CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203109
Priority or Standard	P
Submit Date(s)	November 30, 2011
Received Date(s)	November 30, 2011
PDUFA Goal Date	May 30, 2012
Division / Office	DCRP/ODEI
Reviewer Name	Maryann Gordon, M.D.
Established Name	sildenafil
(Proposed) Trade Name	Revatio®
Therapeutic Class	phosphodiesterase type 5 inhibitor
Applicant	Pfizer
Formulation(s)	Powder for oral suspension
Dosing Regimen	Three times daily
Indication(s)	Pulmonary arterial hypertension
Intended Population(s)	Children ages 1-17 years

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1 Recommendations/Risk Benefit Assessment

The risk of using sildenafil (higher mortality rate seen with the higher doses) does not outweigh the drug's purported benefits.

1.1 Recommendation on Regulatory Action

This reviewer recommends that sildenafil not be approved for use in children with pulmonary arterial hypertension. The oral suspension should not be made available because of its possible off label use in children.

The safety findings in this NDA need to be reflected in the label for Revatio tablets. A controlled, randomized, long term safety study in adults with pulmonary arterial hypertension is recommended.

1.2 Risk Benefit Assessment

A higher mortality rate was observed with the higher doses of sildenafil compared to lower doses. Any benefit of the drug was only seen at the higher doses not considered to be safe. The safety of long term use of the lower dose compared to placebo is unknown.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

NA

1.4 Recommendations for Postmarket Requirements and Commitments

A controlled, randomized, long term safety study with the sildenafil tablet in adults with pulmonary arterial hypertension is recommended.

2 Introduction and Regulatory Background

The original NDA for Revatio (sildenafil) was submitted to the FDA on December 3, 2004 and approved for marketing on 03 June 3, 2005 (NDA 21-845). The approved indication is for the treatment of adults with pulmonary arterial hypertension (PAH).

The current application is for the use of REVATIO for the treatment of pediatric patients with PAH (WHO Group I) to improve exercise ability (b) (4). This application presents data on the powder for oral suspension formulation for those children unable to take sildenafil tablets.

The FDA issued the Sildenafil Pediatric Written Request on December 17, 2001. Since then, it was revised over time following interactions between the FDA and Pfizer as data from the adult

and pediatric development programs became available. Complete discussion of these interactions is found in Section 2.5.1.4 of the NDA.

As part of these interactions and the recognition that there is no exercise capacity endpoint available for demonstrating clinical benefit in children across the whole age range (1-17 years), the Division of Cardio Renal Drug Products investigated the utility of alternative endpoints in this population. Analyses conducted within the Agency indicated that drug-induced changes in exercise capacity were associated with drug-induced changes in PVRI in adult patients with PAH.

Though hemodynamic measures form the primary basis for diagnosing PAH and for assessing the severity and rapidity of disease progression in children and adults, these endpoints had not previously formed the primary basis of decision-making for assessing efficacy in adults with PAH for regulatory purposes. Consequently an Advisory Committee (AC) meeting was held on July29, 2010 to discuss the utility of hemodynamic parameters to assess treatment benefit in pediatric patients with PAH. The AC concluded that, for a product with an approved indication in adults with PAH, a treatment effect on PVRI can be used to demonstrate effectiveness and to derive dosing information in the pediatric PAH population. Additionally, exercise, as a secondary endpoint, should be measured in patients able to perform the test.

The current version of the Sildenafil Pediatric Written Request, finalized on June 7, 2011, recognized that in addition to exercise capacity endpoints, PVRI was thought to be an important measure of a treatment response in children with PAH, for a product with an approved indication in adults with PAH. The FDA agreed on 11 July 11, 2011 that this approach met the efficacy requirement of the Sildenafil Pediatric Written Request.

2.1 Product Information

Sildenafil citrate is an inhibitor of phosphodiesterase type 5 (PDE5). It was originally approved in 1998 for the treatment of male patients with erectile dysfunction, under the trade name Viagra, in the United States, NDA 20-895.

Subsequent to the approval of VIAGRA, there was a growing understanding of the role of PDE5 and the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway in the pathology of pulmonary arterial hypertension (PAH). This ultimately led to the approval of sildenafil citrate, under the trade name Revatio, for the treatment of PAH in adults in 2005 (NDA 21-845). The approved dosage regimen for oral Revatio consists of one 20 mg tablet administered 3 times daily.

To date, oral Revatio has been approved for use in adults in more than 50 countries and has been approved in the EU for pediatric use (May 2011). It is estimated that approximately (b) (4) patient-years of exposure to sildenafil (PAH patients) occurred from second quarter of 2005 through the fourth quarter of 2010.

In addition, intravenous Revatio has been approved for use in PAH in over 30 countries including the US.

This current NDA pertains to children aged 1 to 17 years who have been diagnosed with PAH.

2.2 Tables of Currently Available Treatments for Proposed Indications

None currently approved for the pediatric population in the United States.

2.3 Availability of Proposed Active Ingredient in the United States

Available

2.4 Important Safety Issues with Consideration to Approved Drug (sildenafil)

Contraindications include those needing organic nitrates and those with a history of hypersensitivity reaction to sildenafil or any component of the tablet.
Warnings and precautions include the following:
• Cardiovascular effects: Carefully consider whether patients with certain underlying conditions (e.g., resting hypotension, fluid depletion) could be adversely affected by vasodilatory effects of REVATIO. Not recommended in patients with pulmonary veno-occlusive disease.
• Use with alpha-blockers: Note additive blood pressure-lowering effects.
• Bleeding: In patients with PAH secondary to connective tissue disease (CTD), higher rates of epistaxis with REVATIO than placebo, including with concomitant oral vitamin K antagonists.
• Use with ritonavir and other potent CYP3A inhibitors: Coadministration not recommended.
• Effects on the eye: Consider discontinuing REVATIO if sudden loss of vision occurs, which could be non-arteritic ischemic optic neuropathy (NAION).
• Hearing impairment: Discontinue REVATIO if sudden decrease or loss of hearing occurs.
• Use with PDE5 inhibitors: Avoid use with VIAGRA or other PDE5 inhibitors.
• Prolonged erection: Advise patients to seek emergency treatment if an erection lasts > 4 hours. Use REVATIO with caution in patients predisposed to priapism.
• Pulmonary hypertension secondary to sickle cell disease: REVATIO may cause serious vaso-occlusive crises.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Pfizer initiated the pediatric program in parallel with the adult program. IND 63,175 was submitted to FDA in August 2001. FDA issued a Pediatric Written Request (WR) on December 17, 2001, in which the sponsor Pfizer was asked to perform “a controlled trial measuring either clinical events or functional improvement in which oral sildenafil and placebo are each added to standard therapy in pediatric patients aged birth to 16 years (infants to adolescents) with primary or secondary pulmonary hypertension (identified as Study A1481131) followed by an open-label safety extension study (identified as Study A1481156). Ongoing interactions between the FDA

and Pfizer and submission of efficacy and safety data in the adult PAH population, resulted in revisions to the sildenafil WR.

As part of these ongoing communications and a separate FDA initiative to review appropriate endpoints in pediatric PAH, the FDA and Pfizer participated in an Advisory Committee (AC) meeting on July 29, 2010, regarding the suitability of using hemodynamic endpoints to demonstrate effectiveness and derive dosing information in the pediatric PAH population, for drug products with an approved indication in adult PAH.

Based on the outcome of this advisory committee meeting, a revised WR was issued on June 7, 2011. Details of the extensive interactions between FDA and Pfizer are provided in Module 1.6.3 of this application (History of FDA Interactions).

2.6 Other Relevant Background Information

Cross references to other applications are shown below.

