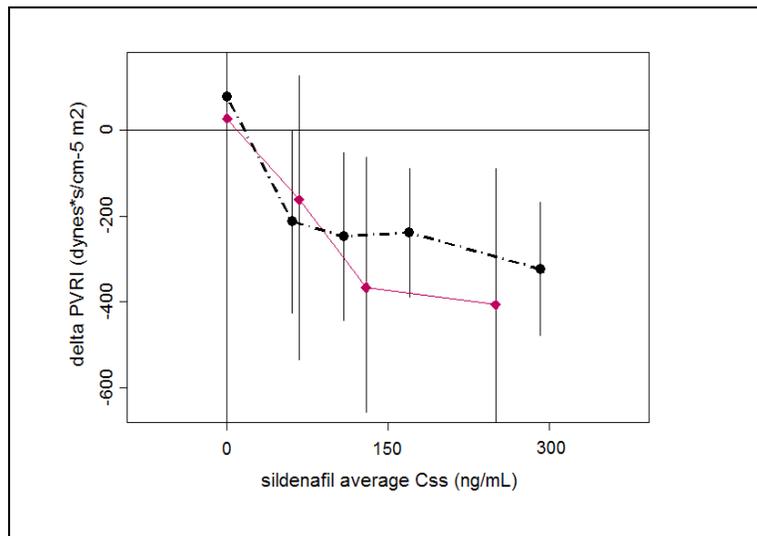


Note: For dose-response the percentages next to the point estimate are placebo-corrected. For the exposure-response, solid symbols and bars represent the mean and 95% confidence interval of PVRI decrease from baseline for each concentration quantile. The interquartile ranges for the low, medium and high 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/cm⁵ m²)

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.

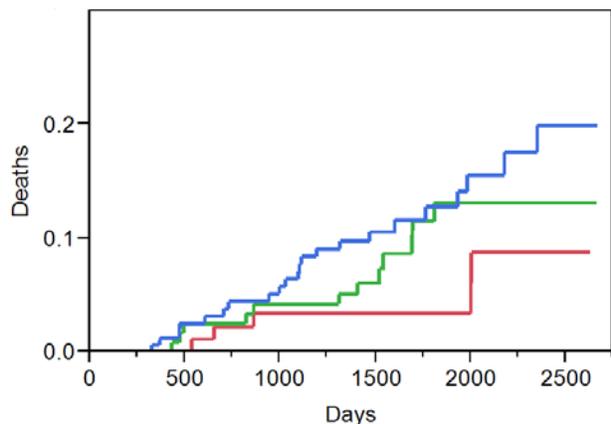
Evaluation of the individual stratified dosing cohorts also revealed an imbalance in deaths across dosing groups, in a dose-response manner. Results on Table 5 also show that subjects who initially received placebo in A1481131 and further randomized to sildenafil in the long-term extension, had better 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.

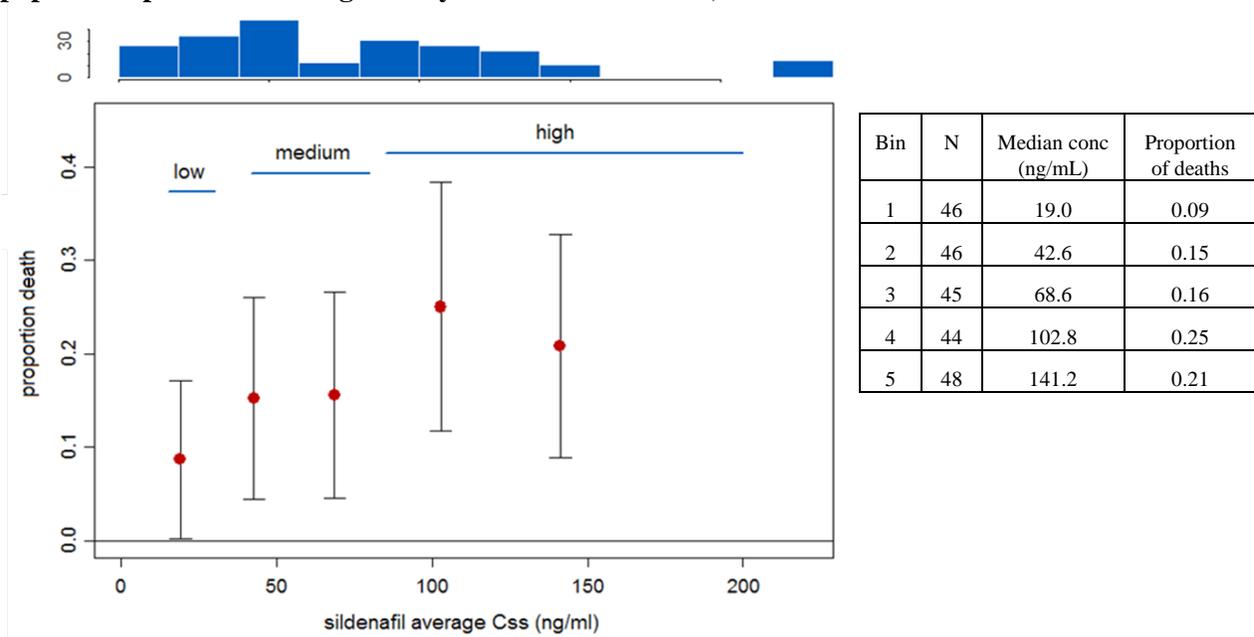
In comparison to historical control, the survival rates obtained in this trial are higher than reported in children with PAH prior to the availability of targeted PAH therapies. Survival at three years was 87%, 88% and 80% for low, medium and high doses, respectively. Prior to available therapies, the 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.

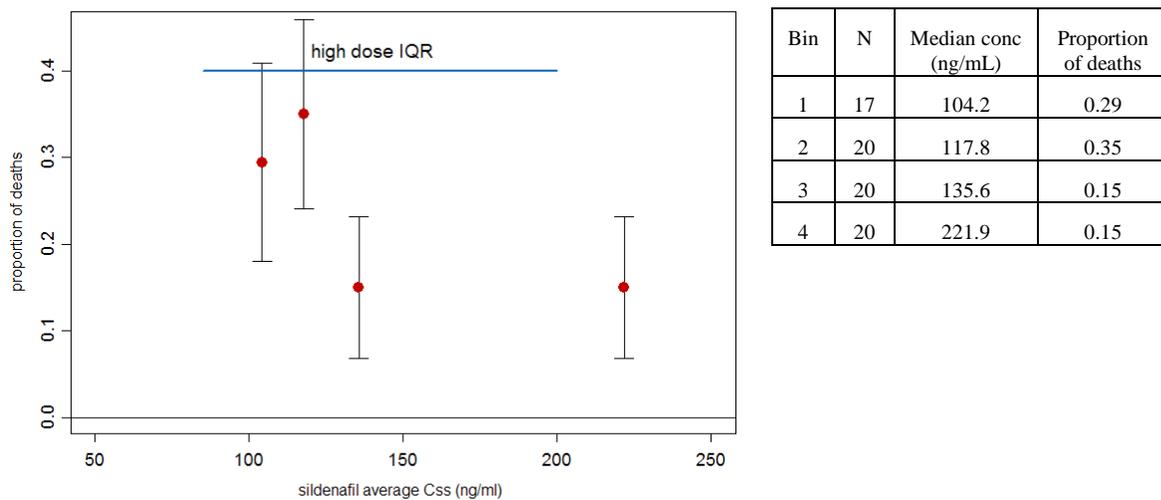
⁴ Hislop A, Moledina S, Foster H, et al. Long-term efficacy of bosentan in treatment of pulmonary arterial hypertension in children. *Eur Resp J* 2011; 38: 70-77.