IND#	Submission Date	Drug
63,175 (Pediatric Pulmonary Arterial Hypertension)	31 August 2001	REVATIO® (sildenafil citrate) tablets, UK-92,480, 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*pyrazolo[4,3-*d*] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate
64,924 (Pulmonary Arterial Hypertension)	06 June 2002	REVATIO® (sildenafil citrate) tablets, UK-92,480, 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*pyrazolo[4,3-*d*] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate

NDA#	Submission Date	Drug
20-895	29 September 1997	VIAGRA® (sildenafil citrate) tablets, UK-92,480, 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5-yl)-4-ethoxyphenyl]sulfonyl]-4-methylpiperazine citrate
21-845	02 December 2004	REVATIO® (sildenafil citrate) tablets, UK-92,480, 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*pyrazolo[4,3-*d*] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate
22-473	21 January 2009	REVATIO® (sildenafil citrate) Injection, UK-92,480, 1-[[3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1*H*pyrazolo[4,3-*d*] pyrimidin-5-yl)-4-ethoxyphenyl] sulfonyl]-4-methylpiperazine citrate

3 Ethics and Good Clinical Practices

According to the study reports, the studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory
requirements were followed.

3.1 Submission Quality and Integrity

The sponsor stated that they monitored the studies through routine center visits. At these visits, study procedures were reviewed, CRF data compared to original clinical records, data queries resolved, and protocol deviations discussed with the investigator. Telephone and e-mail contact was maintained with the investigators between center visits. In addition, the overall study conduct was subject to internal quality review by the sponsor. Quality assurance audits were performed at selected centers by the sponsor's own independent quality assurance group or by CRO and/or individual contract personnel under the group's direction. These audits were conducted according to the sponsor's procedures and GCP guidelines. Periodically some/all of the facilities used in the study (e.g., laboratory) may have been reviewed or inspected by the IRB/IEC and/or regulatory authorities.

3.2 Compliance with Good Clinical Practices

There is no reason known to this reviewer to question that the clinical trials were performed under acceptable ethical standards and with Good Clinical Practice.

3.3 Financial Disclosures

There are two covered studies for this NDA. The financial disclosure data for A1481131 covers the time period from the start of the study through end of the study plus one year and Pfizer continues to track financial disclosure data for A1481156 through April 2012.

Pfizer stated that it has examined its financial data regarding significant payments of other sorts made to all investigators who participated in the study and equity information as provided by those investigators, as defined in 21 CFR 54.2. With a total of 426 investigators listed in the two covered studies, 10 investigators had significant payments of other sorts and no investigators disclosed equity in the sponsor.

Pfizer stated that it was unable to obtain financial disclosure information specific to equity in Pfizer for 2 sub-investigators in study A1481131. Pfizer has examined the financial data regarding the other categories of financial arrangements including significant payments of other sorts for all investigators who participated on the covered study. Additionally, all investigators were contacted at the time of the submission to remind them of their obligation to disclose financial information for Pfizer Inc and affiliated companies, including Wyeth and its affiliates, which are wholly owned by Pfizer.

CERTIFICATION
Per US FDA Form 3454, certification is provided for 416 of the 426 investigators listed in the study reports indicating:

- Certified investigators. A total of 409 of the investigators are certified as having no Financial Arrangement as defined in 21 CFR 54.2.
- Due diligence in collecting the information on Equity. A total of 7 of the investigators did

not respond or could not be reached by our due diligence effort.

Note that all investigators are assessed for equity, significant payments of other sorts, variable compensation and propriety interest. With the exception of equity, all other financial arrangements are checked via internal Pfizer procedures.

DISCLOSURE US FDA Form 3455, *10 of the 426 investigators listed on the study report had significant payments of other sorts to disclose. All Investigator Initiated Research Grants associated with the sponsors' investigators were paid directly to the Institution rather than to the individual investigator. Copies of the forms are found in Module 1, Section 1.3.4 of the NDA.

* This number represents the total number of 3455 forms and not by total unique investigators. Due to a difference in time period of each study, separate 3455 forms were prepared for each investigator who participated in both studies.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Pending

4.2 Clinical Microbiology

NA

4.3 Preclinical Pharmacology/Toxicology

Pending

4.4 Clinical Pharmacology

Pending

4.4.1 Mechanism of Action

Sildenafil is an inhibitor of cGMP specific phosphodiesterase type-5 (PDE5) in the smooth muscle of the pulmonary vasculature, where PDE5 is responsible for degradation of cGMP. Sildenafil, therefore, increases cGMP within pulmonary vascular smooth muscle cells resulting in relaxation. In patients with pulmonary arterial hypertension, this can lead to vasodilation of the pulmonary vascular bed and, to a lesser degree, vasodilatation in the systemic circulation. Studies in vitro have shown that sildenafil is selective for PDE5. Its effect is more potent on PDE5 than on other known phosphodiesterases (10-fold for PDE6, > 80-fold for PDE1, > 700-fold for PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10, and PDE11). The approximately

4,000-fold selectivity for PDE5 versus PDE3 is important because PDE3 is involved in control of cardiac contractility. Sildenafil is only about 10-fold as potent for PDE5 compared to PDE6, an enzyme found in the retina and involved in the phototransduction pathway of the retina. This lower selectivity is thought to be the basis for abnormalities related to color vision observed with higher doses or plasma levels.

In addition to pulmonary vascular smooth muscle and the corpus cavernosum, PDE5 is also found in other tissues including vascular and visceral smooth muscle and in platelets. The inhibition of PDE5 in these tissues by sildenafil may be the basis for the enhanced platelet anti-aggregatory activity of nitric oxide observed in vitro, and the mild peripheral arterial-venous dilatation in vivo.

4.4.2 Pharmacodynamics

Effects of REVATIO on Blood Pressure
Single oral doses of sildenafil 100 mg administered to healthy volunteers produced decreases in supine blood pressure (mean maximum decrease in systolic/diastolic blood pressure of 8/5 mmHg). The decrease in blood pressure was most notable approximately 1-2 hours after dosing, and was not different from placebo at 8 hours. Similar effects on blood pressure were noted with 25 mg, 50 mg and 100 mg doses of sildenafil, therefore the effects are not related to dose or plasma levels within this dosage range. Larger effects were recorded among patients receiving concomitant nitrates.

Single oral doses of sildenafil up to 100 mg in healthy volunteers produced no clinically relevant effects on ECG. After chronic dosing of 80 mg TID to patients with pulmonary arterial hypertension, no clinically relevant effects on ECG were reported.

After chronic dosing of 80 mg TID sildenafil to healthy volunteers, the largest mean change from baseline in supine systolic and supine diastolic blood pressures was a decrease of 9.0 mmHg and 8.4 mmHg, respectively.

After chronic dosing of 80 mg TID sildenafil to patients with systemic hypertension, the mean change from baseline in systolic and diastolic blood pressures was a decrease of 9.4 mmHg and 9.1 mmHg, respectively.

After chronic dosing of 80 mg TID sildenafil to patients with pulmonary arterial hypertension, lesser reductions than above in systolic and diastolic blood pressures were observed (a decrease in both of 2 mmHg).

Effects of REVATIO on Vision
At single oral doses of 100 mg and 200 mg, transient dose-related impairment of color discrimination (blue/green) was detected using the Farnsworth-Munsell 100-hue test, with peak effects near the time of peak plasma levels. This finding is consistent with the inhibition of

PDE6, which is involved in phototransduction in the retina. An evaluation of visual function at doses up to 200 mg revealed no effects of REVATIO on visual acuity, intraocular pressure, or pupillometry.

4.4.3 Pharmacokinetics

Absorption and Distribution
REVATIO is rapidly absorbed after oral administration, with a mean absolute bioavailability of 41% (25-63%). Maximum observed plasma concentrations are reached within 30 to 120 minutes (median 60 minutes) of oral dosing in the fasted state. When REVATIO is taken with a high-fat meal, the rate of absorption is reduced, with a mean delay in Tmax of 60 minutes and a mean reduction in Cmax of 29%. The mean steady state volume of distribution (Vss) for sildenafil is 105 L, indicating distribution into the tissues. Sildenafil and its major circulating N-desmethyl metabolite are both approximately 96% bound to plasma proteins. Protein binding is independent of total drug concentrations.

Bioequivalence was established between the 20 mg tablet and the 10 mg/ml oral suspension when administered as a 20 mg single oral dose of sildenafil (as citrate).

Metabolism and Excretion
Sildenafil is cleared predominantly by the CYP3A (major route) and cytochrome P450 2C9 (CYP2C9, minor route) hepatic microsomal isoenzymes. The major circulating metabolite results from N-desmethylation of sildenafil, and is, itself, further metabolized. This metabolite has a phosphodiesterase selectivity profile similar to sildenafil and an in vitro potency for PDE5 approximately 50% of the parent drug. In healthy volunteers, plasma concentrations of this metabolite are approximately 40% of those seen for sildenafil, so that the metabolite accounts for about 20% of sildenafil's pharmacologic effects. In patients with pulmonary arterial hypertension, however, the ratio of the metabolite to sildenafil is higher. Both sildenafil and the active metabolite have terminal half-lives of about 4 hours. After either oral or intravenous administration, sildenafil is excreted as metabolites predominantly in the feces (approximately 80% of the administered oral dose) and to a lesser extent in the urine (approximately 13% of the administered oral dose).

Population Pharmacokinetics
Age, gender, race, and renal and hepatic function were included as factors assessed in the population pharmacokinetic model to evaluate sildenafil pharmacokinetics in patients with PAH. The dataset available for the population pharmacokinetic evaluation contained a wide range of demographic data and laboratory parameters associated with hepatic and renal function. None of these factors had a significant impact on sildenafil pharmacokinetics in patients with PAH.
In patients with PAH, the average steady-state concentrations were 20-50% higher when compared to those of healthy volunteers. There was also a doubling of Cmin levels compared to healthy volunteers. Both findings suggest a lower clearance and/or a higher oral bioavailability of sildenafil in patients with pulmonary arterial hypertension compared to healthy volunteers.

5 Sources of Clinical Data

The clinical study reports, required case record forms, and data related to the relevant clinical trials were submitted electronically.

5.1 Tables of Studies/Clinical Trials

See Table 2 in section 5.3

5.2 Review Strategy

This was a review written by a single medical reviewer.

5.3 Discussion of Individual Studies/Clinical Trials

Efficacy data for sildenafil with respect to pediatric PAH patients (1-17 years of age) were obtained from study A1481131. Supportive data is included from an interim data cut of the long-term extension study A148115. All studies contained in the sildenafil pediatric PAH program are outlined in the table below.

Table 2. List of Clinical Studies in the REVATIO Pediatric Program

Study Title and Design	Dose or Study Treatments	Endpoints
A1481131: Phase 3 randomized, double-blind, multi-centre, placebo controlled parallel group, dose ranging study. Subject's aged 1 to 17 years with body weight ≥8 kg, and with primary pulmonary hypertension (PH), PAH secondary to congenital heart disease (PAH associated with congenital systemic-to-pulmonary shunts, d-transposition of the great arteries and PAH in subjects who had undergone surgical repair of other congenital heart lesions ≥6 months prior to screening), or collagen vascular disease.	10, 20, 40, or 80 mg TID depending upon bodyweight to achieve steady state concentrations of 47, 140, and 373 ng/mL in the low, medium, and high doses, respectively. Placebo	Efficacy (16 week), safety, tolerability, and PK.
A1481156: Long-term randomized extension to Study A1481131	As for A1481131 above, excluding placebo.	Long-term safety, tolerability, and I year efficacy.
A1481134: Phase 3, Randomized, Double-blind, Multicentre Study to Assess IV Sildenafil Citrate as Treatment of PH Post-Corrected Heart Surgery for CHD (18 Patients; Terminated Prematurely due to Lack of Recruitment)	Target Plasma Concentration of 40, 120, 360 ng/mL in the low, medium and high doses, respectively. Loading Dose followed by 24-72 hr Infusion (Concentration 1 mg/mL)	Efficacy, Safety, Tolerability and PK
A1481157: (Part 1) Multicentre, Randomized, Placebo-controlled, Dose-ranging Study, IV Sildenafil Citrate for PPHN (36 Patients; Terminated Prematurely due to Lack of Recruitment)	Target Plasma Concentration up to 150 ng/mL. Loading Dose followed by Infusion for up to 7 Days.	PK and Safety

Study Title and Design	Dose or Study Treatments	Endpoints
A1481261: A single-blind study in healthy adult volunteers to investigate the palatability of different oral suspension formulations of sildenafil citrate	- Sildenafil citrate in purified water at 10 mg active/mL with flavoring agents (b) (4) and sweeteners (b) (4) - Sildenafil citrate in purified water at 10 mg active/mL with flavoring agents (b) (4) and sweeteners (b) (4) - Sildenafil citrate in purified water at 10 mg active/mL with flavoring agents (b) (4) and sweeteners (b) (4) - Sildenafil citrate in purified water at 10 mg active/mL with flavoring agents (b) (4) and sweeteners (b) (4) - Placebo (Control) formulation - Flavor agents (b) (4) and sweeteners (b) (4) in solution with purified water.	To assess the palatability of 4 prototype suspension formulations containing 10 mg sildenafil citrate, sweeteners and proprietary flavor agents and a placebo suspension formulation containing a combination of flavor agents and sweeteners.
A1481275: 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	- REVATIO 20 mg intact tablet. - REVATIO 20 mg crushed tablet mixed with apple sauce. - REVATIO 20 mg extemporaneously prepared suspension.	Bioavailability, safety and tolerability

Study Title and Design	Dose or Study Treatments	Endpoints
A1481293: A 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	- REVATIO 20 mg IR oral tablet - 2 x 10 mg sildenafil citrate IR oral tablet - 2 mL of the sildenafil citrate 10 mg/mL POS (provided as a powder in a bottle for constitution with water).	Bioequivalence, safety and tolerability

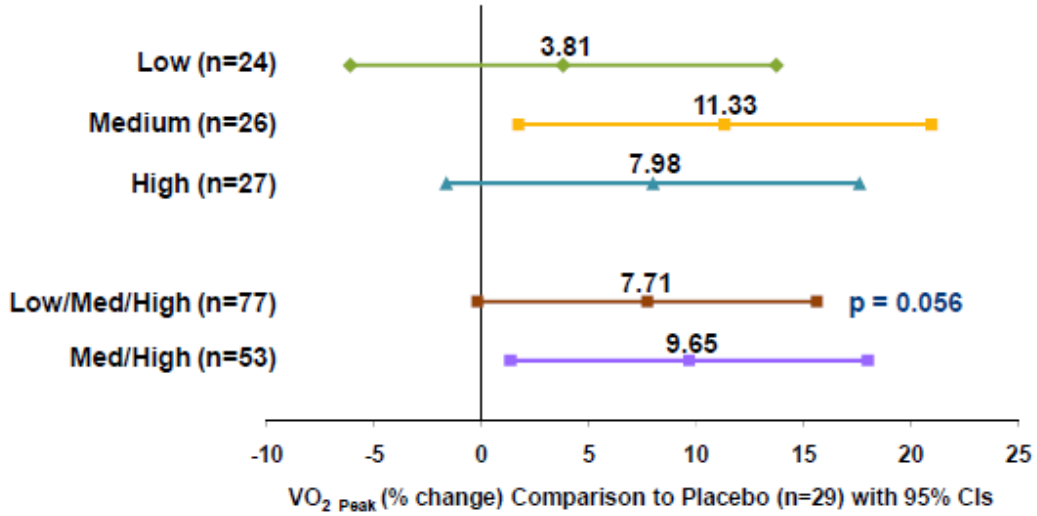
CHD – Congenital heart disease; EP- Extemporaneously Prepared; IR- Immediate Release; PH- Pulmonary Hypertension; POS- Powder for Oral Suspension; PPHN – Pediatric Pulmonary Hypertension of the Newborn; PD – Pharmacodynamics; PK- Pharmacokinetics.
† Please note that although the protocol title includes the term bioequivalence, the study was sample sized as a bioavailability study..

6 Review of Efficacy

Efficacy Summary

The determination of efficacy was derived from one study, A1481131. The study failed to show a significant effect of sildenafil on the primary endpoint (percent change from baseline in peak VO2 consumed at week 16) in children with PAH who were developmentally able to exercise (n=115). The combined doses (low, medium and high) produced a statistically insignificant 7.71 % increase in the peak VO2 (combined doses) treatment effect (p=0.056). The low dose of sildenafil improved peak VO2 by 3.81%, a clinically insignificant response.