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



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



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%)

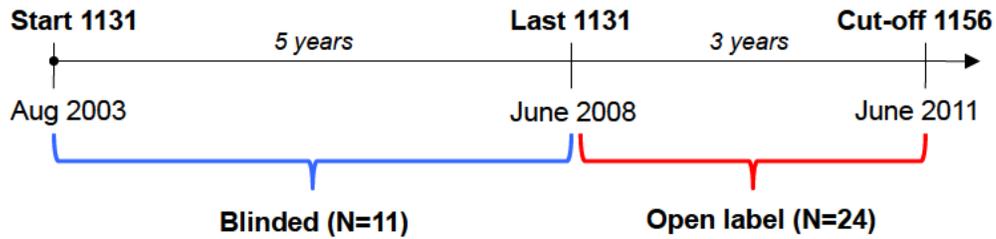
To account for the titration, modal dose (the dose that the patient was on for majority of the trial) was assessed for a dose response relationship with mortality (Table 7). According to the assessment via modal dose (last column), *the low and medium doses are similar in proportion of deaths while the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

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

Modal Dose	Randomized Dose			Total
	Low	Medium	High	
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

Weight Group (kg)	Low Dose		Medium Dose		High Dose	
	Dose, N		Dose, N		Dose, N	
	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

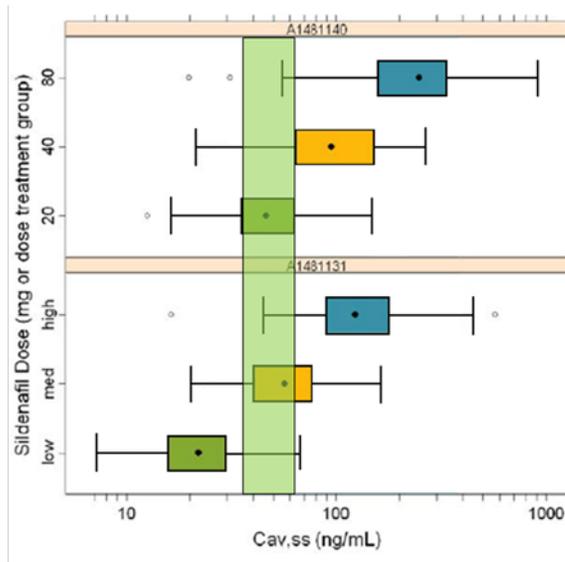
Weight Group (kg)	Low Dose		Medium Dose		High Dose	
	Dose, <i>N</i>		Dose, <i>N</i>		Dose, <i>N</i>	
	Geometric mean (ng*h/mL)	CV%	Geometric mean (ng*h/mL)	CV%	Geometric mean (ng*h/mL)	CV%
8 – 20	NA, NA		10 mg, 15		20 mg, 33	
	--	--	339.6	44.8	857.8	50.0
>20 – 45	10 mg, 30		20 mg, 29		40 mg, 29	
	190.5	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 than 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

Parameter	N	Geometric Mean		Ratio	90% CI		
		Suspension (S)	Tablet (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

Parameter	N	Geometric Mean		Ratio	90% CI		
		Suspension (S)	Tablet (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)

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 \times 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 $\leq 6.3\%$ for sildenafil and $\leq 5.3\%$ 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	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 AUC_{inf}, AUC_{last}, and C_{max} 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 [REDACTED] (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 [REDACTED] (b) (4) [REDACTED] 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 ^e															
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	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 AUC_{last} and C_{max} were 103.42% and 85.22%, respectively. The ratio of the adjusted geometric means of AUC_{inf} 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 (C_{max}) 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, AUC_{last} and C_{max} were 100.69% and 91.01%, respectively. The ratio of the adjusted geometric means of AUC_{inf} 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, AUC_{last} and C_{max} were 102.70% and 93.64%, respectively. The ratio of the adjusted geometric means of AUC_{inf} 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 AUC_{last} and C_{max} 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 C_{max} 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 C_{max} 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 AUC_{last} and C_{max} 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 C_{max} 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 AUC_{last} and C_{max} 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 C_{max} 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
$\geq 8-20$	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
Sildenafil citrate film coated tablet	10 mg tablet	CF0250402	(b) (4)
		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	05-020983	
		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 ^b	X ^b		X	X	X ^b				
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.

Dose	Sildenafil				Placebo
	Low	Medium	High	Combined	
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 VO₂ 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).

Dose	Sildenafil				Placebo
	Low	Medium	High	Combined	
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

Dose	Sildenafil				Placebo
	Low	Medium	High	Combined	
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 ^b (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 of subjects 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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/s/

SATJIT S BRAR
04/27/2012

YANING WANG
04/27/2012

RAJANIKANTH MADABUSHI
04/27/2012

ONDQA BIOPHARMACEUTICS PRODUCT QUALITY REVIEW

NDA Number	203-109 (0000)
Product/generic name of the actives, strength and dosage form	Revatio® (sildenafil citrate) 10 mg/mL Powder for Oral Suspension
Submission dates	Original NDA 11/30/2011 and the 2/29/2012 amendment (SDN 15) in response to 1/25/2012 IR letter
Applicant	Pfizer Inc., New York, NY
Medical Division	Division of Cardiovascular and Renal Products
Type of Submission	Original NDA/505 b(1)
Primary CMC/Quality Reviewer	Mohan Sapru, Ph.D.
Biopharmaceutics Reviewer	Arzu Selen, Ph.D.

BACKGROUND

Sildenafil citrate is an inhibitor of phosphodiesterase type 5 (PDE5). The first sildenafil NDA, NDA 20-895, for the tablet formulation was approved in 1998 for the treatment of male patients with erectile dysfunction. It is in the market under the trade name Viagra®. The sildenafil citrate (Viagra) tablet strengths are 25-, 50- and 100 mg (as base equivalents).

Safety and efficacy of sildenafil citrate tablets was also explored for the treatment of PAH (pulmonary arterial hypertension, also referred to as Primary Pulmonary Hypertension). The sildenafil citrate tablet was approved with the trade name Revatio® for the treatment of PAH in 2005 (NDA 21-845). The approved dosage regimen for oral Revatio, in adults, is one 20-mg tablet administered 3 times daily (TID).