Figure 4. Treatment Difference in Percentage Change from Baseline in Study A1481131 for VO_{2peak} at Week 16: Mean and 95% Confidence Intervals – ITT population



There was evidence of an effect of sildenafil on hemodynamic parameters, particularly PVRI. However, the effect was limited to the high dose (-407.5 dyne.s.cm-5.m2); the effect of the lower dose was negligible (8.0 dyne.s.cm-5.m2).

Table 20. Change from Baseline in PVRI (CRF Data) at Week 16 – ITT Population

	Sildenafil				
Treatment Group	**Low**	**Medium**	**High**	**Combined**	**Placebo**
Number of subjects	36	49	67	152	50
Mean (SD) PVRI, dyne.s.cm^{-5}.m^2					
Baseline[a]	1877.7 (1214.5)	1518.1 (1102.6)	1669.9 (1518.1)	1669.9 (1326.3)	1286.4 (958.8)
Week 16	1885.6 (1278.4)	1278.4 (878.9)	1262.4 (1078.7)	1414.2 (1094.6)	1414.2 (1102.6)
Change from baseline	8.0 (870.9)	-231.7 (918.9)	-407.5 (1174.5)	-255.7 (1038.7)	127.8 (735.1)
Mean difference versus placebo (SE)	-47.9 (215.7)	-359.6 (191.8)	-575.3 (183.8)	-327.6 (159.8)	NA
95% Confidence interval[b]	-471.4, 375.5	-743.1, 24.0	-934.8,-215.7	-639.2, -16.0	NA
P-value[b]	NA	NA	NA	0.041	NA

Source: Study A1481131 CSR Tables 5.4.1 and 5.4.2.1 (Module 5.3.5.1)
ITT=intention-to-treat population; SE=standard error; SD=Standard Deviation; NA=not applicable
[a] Baseline was the last PVRI assessment up to 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 covariates

Introduction

While most of the therapies developed for adults with PAH have been approved based on their effectiveness in prolonging submaximal exercise (6-minute walk test), it is proving difficult to evaluate exercise in children. The submaximal testing has been shown not to be appropriate for children because 1) the majority of children have relatively preserved right heart function

compared to adults and can have near normal submaximal exercise tolerance even in severe disease; 2) cooperation and motivation for submaximal exercise testing may vary in children, challenging consistency, reproducibility and interpretability.

Initially, the sponsor for this application chose to use cardiopulmonary exercise testing (CPET), a comprehensive maximal exercise test as the primary endpoint.

As stated above, not all children are able to perform any exercise test. Children below the age of 7 years are routinely excluded as are children with medical conditions such as Down syndrome. As a result of these limitations and in discussion with FDA, the efficacy endpoints that could be assessed in all children, including those unable to reliably perform exercise testing, were the effects of sildenafil on hemodynamic parameters (including PVRI and mPAP) and WHO functional class. However, the meaningfulness of hemodynamic endpoints to evaluate patients with PAH is controversial.

Analyses performed by the Agency using data obtained from adults indicate that drug-induced changes in exercise capacity could be associated with drug-induced changes in PVRI in adult patients with PAH. Though hemodynamic measures form the primary basis for making the diagnosis of PAH and for assessing the severity and rapidity of disease progression in both children and adults, these endpoints have not previously formed the primary basis of decision-making for assessing efficacy for regulatory purposes. An Advisory Committee meeting was held on July 29, 2010 to discuss the usefulness of changes in PVRi in specific populations. The committee concluded that, for a product with an approved indication in adults with PAH, a treatment effect on PVRI can be used to demonstrate effectiveness and to derive dosing information in the pediatric PAH population.

For this application, it was decided that while exercise data were required from children who could perform the testing, the change in PVRI could be used in this program as the measure of effectiveness that covers the pediatric age range 1 to 17 years.

6.1 Indication

Pulmonary arterial hypertension (PAH) in pediatric patients (ages 1-17 years).

6.1.1 Methods

Study A1481131 was a randomized, double-blind, multi-center, placebo controlled parallel group dose ranging study, in treatment naïve subjects with body weight $\geq$ 8 kg.

For each subject, the study consisted of an initial screening visit, a baseline visit, 16 weeks of double-blind treatment, and a follow-up visit.

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.

The efficacy assessments included the CPX test (only those 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.

6.1.2 Demographics

The main criteria for study inclusion were: subjects with primary PAH and secondary PAH associated with congenital systemic-to-pulmonary shunts with a baseline resting room air oxygen saturation (SaO2) $\geq$ 88 or with d-transposition of the great arteries repaired within the first 30 days of life; in subjects who had undergone surgical repair of other congenital heart lesions $\geq$6 months prior to screening and did not have clinically significant residual left-sided heart disease consistent with the exclusion criteria, aged from 1 to 17 years (subject to country specific protocols) and weighing $\geq$8 kg who had symptomatic PAH were included.

Subjects were excluded from the study if they had PH secondary to other diseases, left-sided heart disease and other similar heart-related diseases, or had treatment with off-label sildenafil, an endothelin-A receptor antagonists or prostacyclin/prostacyclin analogue within 30 days prior to randomization, or who were taking prohibited medications.

There were 234 subjects randomized. The subjects' demographics, by treatment group, are shown below.

Table S3. Demographic Characteristics.

	Sildenafil				
Dose	Low	Medium	High	Combined	Placebo
Number of subjects	42	55	77	174	60
Male, n (%)	17 (40.5)	24 (43.6)	26 (33.8)	67 (38.5)	22 (36.7)
Female, n (%)	25 (59.5)	31 (56.4)	51 (66.2)	107 (61.5)	38 (63.3)
Age (years), n (%):					
1-4	0	9 (16.4)	19 (24.7)	28 (16.1)	7 (11.7)
5-12	25 (59.5)	28 (50.9)	36 (46.8)	89 (51.1)	37 (61.7)
13-17	17 (40.5)	18 (32.7)	22 (28.6)	57 (32.8)	16 (26.7)
≥18	0	0	0	0	0
Race, n (%):					
White	19 (45.2)	26 (47.3)	28 (36.4)	73 (42.0)	24 (40.0)
Black	1 (2.4)	1 (1.8)	1 (1.3)	3 (1.7)	2 (3.3)
Asian	6 (14.3)	13 (23.6)	15 (19.5)	34 (19.5)	7 (11.7)
Other	18 (38.1)	15 (27.3)	33 (42.9)	64 (36.8)	27 (45.0)
Region, n (%):					
America[a]	10 (23.8)	11 (20.0)	16 (20.8)	37 (21.3)	17 (28.3)
Asia	6 (14.3)	13 (23.6)	15 (19.5)	34 (19.5)	7 (11.7)
Europe	16 (38.1)	18 (32.7)	22 (28.6)	56 (32.2)	16 (26.7)
South America	10 (23.8)	13 (23.6)	24 (31.2)	47 (27.0)	20 (33.3)
Mean weight (range), kg	38.2 (20.0-105.0)	32.1 (8.6-106.0)	25.8 (8.2-61.0)	30.8 (8.2-106.0)	29.3 (9.1-60.0)
Mean height (range), cm	141.6 (111.0-172.0)	130.5 (77.0-192.5)	120.8 (72.0-180.0)	128.9 (72.0-192.5)	128.4 (78.0-173.0)
Mean BMI (SD), kg/m^2	18.2 (4.8)	17.6 (3.9)	16.3 (3.4)	17.2 (4.0)	16.9 (3.6)

BMI=body mass index
[a] America=includes USA, Canada and Mexico

Most subjects were female and between 5 and 17 years of age and most were white or Asian. The majority of subjects were residing outside the United States.

The subjects' diagnoses and duration of PAH are shown in the table below.