As part of the pediatric development history, the Applicant states that the pediatric program for Revatio was initiated in parallel with the adult program (IND 63,175) and the Pediatric Written Request letter was first issued in December 2001 (it has been amended since then).

In addition to other product quality attributes, the Applicant is indicating that (b) (4) as it was considered to be a dosage form suitable for pediatric use.

SUBMISSION

This submission is for a new formulation of sildenafil citrate, powder for oral suspension (POS), and for supporting its use for PAH in pediatric patients (1 to 17 years of age) (b) (4). The Applicant is proposing sildenafil citrate (b) (4).

For assessment of the clinical studies (including clinical trial Study A1481131 and its safety extension, Study A1481156), please see the medical officer, Dr. Maryann Gordon's clinical reviews (dated 4/11/2012 and 4/18/2012).

In the pediatric trial (Study A1481131) either intact sildenafil citrate immediate release tablets or crushed tablets mixed with applesauce were administered over a dosing range of 10- to 80 mg. The Studies A1481275 and A1481293 were conducted in healthy adult volunteers for comparison of the in vivo performance of the POS to the formulations used during the pediatric program (Study A1481131). The bioequivalence studies and the products used are summarized in the following table.

Table 1: Overview of the study design of the sildenafil citrate bioequivalence studies comparing sildenafil citrate POS and Revatio IR tablets.

Study number	Study design	Products used
A1481275	Open label 3-way crossover relative BA and BE study comparing crushed Revatio 20-mg sildenafil citrate tablet mixed with applesauce, the extemporaneously prepared suspension, and the intact Revatio sildenafil citrate 20 mg IR tablet. Studied in adult healthy volunteers (n=18)	<ul style="list-style-type: none"> • Commercially available Revatio 20-mg tablets. • Applesauce and (b) (4) as commercially available.
A1481293	Open label 3-way crossover BE study comparing sildenafil citrate 10 mg/mL POS, sildenafil citrate 2X10-mg IR tablet and sildenafil citrate 20 mg IR tablet. Studied in adult healthy volunteers (n=42)	<ul style="list-style-type: none"> • 20-mg Revatio IR tablets (commercial supplies) • 10-mg sildenafil citrate IR tablets (lot number: 07-061004) • 10 mg/mL sildenafil citrate POS (Lot number: 10-082576)

The Applicant is claiming that bioequivalence between the suspension formulation and the Revatio IR tablets was established; please see Dr. Satjit Brar's clinical pharmacology review for his assessment of the bioequivalence studies.

BIOPHARMACEUTICS EVALUATION

The following are the aspects of this submission that are pertinent for this biopharmaceutics review:

1. The Applicant's proposal (b) (4).
2. Suitability of the dosage form for the pediatric patients such as (b) (4), dosage form and dosing recommendations
3. Evaluation of data supporting product integrity including stability, and palatability after constitution and instructions for administration

Drug Substance

The pH of the aqueous solution of sildenafil citrate is approximately 4 (b) (4). The Solubility determination (b) (4) at 25°C revealed a maximum solubility of approximately 24 mg/mL at pH 2.0. The solubility of sildenafil citrate is approximately 3 mg/mL at pH of 4.7, 1.3 mg/mL at pH 5 and less than 0.1 mg/mL in the pH range of 6 to 8. Sildenafil has a basic pKa of 6.5 and an acidic pKa of 9.2. The solubility profile of sildenafil citrate is shown in Figure 1 and the data are listed in Table 2.

Figure 1

Figure P.2.1.1-1 Shows the pH Solubility Profile at 23°C.

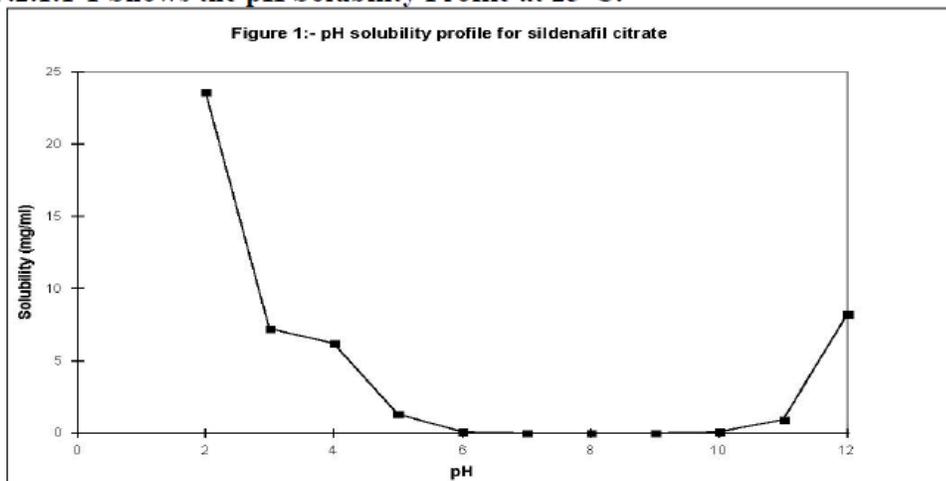


Table 2: Equilibrium Solubility of Sildenafil Citrate

Media	Solubility in mg/mL, 25°C
Water (b) (4)	3.5 final pH 3.9)*
(b) (4) pH 1.2	10.6**
(b) (4) pH 2.0	23.6
(b) (4) pH 3.0	7.2
(b) (4) pH 4.0	6.2
(b) (4) pH 5.0	1.3
(b) (4) pH 6.0	0.1
(b) (4) pH 7.0, pH 8, pH 9 and pH 10	<0.1
(b) (4) pH 11	0.9
(b) (4) pH 12	8.2

* Solubility in (b) (4) water was obtained at 23°C.

** At pH 1.2 solubility was lower than expected; this is attributed to be caused by precipitation of hydrochloride salt.

(b) (4)
sildenafil citrate drug substance used for manufacturing of the Revatio 20 mg tablets for which the sildenafil citrate drug substance particle size requirements are the following:

(b) (4)
(b) (4)

Formulation Optimization

The Applicant optimized the product (b) (4)
(b) (4)

Drug Product

Additional supportive information for this product and other comparative data for further characterization of this product are included in Appendix 1 of this review.

The formulation is packaged in an amber glass bottle and filled with 32.27 g of dry powder blend for constitution. After addition of 90 mL of water, approximately 112 mL of constituted 10 mg/mL suspension is obtained. (b) (4)
(b) (4)

All excipients are compendial grade with the exception of the grape flavor (food grade), and all are generally recognized as safe (GRAS). The excipients in the dry powder blend, (b) (4)
(b) (4) silicon dioxide and titanium dioxide, (b) (4)
(b) (4) The formulation pH is (b) (4) 3.5, within an acceptable range of pH 3.0 to 4.0 and (b) (4) sodium benzoate.

Please see Dr. Mohan Sapru's review for his assessment of manufacturing of this proposed product as well as other CMC/product quality aspects this submission.

(b) (4)
(b) (4) A comparison of the composition of the Revatio IR tablet and the proposed sildenafil citrate POS dosage form is provided in Table 3.

Table 3

Table 3.2.P.2.2-5. Unit Composition of Sildenafil Citrate Immediate Release Dosage Forms Utilized in Studies A1481131, A1481275 and A1481293

Dosage Form Type	20 mg Immediate Release Film-Coated Tablet (Revatio Tablet)	10 mg Immediate Release Film-Coated Tablet	POS Powder for Oral Suspension (10 mg/mL)
Strength	20 mg per tablet	10 mg per tablet	20 mg (dosed in 2 mL volume)
Clinical Study	A1481131, A1481275, A1481293	A1481293, A1481131	A1481293
Sildenafil Citrate (mg)	28.090 mg ^b	(b) (4)	28.090 mg ^b
Excipients:	(b) (4)		
Microcrystalline cellulose	(b) (4)		
Dibasic calcium phosphate	(b) (4)		
Croscarmellose sodium	(b) (4)		
Magnesium stearate	(b) (4)		
(b) (4)	(b) (4)		
Sucralose	(b) (4)		
Grape flavour	(b) (4)		
Titanium dioxide	(b) (4)		
Sodium benzoate	(b) (4)		
Sodium citrate dihydrate	(b) (4)		
Colloidal silicon dioxide, anhydrous	(b) (4)		
Sorbitol ^d	(b) (4)		
Xanthan Gum	(b) (4)		
Citric Acid Anhydrous	(b) (4)		
(b) (4)	(b) (4)		
Total Weight	(b) (4) in	(b) (4)	
Unit Dose	(b) (4)	(b) (4)	

^b Equivalent to 20 mg sildenafil based on a theoretical potency of (b) (4)

^c Equivalent to 10 mg sildenafil based on a theoretical potency of (b) (4)

^d While sorbitol has been linked in the literature to effects on gastrointestinal emptying times, this amount of sorbitol per dose would not be expected to impact the pharmacokinetics of sildenafil citrate based upon literature precedent (reference Chen et. al)

(b) (4)

The following excipients in Table 4 are used (b) (4) sildenafil citrate POS.

Table 4: (b) (4) Excipients

Excipient	Function	Comments
(b) (4)	(b) (4)	(b) (4)
sucralose and sorbitol	(b) (4)	(b) (4)
The grape flavor	(b) (4)	(b) (4)

The other critical components of the POS formulation are the (b) (4) sodium benzoate and titanium dioxide. Sodium benzoate at a concentration of (b) (4)

(b) (4). Titanium dioxide (b) (4)

The (b) (4) pH of the suspension product at approximately 3.5. (b) (4)

(b) (4)

(b) (4)

(b) (4). At pH 2, solubility of sildenafil citrate is 24 mg/mL (b) (4)

In Vitro Product Performance and Justification of Dissolution Method Parameters

The Applicant in the original submission states that during product development, (b) (4)

(b) (4)

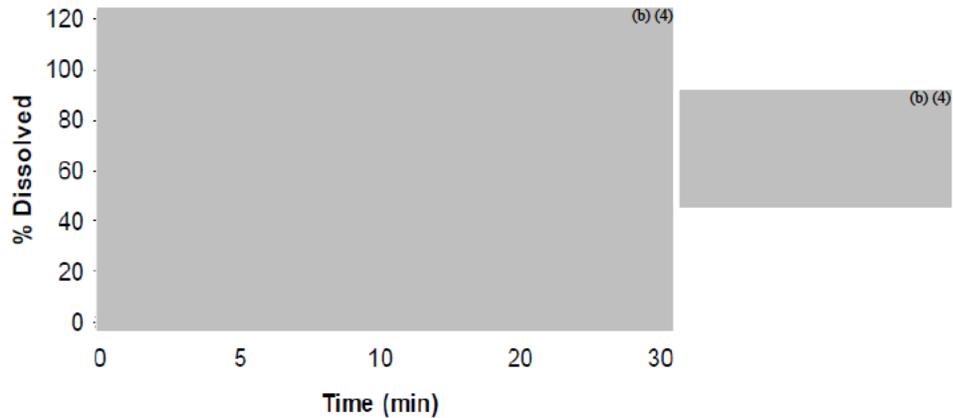
While this reviewer agrees that in general drug solubility should decrease in more viscous media, other contributing factors should also be considered. In this case, the pH of the constituted product and viscosity of the product need to be considered in a multivariate manner as well as relevance of the dissolution method.

As illustrated in the following figure, Figure 2, regardless of the starting point of viscosity, by 20 min into the dissolution testing, dissolution is at least (b) (4) % of the label claim. The amount of xanthan gum in the formulation is (b) (4) (b) (4)

(b) (4) Under these conditions, no difference (with respect to acceptability) between the products would be detected if a 20 min time point would be selected for dissolution testing. Typically, for IR products, it is a single point determination at 15 or 20 min. Furthermore, these results show that this dissolution method is more influenced with the method parameters and is not suitable for characterization of this product.

Figure 2

Figure 3.2.P.2.2-4. Evaluation of Viscosity on Dissolution using 0.01N HCl (approximately pH 2)



For this product, the submitted dissolution testing approach is not informative given the API solubility profile, the dose (constituted 10 mg/mL suspension) and the explored dissolution test

method (b) (4)
(b) (4) The Applicant used these results to (b) (4) with this method they were showing that solution profile was maintained (i.e. over (b) (4) % dissolved in 20 minutes). As it was discussed with the Applicant during the April 12, 2012 teleconference, these results are influenced with (driven by) the methodology and this dissolution test method is not suitable for characterization of this product.

(Note: During the April 12, 2012 teleconference, an agreement was reached with the Applicant for an interim dissolution test method and dissolution acceptance criterion based on the results submitted by the Applicant in response to our IR letter dated January 25, 2012. The agreed interim dissolution method and acceptance criterion are included under the recommendation section of this document. Due to pending data (to be submitted by May 7, 2012) at this time, the review recommendation is "Complete Response". Plans for timings, deliverables and agreements are detailed in the meeting minutes written by ONDQA RPM Ms. Teshara Bouie).

Other Dissolution Test Results included in the Submission for Sildenafil Citrate POS

The Applicant also submitted the following dissolution test results using different media and test conditions as supportive information to justify their proposal (b) (4) at release for sildenafil citrate POS (b) (4)

The following figure, Figure 3, shows comparison of dissolution profiles of the sildenafil citrate POS and the commercial Revatio 20 mg IR tablet. The dissolution method for the Revatio IR tablet uses (b) (4)

(b) (4)
(b) (4)
(b) (4)



The drug product stability and dissolution testing

For product stability assessments, please see Dr. Mohan Sapru’s CMC/product quality review.

The Applicant states that the stability samples were evaluated for appearance, assay, degradation products, dissolution, (b) (4) as well as physical characteristics, viscosity, pH, (b) (4) and microbial limits. The stability listings also include dissolution assessment (b) (4) On one occasion, in (b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)

In the stability study, up to 18 months, decrease in the viscosity of the constituted suspension produced from samples stored at 25°C/60% RH and 30°C/75% RH (b) (4) compared to those observed for the samples stored up to 6 months at the accelerated condition (40°C/75% RH). (Please see Appendix 2).