Table 2.2.1 Page 1 of 1
Sildenafil Protocol A1481131
Primary Diagnoses and Durations

	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	Sildenafil Combined Doses	Placebo
Number of Subjects	42	55	77	174	60
Primary Diagnosis MedDRA (v11.0) Lower Level Term					
PRIMARY PULMONARY HYPERTENSION					
Number of Subjects	12	19	26	57	21
Duration Since First Diagnosis (yrs)					
Mean	1.122	1.671	1.460	1.459	2.225
Range	0.005-7.042	0.003-7.280	0.008-8.290	0.003-8.290	0.027-12.422
Unspecified (N)	0	0	0	0	0
SECONDARY PULMONARY ARTERIAL HYPERTENSION					
Number of Subjects	30	36	51	117	39
Duration Since First Diagnosis (yrs)					
Mean	7.468	6.412	5.099	6.110	5.663
Range	0.005-16.255	0.085-16.079	0.003-15.699	0.003-16.255	0.038-16.958
Unspecified (N)	0	0	0	0	0

Duration (years) from first diagnosis to Day 1 of study

Approximately one third of subjects had primary PAH and the remaining subjects had secondary PAH. Mean duration since first diagnosis was longer for the subjects with secondary (approximately 6 years) compared to those with primary (approximately 1.5 years).

Table 7. Summary of Primary Diagnosis for Subjects in Study A1481131

Primary Diagnosis	Sildenafil Combined Dose	Placebo	All Subjects
All subjects (N=234)			
Primary PAH	32.8%	35.0%	33.3%
Secondary PAH	65.5%	63.3%	65.0%
Congenital systemic-to-pulmonary shunts	35.6%	38.3%	36.3%
Surgical repairs	29.9%	25.0%	28.6%

The most common underlying disease associated with secondary PAH was congenital systemic-to-pulmonary shunt (85 subjects), followed by surgical repair of congenital heart defects (ventricular septal defect: 31 subjects, atrial septal defect: 8 subjects, patent ductus arteriosus: 11 subjects). There were four subjects with D-transposition of the great arteries.

6.1.3 Subject Disposition

Of the 324 subjects screened, 235 subjects were randomized to 1 of 4 treatment groups. One subject (10463, sildenafil medium dose) withdrew prior to taking any study treatment because the hemodynamic entrance criteria were not met. A total of 228 subjects completed the study and six subjects discontinued prematurely (mostly because of adverse events). See table below.

Table T7. Disposition

	Sildenafil				
Dose	Low	Medium	High	Combined	Placebo
Number (%) of subjects:					
Randomized	42	56	77	175	60
Treated	42	55[a]	77	174[a]	60
Completed	40 (95.2)	55 (98.2)	75 (98.7)	170 (97.1)	58 (96.7)
Entered Study A1481156	38 (90.5)	53 (94.6)	74 (96.1)	165 (94.3)	55 (91.7)
Had follow-up visit and did not enter Study A1481156	1 (2.4)	1 (1.8)	1 (1.3)	3 (1.7)	3 (5.0)
Did not have follow-up visit and did not enter Study A1481156	1 (2.4)	1 (1.8)	0	2 (1.1)	0
Discontinued prior to treatment	0	1 (1.8)	0	1 (0.6)	0
Discontinued[b]	2 (4.8)	0	2 (2.60)	4 (2.3)	2 (3.3)
Had follow-up visit	1 (2.4)	0	1 (1.3)	2 (1.1)	0
Did not have follow-up visit	1 (2.4)	0	1 (1.3)	2 (1.1)	2 (3.3)
Reason for Discontinuation					
Adverse event	1 (2.4)	0	1 (1.3)	2 (1.1)	0
Lost to follow-up	0	0	0	0	1 (1.7)
Other	1 (2.4)	0	1 (1.3)	2 (1.1)	0
No longer willing to participate	0	0	0	0	1 (1.7)
Analyzed for efficacy					
ITT[c]	42 (100)	55 (98.2)	77 (100)	174 (99.4)	60 (100)
Per Protocol	23 (54.8)	23 (41.1)	27 (35.1)	73 (41.7)	24 (40.0)
Aged ≥5 years	42 (100)	46 (82.1)	58 (75.3)	146 (83.4)	53 (88.3)
CHQ-PF28[d]	37 (88.1)	34 (60.7)	48 (62.3)	119 (68.0)	46 (76.7)
Developmentally able	28 (66.7)	28 (50.0)	29 (37.7)	85 (48.6)	30 (50.0)
Analyzed for safety					
Adverse events	42 (100)	55 (98.2)	77 (100)	174 (99.4)	60 (100)
Laboratory data	42 (100)	55 (98.2)	76 (98.7)	173 (98.9)	60 (100)
Visual safety	42 (100)	55 (98.2)	75 (97.4)	172 (98.3)	60 (100)

Source: Table 1.1 and Table 4.1
CHQ-PF28=Child Health Questionnaire-Parent Report
[a] Subject 10463 was randomized but not treated
[b] Discontinuations occurring >7 days after the last dose of study treatment were attributed to the last study treatment received
[c] Subjects who were randomized to study treatment and received ≥1 dose of study treatment
[d] Subjects who fulfilled the criteria for the ITT were ≥5 years old and had CHQ-PF28 assessments in their first language

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint was the percent change in peak VO2 (normalized to body weight) at trough plasma levels from baseline to Week 16 assessed by the cardiopulmonary exercise (CPX) test (cycle ergometry). The baseline value was taken as the average of the screening and baseline readings.

Cycle Ergometry
CPX was performed at screening, baseline, Week 8 (at peak plasma levels of sildenafil) and Week 16/end-of-study (at trough plasma levels of sildenafil). The cycle ergometry protocol imposed a progressively increasing workload on the subject until the limit of subject's tolerance was reached. The exercise test was conducted in a fasted condition.

Subjects were encouraged to exercise for as long as they could, but could stop at any time. They were instructed to maintain between 50-60 revolutions/minute. Subjects were instructed to alert the study team if they felt chest pain or pre-syncopal symptoms. The actual exercise time was approximately 8 to 12 minutes. The same workload increment was maintained throughout the study where possible. Every effort was made to keep the coach and equipment consistent between tests when possible.

Data were collected and sent to a core laboratory for interpretation. If the CPX test was deemed inadequate by the core laboratory (e.g., primary endpoint could not be determined) the subject was asked to repeat the test.

The measurements obtained during testing included peak volume of oxygen consumed (VO2), exercise time to peak VO2, total ventilation (VE), respiratory exchange ratio (RER) (ratio of carbon dioxide produced to oxygen consumed [VCO2/VO2]), end tidal O2 and CO2, percent predicted peak VO2 and anaerobic threshold (AT). Respiratory gas exchange and minute ventilation were determined on a breath-by-breath system throughout. Blood pressure, heart rate and ECG were monitored continuously during the CPX test.

The number of subjects excluded from efficacy analyses by treatment group are shown in the table below.

Table T9. Subjects Excluded from Efficacy Analyses

	Sildenafil				
Dose	Low	Medium	High	Combined	Placebo
Number (%) of subjects:					
Randomized	42	56	77	175	60
Treated	42	55[a]	77	174[a]	60
Analyzed for efficacy					
ITT population[b]	42 (100)	55 (98.2)	77 (100)	174 (99.4)	60 (100)
Developmentally able (peak VO_2)	28 (66.7)	28 (50.0)	29 (37.7)	85 (48.6)	30 (50.0)
Analyzed for primary analysis	24 (57.1)	26 (46.4)	27 (35.1)	77 (44)	29 (48.3)
PP population	23 (54.8)	23 (41.1)	27 (35.1)	73 (41.7)	24 (40.0)
Reason for exclusion from primary analysis[c]					
Discontinued	1 (3.6)	0	1 (3.4)	2 (2.4)	0
Machine failure/damage	1 (3.6)	0	1 (3.4)	2 (2.4)	1 (3.3)
Too ill	1 (3.6)	0	0	1 (1.2)	0
Other[d]	1 (3.6)	2 (7.1)	0	3 (3.5)	0
Reason for exclusion from PP population					
Failed inclusion/exclusion criteria	1 (3.6)	1 (3.6)	1 (3.4)	3 (3.5)	1 (3.3)
Non compliance	0	0	0	0	0
Prohibited concomitant medication	0	0	0	0	0
No baseline or Week 16 VO_2	5 (17.9)	4 (14.3)	2 (6.9)	11 (12.9)	5 (16.7)
Received incorrect medication	0	1 (3.6)	0	1 (1.2)	0

Source: Tables 1.1, 5.1.1 and 5.1.2, and Appendix A, Item 8
ITT=intention-to-treat; PP=per protocol
[a] Subject 10463 was randomized but not treated
[b] Subjects who were randomized to study treatment and received ≥1 dose of study treatment
[c] All subjects were excluded from the primary analysis because they had a missing Week 16 assessment. The denominator used for percentages was the number of subjects developmentally able to perform the CPX test. Reasons for exclusion from primary analysis are documented in various sources including CRFs
[d] Other category included inadequate CPX test result, no staff available at site to run the CPX test or the test was erroneously not done

The reasons for the 119 subjects who were unable to perform the exercise tests are shown in the table below.

Table 12. Summary of Reasons for Subjects being Unable to Perform CPET in Study A1481131

Treatment Group	Sildenafil				Placebo
	Low (N=42)	Medium (N=55)	High (N=77)	Combined (N=174)	(N=60)
Number of subjects unable to exercise	14 (33.3)	27 (49.1)	48 (62.3)	89 (51.1)	30 (50.0)
Number of subjects <7 years of age[a]	2 (4.8)	17 (30.9)	28 (36.4)	47 (27.0)	16 (26.7)
Without Down syndrome	2 (4.8)	12 (21.8)	24 (31.2)	38 (21.8)	10 (16.7)
With Down syndrome	0	5 (9.1)	4 (5.2)	9 (5.2)	6 (10.0)
Number of subjects ≥7 years of age[a]	12 (28.6)	10 (18.2)	20 (26.0)	42 (24.1)	14 (23.3)
With Down syndrome	6 (14.3)	6 (10.9)	13 (16.9)	25 (14.4)	6 (10.0)
Other reasons	6 (14.3)	4 (9.1)	7 (9.1)	17 (9.8)	8 (13.3)

Source: Study A1481156 Interim CSR (May 2009) Table 5.2.12 (Module 5.3.5.2)
a: Age at time of screening
Note: There were also 2 Down syndrome subjects who were developmentally able to perform CPET (one each in the low and medium dose groups)

Results
Of the 115 subjects deemed to be developmentally able to exercise, 106 were included in the primary efficacy analyses. The results are shown below.

Table T14. Percentage Change from Baseline in Peak Volume of Oxygen Consumed (VO2) at Week 16 (LOCF) – ITT

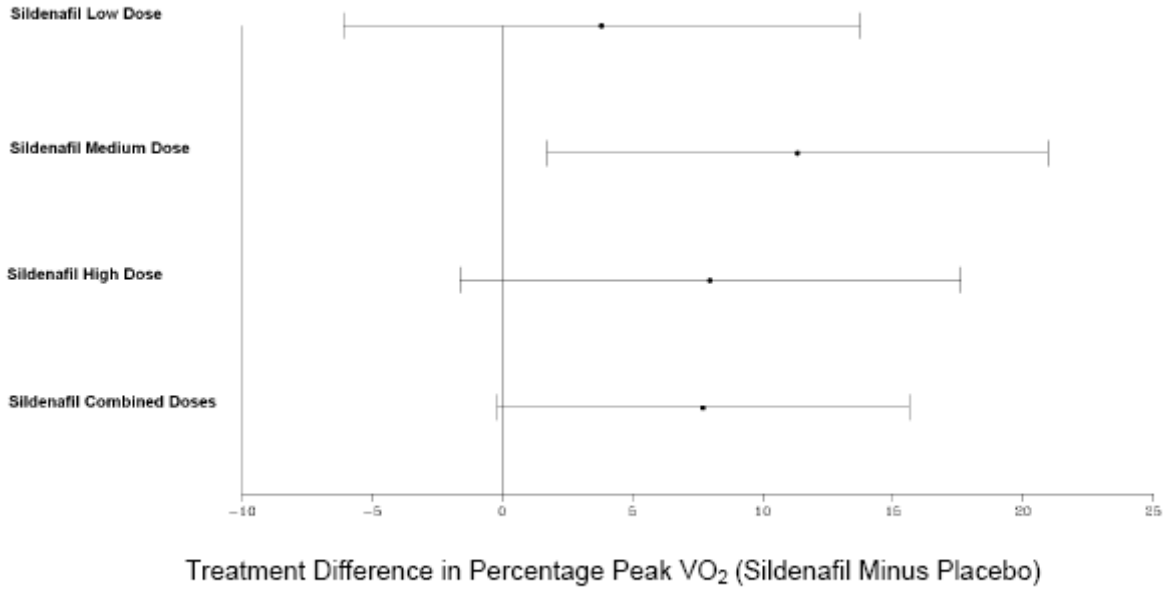
Dose	Sildenafil				Placebo
	Low	Medium	High	Combined	
Number of subjects[a]	24	26	27	77	29
Mean (SD) VO_2, mL/kg/minute					
Baseline[b]	17.37 (4.36)	18.03 (4.70)	17.43 (3.70)	17.61 (4.22)	20.02 (3.80)
Week 16	18.40 (5.61)	20.39 (6.16)	19.00 (3.59)	19.28 (5.21)	20.01 (4.44)
Change from baseline	1.03 (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

Source: Tables 5.2.1.1 and 5.2.2
VO_2=volume of oxygen consumed; LOCF=last observation carried forward; ITT=intention-to-treat population; SD=standard deviation; SE=standard error; NA=not applicable
[a] ITT subset of developmentally able subjects
[b] Baseline was the average of all assessments on or before the first day of study treatment
[c] Analyses were performed using analysis of covariance with etiology, weight and baseline peak VO_2 as the covariates

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 (p=0.056). The medium dose had the best results (11.33). The low dose showed only 3.81 mean difference versus placebo.

Figure F2. Treatment Difference in Percentage Change from Baseline in Peak VO_2 at Week 16 (LOCF): Mean and 95% Confidence Intervals - ITT



Source: Figure 1.1.1
Baseline was the average of all assessments on or before the first day of study treatment
ITT subset of developmentally able subjects

Time to peak VO2 was examined. The table below shows the means at baseline, at week 16, the change from baseline, and the percentage change from baseline.

Table 15. Percentage Change from Baseline in Study A1481131 for Time to VO_{2peak} at Week 16 - ITT

	Sildenafil				
Treatment Group	Low	Medium	High	Combined	Placebo
Number of subjects[a]	24	26	27	77	29
Mean (SD) time to VO_{2peak}, seconds					
Baseline[b]	414.54 (123.13)	452.27 (141.88)	433.81 (108.69)	434.04 (124.44)	466.43 (139.14)
Week 16	479. 38 (183.02)	516.69 (185.73)	465.15 (104.51)	486.99 (160.34)	475.28 (166.82)
Change from baseline	64.83 (103.69)	64.42 (102.70)	31.33 (107.04)	52.95 (104.40)	8.84 (96.09)
Percentage change from baseline	15.21 (26.28)	15.97 (22.92)	11.16 (28.62)	14.04 (25.82)	4.56 (34.85)
Mean difference vs. placebo (SE)[c]	10.34 (7.84)	11.43 (7.67)	5.96 (7.62)	9.24 (6.20)	NA
95% Confidence interval[c]	-5.21, 25.90	-3.78, 26.64	-9.16, 21.08	-3.05, 21.54	NA
P-value[c]	NA	NA	NA	0.139	NA