The Applicant is claiming that in use stability testing of sildenafil citrate POS was also performed following constitution with 90 mL water yielding a final concentration of 10 mg/mL and that no

significant changes were observed in any of the parameters measured during the in use study on POS samples that had been stored (25°C/60% RH and 30°C/75% RH) for 9 and 12 months. Please see Dr. Sapru’s review for his assessment.

Dose Delivery and the Effect of Viscosity on Dose Delivery

The accuracy of dosing over a range of suspension viscosities (b) (4) was evaluated and dose uniformity/delivery was within (b) (4) of the target dose over the 30 day in use period as shown in Table 5.

Table 5

Table 3.2.P.2.2-4. Dose Delivery of 10 mg (1 mL dose) as Function of Viscosity (Percent of Intent)

Initial Viscosity	Potency by HPLC (% of intent)				
	Initial	Day 7	Day 14	Day 21	Day 30
(b) (4)	(b) (4)				

The instructions for dosing of the sildenafil citrate POS indicate that the product should be shaken for at least 10 seconds prior to dosing and the formulation was tested by inverting once, five-times and shaken for 10 seconds as indicated in the dosing instructions. An additional assessment was made by shaking the product for 10 seconds and holding the product for 7 minutes before the doses were withdrawn per patient instructions.

The results in figure 5 show that even with minimal agitation (5 inversions) the product is adequately suspended and 90% or greater of the dose is delivered at the viscosity values tested (b) (4)

Figure 5



The effect of viscosity on dose delivery and particle suspendability was evaluated over the range of (b) (4) cps. The settling of the sildenafil citrate POS was also explored by shaking samples for 10 seconds and allowing the samples to stand undisturbed for 3, 6, and 9 minutes (Figure 6). The samples for potency assay were taken from the midpoint of the suspension without any inversion. The potency values remained within dose uniformity targets of (b) (4) of label claim regardless of the hold time.

Figure 6



Interim Dissolution Method and Acceptance Criterion

The Applicant did not initially provide any dissolution data in their response (2/6/2012) to our IR request dated 1/25/2012, however, subsequently, on 2/29/2012, they provided dissolution testing results using the three pH media (pH 3.5, pH 4 and pH 5) and the two paddle speeds 50 rpm and 75 rpm. The following figure, Figure 7, shows the minimum, maximum and mean values that were obtained at each pH medium (using the McIlvaine buffer) when tested at 50 rpm using USP Apparatus 2.

Figure 7

Sildenafil citrate POS in various pH medium using USP Apparatus 2 (paddle) at 50 rpm (n=12)



Please see Appendix 3 for the dissolution data and the profiles that were submitted testing 10 mg/mL sildenafil citrate POS.

As evident in the above results, pH 5 buffer medium was considered informative considering that the initial noise due to system dynamics was minimal as well as scientifically the pH medium is more relevant and in line with the solubility profile of sildenafil citrate.

To move forward with an interim dissolution method and dissolution acceptance criterion, Pfizer agreed to submit the following dissolution data using the pH 5 buffer medium by 5/7/2012:

- 1) Dissolution data using the product used in Study A1481293 (i.e. biobatch, lot number: 10-08257).
The Applicant initially suggested (b) (4) they would submit dissolution results from the stability batches. It is the understanding of this reviewer that they will also include this information in the pending response.
- 2) For further characterization of the product with viscosity values observed during stability testing with the potential interim dissolution method, the Applicant will provide dissolution profile (multi point) data testing of the products with viscosities covering the viscosity range observed in the stability studies such as the top, middle and bottom of the viscosity range (approximately (b) (4)) and also include product with viscosity value observed on Day 30 of the in-use stability testing (approximately (b) (4)).

We made suggestions such as exploring lower paddle speed, lower dissolution medium volume and possibly testing in pH values of 5 or higher for developing an optimized/informative dissolution method for the proposed product. The Applicant committed to providing a full dissolution method report within 6 months of the NDA action date. For further details of the meeting discussions, please see the meeting minutes written by Ms. Teshara Bouie, ONDQA RPM.

The Applicant also agreed to update the product specification table with the addition of the interim dissolution method including the dissolution acceptance criterion.

SUMMARY

1. **The Applicant's proposa** (b) (4)
This was not acceptable as discussed above. (b) (4)
Instead, we have agreed on an interim dissolution method that is scientifically informative and can be used as a baseline for characterization of the product used in the BE study and serve for further development of a suitable dissolution method.
2. **Suitability of the dosage form for the pediatric patients such as** (b) (4), **dosage form and dosing recommendations.**
As far as the dosage form (suspension) volume for delivery, and frequency (b) (4) and palatability considerations, the Applicant has provided adequate data and information for a biopharmaceutics product quality assessment as further summarized in the next point. However, the effective use of the product in the pediatric patient

population is based on safety and efficacy assessment of this product for this patient population which is outside the scope of this review.

3. Evaluation of data supporting product integrity including stability, and palatability after constitution and instructions for administration

From a biopharmaceutics perspective, it is a simple/clever formulation where (b) (4)

Overall, the information provided for the product including pH solubility profile and dissolution testing comparison against (b) (4)

are informative although not adequate to serve as a product performance method. However, based on recently submitted data, there is adequate biopharmaceutics information to support product quality.

Information provided showing dose uniformity and consistent delivery of the intended dose according to the product use directions is adequate and acceptable from a biopharmaceutics perspective.

RECOMMENDATION

Recommendation and Conclusion on Approvability

- Due to pending data and information from the Applicant, the recommendation based on review of the biopharmaceutics information in this NDA 203-109 for 10 mg/mL sildenafil citrate oral suspension (POS) is a complete response action.
- Based on the response provided by the Applicant on 2/29/2012 in response to our IR letter dated 1/25/2012, the following dissolution method and dissolution acceptance criterion are acceptable on an interim basis.

Revatio® (sildenafil citrate) 10 mg/mL powder for oral suspension Interim Dissolution Method and Acceptance Criterion					
Apparatus	Rotation Speed	Medium Volume	Temperature	Medium	Acceptance criterion
USP No. 2 (paddle)	50 rpm	900 mL	37°C	pH 5.0 McIlvaine buffer	(b) (4) % at 20 min

- The pending data when submitted will be evaluated and the final dissolution method and acceptance criterion will be determined accordingly.