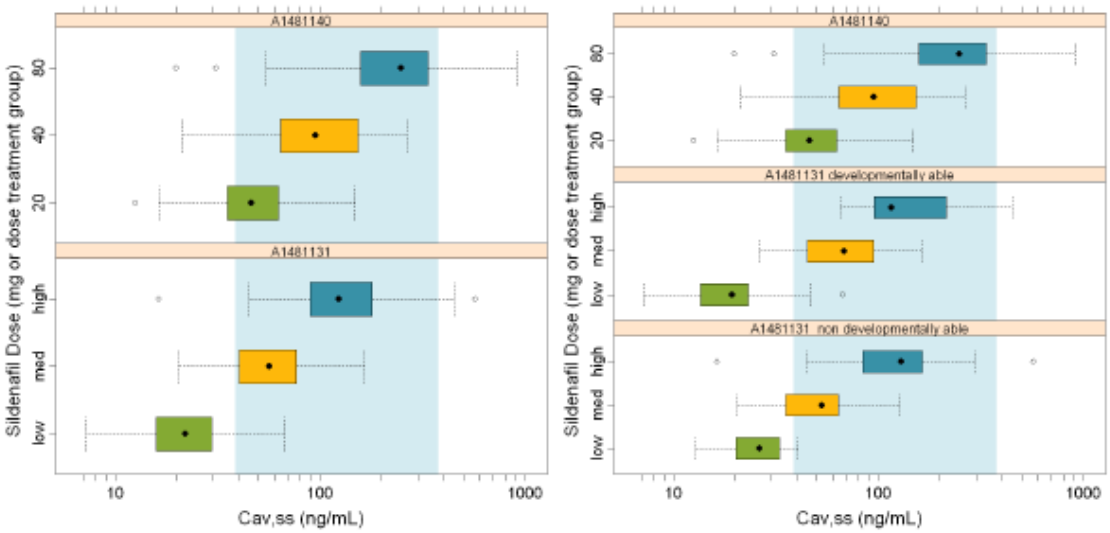
Source: Study A1481131 CSR Tables 5.6.1.1a and 5.6.2a (Module 5.3.5.1)
VO_2=volume of oxygen consumed; ITT=intention-to-treat population; SD=standard deviation; SE=standard error; NA=not applicable
[a] ITT subset of developmentally able subjects
[b] baseline was the average of all assessments on or before to the first day of study treatment
[c] Analyses were performed using analysis of covariance with etiology and weight as the covariates

The percentage change from baseline was greatest for low and medium dose sildenafil groups, less for high dose sildenafil group and minimal for placebo group.

Comparing adult and pediatric dosing

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 Study A1481131 approximate to the exposures of sildenafil 20 mg TID and 40 mg TID in the adult study A1481140, respectively. As a result of higher than expected plasma clearance the low dose group in Study A1481131 did not achieve pharmacologically relevant levels with respect to exercise capacity.

Figure 6. Boxplot of Estimated Exposures for Adult Treatment groups in Study A1481140 (20 mg TID, 40 mg TID, 80 mg TID) and Pediatric Treatment Groups in Study A1481131 (low, medium and high dose groups)



Boxplot of distribution of Cav,ss across both population PK trials (A1481131 and A1481140) and across the respective dose treatment groups, with the pediatric Cav,ss, all subject (left panel), being split according to their developmental status (right panel). The boxes represent the median and inter quartile ranges (IQR), the whiskers 1.5 times the IQR. The lower and upper ends of the blue shaded area correspond to the IC50 of PDE5 and PDE6 inhibition for sildenafil, respectively. (ePharm Artifact ID: 4676306 and 4676308).

6.1.4 Analysis of Secondary Endpoints(s)

Hemodynamic parameters

N.B. Cardiac output (and hence derivation of PVRI) was assessed by either the thermodilution or Fick methods. When the Fick method was used oxygen consumption was either measured or estimated. A large proportion of subjects had their hemodynamic assessment done by the Fick method; 73% (147/202) of subjects who had a valid PVRI measurement at Baseline and Week 16 were assessed using the Fick method.

As the same formula for estimating oxygen consumption was not used by all investigators throughout the study and it is recognized that direct measurement of oxygen consumption is difficult in the clinical setting, post hoc analyses were conducted using a standardized approach to estimating oxygen consumption for those subjects who had their cardiac output determined by the Fick method. The results from the standardized data for PVRI were similar to those presented in the original CSR, with similar improvements over placebo for the 3 dose groups.

The secondary endpoints included:

- pulmonary vascular resistance index (PVRI), mean pulmonary artery pressure (mPAP pulmonary vascular resistance (PVR), cardiac index and right atrial pressure (RAP) assessed by the hemodynamic assessment;
-WHO PH functional class;
-respiratory exchange ratio (RER) and time to peak VO2, assessed by the CPX test;
-physical and psychosocial scales from the Child Health Questionnaire - Parent Form (CHQ-PF28);

Only results from selected secondary endpoints are discussed here.

PVRi
There are 32 subjects excluded from the PVRI analyses. The mean PVRi at baseline, week 16, and change from baseline are shown below.

Table T17. Change from Baseline in Pulmonary Vascular Resistance Index (PVRI) at Week 16 (LOCF) – ITT

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

Source: Tables 5.4.1 and 5.4.2.1
PVRI=pulmonary vascular resistance index; LOCF=last observation carried forward; ITT=intention-to-treat population; SD=standard deviation; 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

Of the 234 subjects randomized, 202 subjects were included in the analysis.

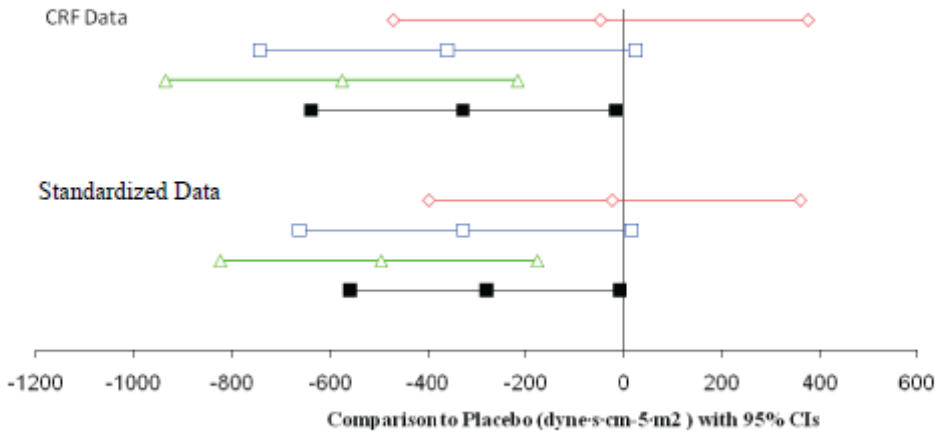
The highest mean PVRI at baseline was in the low dose sildenafil group (23.5 Wood units/m2) and the lowest was in the placebo group (16.1 Wood units/m2).

At endpoint, the sildenafil medium and high dose groups showed larger decreases from baseline compared to placebo (-4.5 and -7.2 Wood units.m2, respectively) in a dose related manner. The low dose group showed results similar to the placebo group (-0.6 Wood unit/m2).

With the exception of placebo and low dose sildenafil, there were clinically significant decreases in mean PVRI from baseline at week 16 (231.7 and 407.5 dyne.s.cm-5.m2, medium dose and high dose, respectively).

Similar results were shown with the standardized data[1].

Figure 8. Treatment Comparisons for PVRI Changes from Baseline: Mean and 95% Confidence Intervals

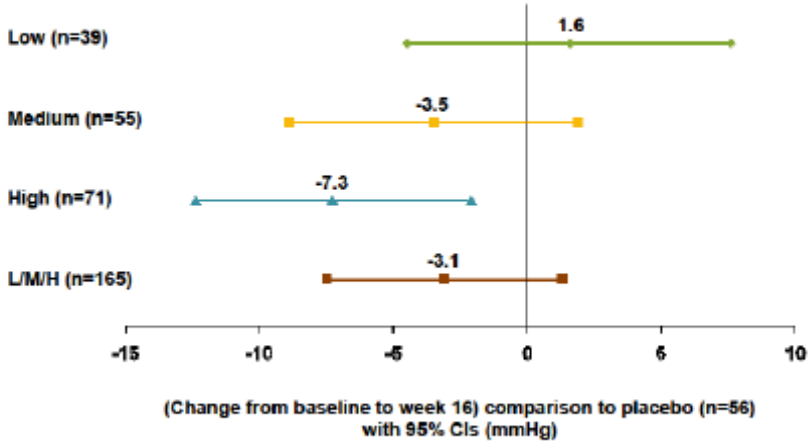


Dose groups: Red – Low, Blue – Medium, Green – High, Black – Combined
Note: PVRI was analysed on the natural scale
Source: A1481131 CSR Table 5.4.2.1 and A1481131_AddHaem Table 5.4.2 (Module 5.3.5.1)

In addition, there was an effect on mPAP with the medium and high dose groups showing improvement compared to placebo (decreases from baseline were 3.5 and 7.3 mmHg, repectively). The difference between low dose and placebo was minimal.