SIGNATURES

Arzu Selen, Ph.D.
Biopharmaceutics Research Lead,
Office of New Drug Quality Assessment

Angelica Dorantes, Ph.D.
Acting Supervisory Biopharmaceutics Lead,
Office of New Drug Quality Assessment

APPENDIX 1: ADDITIONAL BACKGROUND AS SUPPORTIVE/DESCRIPTIVE INFORMATION

Table 3.2.P.2-1. Quality Target Product Profile for Sildenafil Citrate POS 10 mg/mL

Product attribute	Target
Dosage Form	Multidose powder for oral suspension
Dose	(b) (4)
Container	Sufficiently protective container and closure to meet target shelf life
Targeted Shelf life	≥ 2 years at ambient storage for powder blend
Targeted In-Use Period	30 days in use period at ambient or refrigerated storage
Degradants and Impurities	Below qualification threshold, or qualified
Palatability	Acceptable taste

(b) (4)

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APPENDIX 3: The Data Provided by Pfizer on 2/29/2012

Our IR request is identified as FDA Query #5 (related to CMC).

FDA QUERY 5

Provide dissolution testing data (based on n=12 units) carried out at pH 3.5, 4 and 5 using USP Apparatus 1 and 2 (at 50 rpm and 75 rpm) and other conditions that may render a discriminatory dissolution profile.

Figure 1. Revatio POS, 10 mg/mL Dissolution Profiles at 50 rpm Apparatus 2 utilizing pH 3.5 McIlvaine Buffer

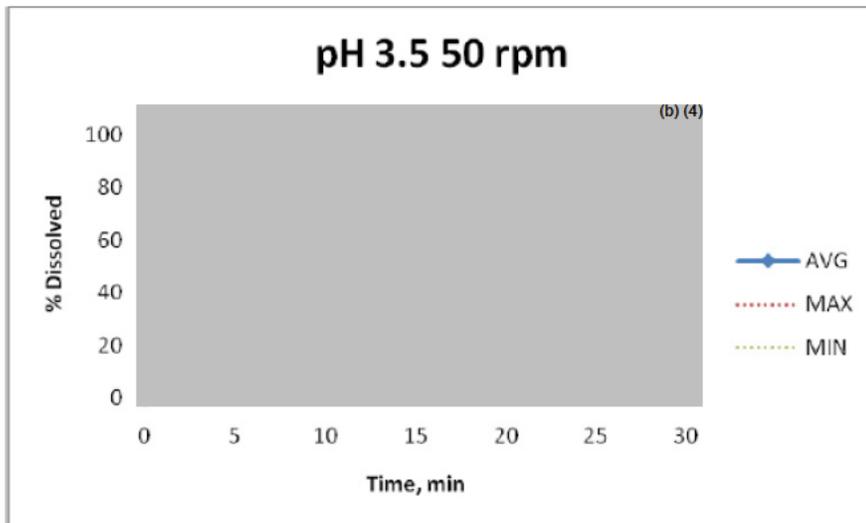


Figure 2. Revatio POS, 10 mg/mL Dissolution Profiles at 75 rpm Apparatus 2 utilizing pH 3.5 McIlvaine Buffer

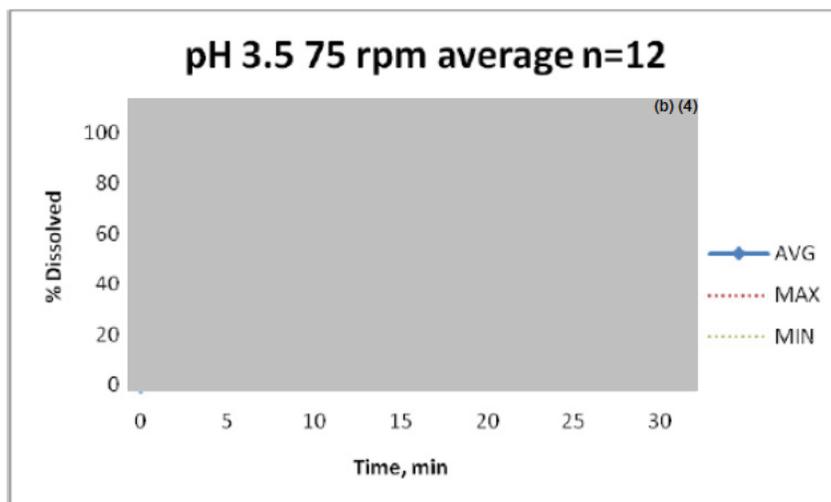


Figure 3. Revatio POS, 10 mg/mL Dissolution Profiles at 50 rpm Apparatus 2 utilizing pH 4.0 McIlvaine Buffer

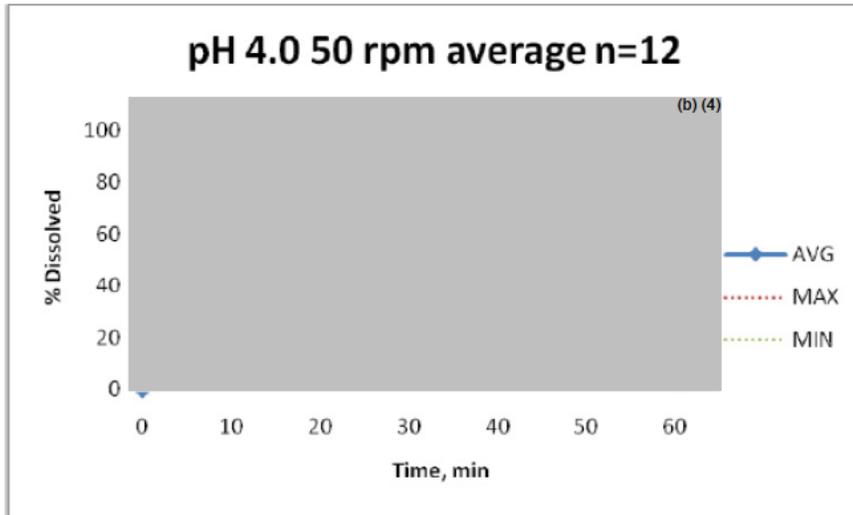
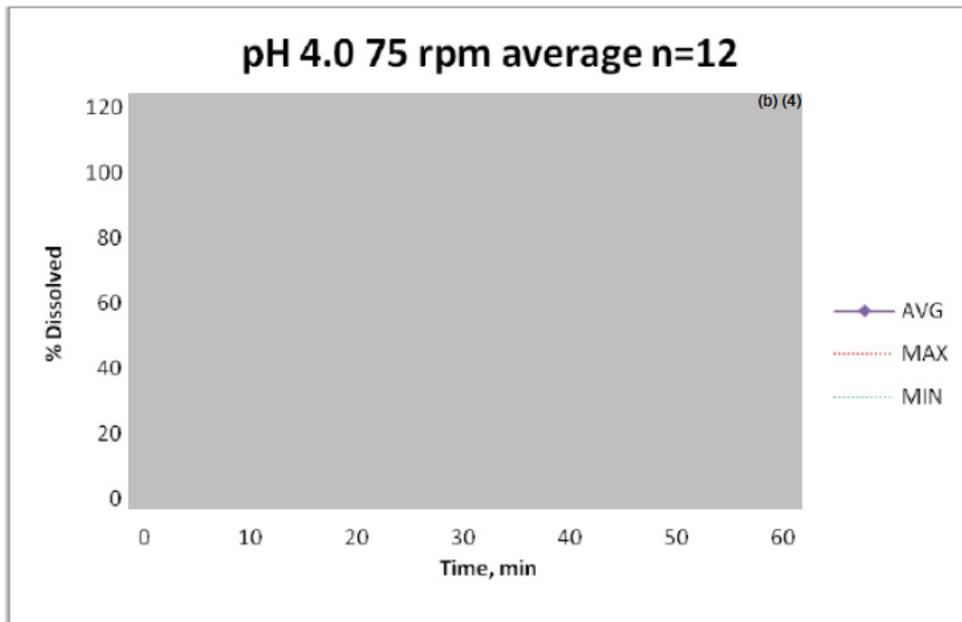


Figure 4. Revatio POS, 10 mg/mL Dissolution Profiles at 75 rpm Apparatus 2 utilizing pH 4.0 McIlvaine Buffer



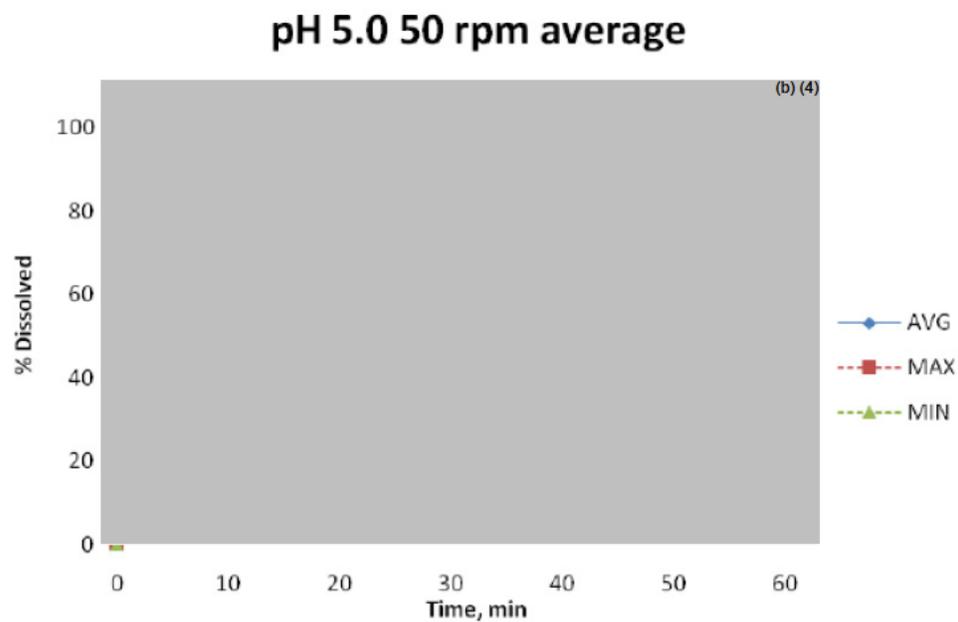


Figure 6. Revatio POS, 10 mg/mL Dissolution Profiles at 75 rpm Apparatus 2 utilizing pH 5.0 McIlvaine Buffer

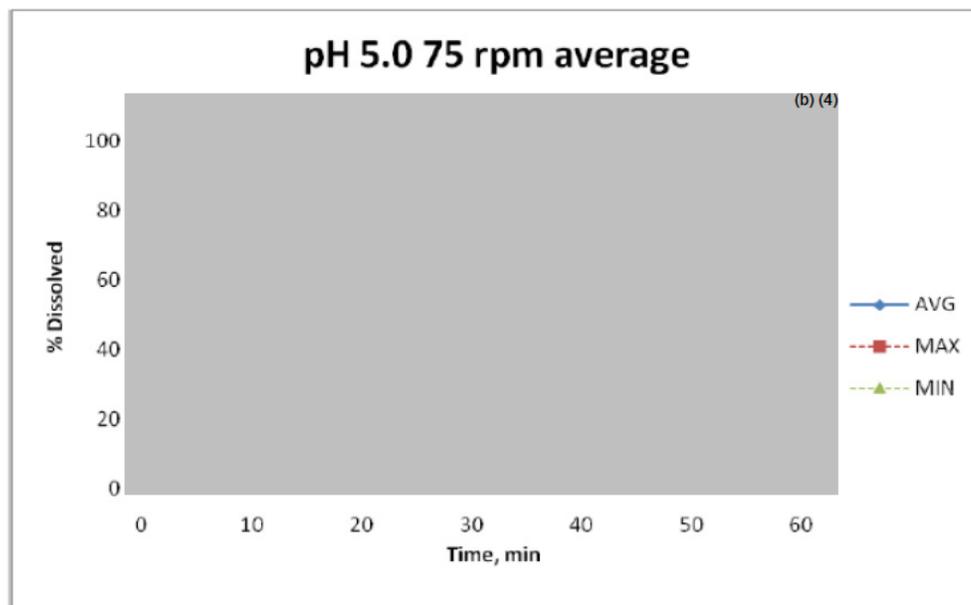


Table 1. Revatio POS, 10 mg/mL Dissolution Profiles at 50 rpm Apparatus 2 utilizing pH 3.5 McIlvaine Buffer

Revatio POS, 10mg/mL pH 3.5 McIlvaine Buffer, 50 rpm paddles				
Vessel	5 min (% dissolved)	10 min (% dissolved)	20 min (% dissolved)	30 min (% dissolved)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Avg				
Max				
Min				
% RSD				

Table 2. Revatio POS, 10 mg/mL Dissolution Profiles at 75 rpm Apparatus 2 utilizing pH 3.5 McIlvaine Buffer

Revatio POS 10mg/mL pH 3.5 McIlvaine Buffer, 75 rpm paddles				
Vessel	5 min (% dissolved)	10 min (% dissolved)	20 min (% dissolved)	30 min (% dissolved)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Avg				
Max				
Min				
% RSD				

Table 3. Revatio POS, 10 mg/mL Dissolution Profiles at 50 rpm Apparatus 2 utilizing pH 3.5 McIlvaine Buffer

Revatio POS, 10mg/mL pH 4.0 McIlvaine Buffer, 50 rpm paddles					
Vessel	5 min (% dissolved)	10 min (% dissolved)	20 min (% dissolved)	30 min (% dissolved)	60 min (% dissolved)
1					(b) (4)
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Avg					
Max					
Min					
% RSD					

Table 4. Revatio POS, 10 mg/mL Dissolution Profiles at 75 rpm Apparatus 2 utilizing pH 4.0 McIlvaine Buffer

Revatio POS, 10mg/mL pH 4.0 McIlvaine Buffer, 75 rpm paddles					
Vessel	5 min (% dissolved)	10 min (% dissolved)	20 min (% dissolved)	30 min (% dissolved)	60 min (% dissolved)
1					(b) (4)
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Avg					
Max					
Min					
% RSD					

Table 5. Revatio POS, 10 mg/mL Dissolution Profiles at 50 rpm Apparatus 2 utilizing pH 5.0 McIlvaine Buffer

Revatio POS, 10mg/mL pH 5.0 McIlvaine Buffer, 50 rpm paddles					
Vessel	5 min (% dissolved)	10 min (% dissolved)	20 min (% dissolved)	30 min (% dissolved)	60 min (% dissolved)
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Avg					
Max					
Min					
% RSD					

Table 6. Revatio POS, 10 mg/mL Dissolution Profiles at 75 rpm Apparatus 2 utilizing pH 5.0 McIlvaine Buffer

Revatio POS, 10mg/mL pH 5.0 McIlvaine Buffer, 75 rpm paddles					
Vessel	5 min (% dissolved)	10 min (% dissolved)	20 min (% dissolved)	30 min (% dissolved)	60 min (% dissolved)
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Avg					
Max					
Min					
% RSD					

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ARZU SELEN
04/25/2012

ANGELICA DORANTES
04/25/2012

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	203139	Brand Name	Revatio
OCP Division (I, II, III, IV, V)	I	Generic Name	Sildenafil citrate
Medical Division	Cardio-Renal Products	Drug Class	PDE5 Inhibitor
OCP Reviewer	Satjit Brar	Indication(s)	Pulmonary arterial hypertension
OCP Team Leader	Pravin Jadhav (PM) Rajanikanth Madabushi	Dosage Form	Tablet
Pharmacometrics Reviewer	Satjit Brar	Dosing Regimen	(b) (4)
Date of Submission	11/30/2011	Route of Administration	Oral
Estimated Due Date of OCP Review	3/30/2012	Sponsor	Pfizer
Medical Division Due Date	3/30/2012	Priority Classification	Priority, 6 months
PDUFA Due Date	5/30/2012		

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Clin. Pharm. and Biopharm. Information

Sildenafil citrate is approved as oral therapy for the treatment of Erectile Dysfunction (Viagra®) and as oral and IV therapy for Pulmonary Arterial Hypertension (PAH) (Revatio®) in adult patients. This application is intended to support the approval of sildenafil in pediatric patients with PAH. This application also presents data for a powder for oral suspension (POS) formulation considered for use in the pediatric population unable to take sildenafil tablets.

The clinical pharmacology data presented focuses on data from three pediatric studies in addition to an ongoing long-term extension study. Clinical pharmacology data from the previously reviewed Viagra and Revatio development programs are also referenced.

Specifically, the pediatric clinical pharmacology program consists of the following studies:

- A1481134: Phase 2, placebo-controlled, study to assess IV sildenafil citrate in PAH patients with post-corrected Heart Surgery for CHD
 - Dose – target plasma concentration of 40, 120, and 360 ng/mL. Loading dose followed by 24-72 hr infusion.
 - Endpoints – Receipt of Additional Therapy, Time to Extubation, Safety and PK
 - *Terminated prematurely due to inadequate recruitment* (18 of 252 patients recruited).
- A1481157: Part 1: Dose-ranging study, IV sildenafil citrate for PPHN (36 patients), Part 2: a double blind placebo controlled study was not conducted due to identified recruitment issues following approval of iNO.
 - Dose – target plasma concentration of up to 150 ng/mL. Loading dose followed by infusion up to 7 days.
 - Endpoints – Safety and PK
 - *Terminated prematurely due to inadequate recruitment* (36 of 256 subjects recruited).
- A1481131: (*PIVOTAL*) 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.
 - Dose – placebo, 10, 20, 40, or 80 mg TID depending on bodyweight.
 - Endpoints – Efficacy (16 week), safety, tolerability and PK

Body Weight (kg)	Dose (mg)		
	Low Dose Treatment Group	Medium Dose Treatment Group	High Dose Treatment Group
$\geq 8-20$	NA	10	20
$>20-45$	10	20	40
>45	10	40	80

- A1481156: Long-term extension to study A1481131.
 - Dose – Same as A1481131 with placebo subjects randomized to low, medium and high doses.
 - Endpoints – Safety, tolerability and long-term efficacy (1 year).

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Three additional studies were conducted as part of the pediatric formulation development Program. The studies were conducted in adult healthy volunteers.

- A1481293: 3-way crossover study conducted to demonstrate bioequivalence of the 10 mg/mL POS formulation and the 10 mg immediate release (IR) tablet relative to the 20 mg IR tablet.
- A1481275: 3-way crossover relative BE study to assess the bioavailability of crushed 20 mg tablet mixed with apple sauce and the intact 20 mg IR tablet, used in Study A1481131, and the interim extemporaneously prepared formulation (20 mg).
- A1481261: a palatability study.

Population PK

Study A1481131 (peds, n=173) and Study A1481140 (adults, n=207).

Population PK/PD

VO₂^{peak} (maximal oxygen consumption) PK/PD – n=115 pediatric subjects

PVRI (pulmonary vascular resistance index) PK/PD – n=403 adults (n=195) and pediatric (n=208) subjects

Extrinsic factors: Co-medications including beta-blockers, digoxin, CYP3A4 and 2C9 substrates/inhibitors/inducers was assessed for their influence on sildenafil PK (from population analysis)

Intrinsic factors: Age, gender, body-weight, PAH etiology, creatinine clearance, clinical labs assessed for their influence on sildenafil PK (from population analysis)

	“X” if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X	7		Also references adult studies under NDA 21-845
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

single dose:				
multiple dose:	x	4		1131, 1156(ext), 1134, 1157
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:	x	4		
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	x	2		
Phase 3 clinical trial:	x	2		1131, 1156 (ext)
Population Analyses -				
Data rich:				
Data sparse:	x	2		
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	2		
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	x			
Literature References				
Total Number of Studies		7		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			Two studies: extemporaneous prepared suspension and oral suspension.
2	Has the applicant provided metabolism and drug-drug interaction information?	x			Assessed via population analysis. Referenced by prior NDA's.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			x	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	x			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			x	
Studies and Analyses					
11	Is the appropriate pharmacokinetic information submitted?	x			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	x			
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	x			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?		x		E-R in label only summarizes safety and not efficacy.
General					
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			x	
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IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. A site inspection needs to be performed for study A1481293, which evaluated the bioequivalence of the Sildenafil Citrate Powder for Oral Suspension. The Division of Bioequivalence and GLP Compliance in the Office of Scientific Investigations has requested the inspection.
2. Initial review of the application shows sildenafil was associated with a harmful effect on survival (extension trial, A1481156) in a dose-response manner. The conclusion is based on dose group assignment at the initiation of studies A1481131/A1481156, and does not take into account further dose titrations during the study. In order to further assess the dose-response relationship with regard to mortality, titration information should be incorporated into the analysis, along with baseline demographics.

Satjit Brar	1/11/2012
_____ Reviewing Clinical Pharmacologist	_____ Date
Pravin Jadhav	1/11/2012
_____ Team Leader/Supervisor	_____ Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SATJIT S BRAR
01/13/2012

PRAVIN R JADHAV
01/13/2012

RAJANIKANTH MADABUSHI
01/17/2012