[1] As the same formula for estimating oxygen consumption was not used by all investigators throughout the study and it is recognized that direct measurement of oxygen consumption is difficult in the clinical setting, post hoc analyses were conducted using a standardized approach to estimating oxygen consumption for those subjects who had their cardiac output determined by the Fick method.

Figure 10. Treatment Differences in Changes from Baseline in Study A1481131 for mPAP at Week 16: Mean and 95% Confidence Intervals – ITT Population



Source: Study A1481131 CSR Table 5.3.2.1 (Module 5.3.5.1)
ITT- Intent-to-treat

Cardiac index showed improvement from baseline in sildenafil groups but not in the placebo group.

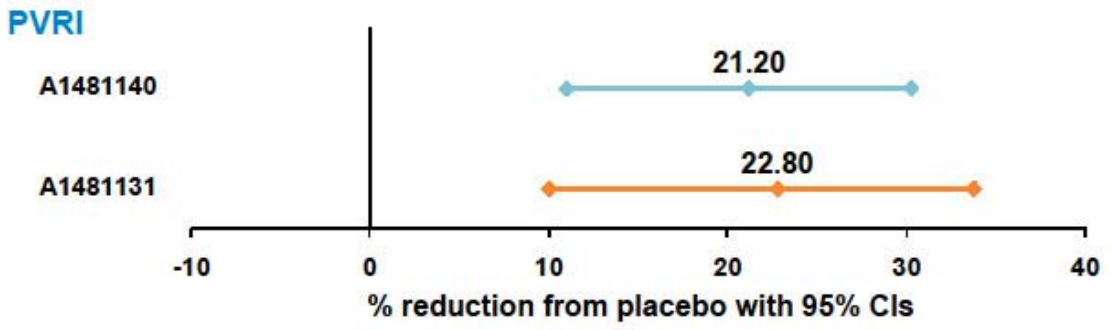
Table 25. Change from Baseline in Study A1481131 for Cardiac Index at Week 16 – ITT Population

	Sildenafil				
Treatment Group	**Low**	**Medium**	**High**	**Combined**	**Placebo**
Number of subjects	37	51	69	157	55
Mean (SD) Cardiac Index, L/min/m^2					
Baseline	3.12 (1.09)	3.25 (1.44)	3.42 (1.67)	3.30 (1.47)	3.96 (2.14)
Week 16	3.39 (1.29)	3.34 (1.48)	3.73 (1.73)	3.53 (1.56)	3.35 (1.04)
Change from baseline	0.27 (1.12)	0.08 (1.41)	0.31 (2.10)	0.23 (1.69)	-0.61 (1.98)
Ratio Comparison to Placebo	1.100	1.043	1.148	1.096	NA
95% Confidence Interval[a]	0.963,1.258	0.925,1.176	1.026,1.286	0.994,1.210	NA
P-value[a]	NA	NA	NA	0.066	NA

Source: Study A1481131_AddHaem Table 5.4.9 and Study A1481131 Hemodynamic Supplemental Report Table 11.7.28A (Module 5.3.5.1)
ITT=intention-to-treat population; SD=standard deviation; NA=not applicable
[a] Analyses were performed using analysis of covariance with etiology, weight, ability to perform the cardiopulmonary exercise test and log baseline Cardiac Index as covariates

Comparison to adult PVRi data

The following figure shows how close the % reduction from placebo in the adult study (A1481140 using 20 mg three times daily) is to that found in the pediatric study (medium and high doses combined) for PVRi.



mPAP
The mean PAP at baseline, week 16, and change from baseline are shown below.

Table S5. Change from Baseline in Mean Pulmonary Artery Pressure (mPAP) at Week 16 (LOCF) – ITT

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

LOCF=last observation carried forward; ITT=intention-to-treat population; SE=standard error; SD=standard deviation; NA=not applicable
[a] Baseline was the last mPAP assessment from 21 days before study treatment to the first day of study treatment
[b] Analyses were performed using analysis of covariance with etiology, weight and ability to perform the cardiopulmonary exercise test as the covariates

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) in a dose related manner. The low dose group showed similar results to the placebo group.

WHO Functional Class
The WHO PH Functional Classification was assessed at baseline, and Weeks 4, 8 and 16.

Overall 32.6%, 51.7%, 15.2% and 0.4% of subjects had WHO Class I, II, III and IV, respectively at baseline. The baseline values are shown in the table below.

Table T18. World Health Organization (WHO) Functional Class at Baseline

	Sildenafil				
	Low	Medium	High	Combined	Placebo
Class, n (%)[a]					
I	9 (22.5)	20[b] (37.0)	21 (27.6)	50 (29.4)	25 (41.7)
II	22[b] (55.0)	25 (46.3)	43 (56.6)	90 (52.9)	29 (48.3)
III	9 (22.5)	8 (14.8)	12 (15.8)	29 (17.1)	6 (10.0)
IV	0	1 (1.9)	0	1 (0.6)	0
Missing	2	1	1	4	0

Source: Table 5.11.1
WHO=world health organization
[a] The number of subjects with known WHO functional class has been used as the denominator for the calculation of percentages
[b] Subjects 11620 (sildenafil low dose) and 11221 (sildenafil medium dose) recorded baseline functional class on Day 2. The investigators confirmed that there was no significant change in functional class from pre-treatment and therefore these records were used as the baseline value.

The number and percent of those who had no change in their functional class, those who improved by 1 class, and those who improved by 2 classes at endpoint are shown below by treatment group.

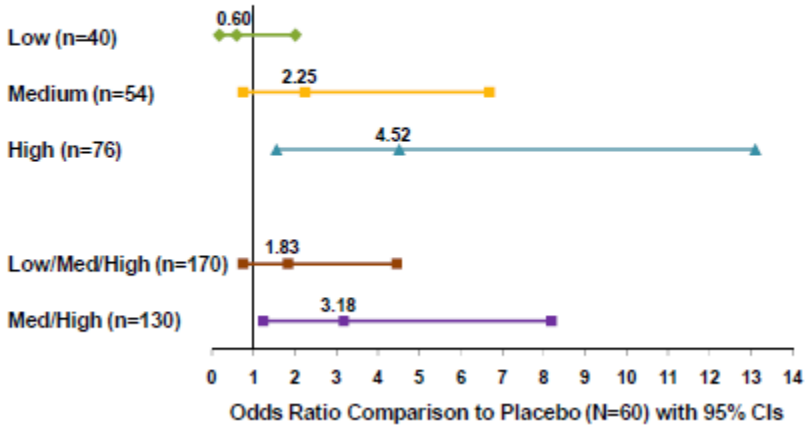
Table T19. Improvements from Baseline in World Health Organization (WHO) Functional Class for Subjects with PAH Class II to IV at Baseline

	Sildenafil				
	Low	Medium	High	Combined	Placebo
Number of subjects	31	34	55	120	35
No change, n (%)	25 (80.6)	24 (70.6)	38 (69.1)	84 (70.0)	31 (88.6)
Improved by 1 class, n (%)	6 (19.4)	10 (29.4)	16 (29.1)	32 (26.7)	4 (11.4)
Improved by 2 classes, n (%)	0	0	1 (1.8)	1 (0.8)	0

Source: Table 5.11.2

The table below shows the odd ratio for improvement in WHO functional class compared to placebo.

Figure 13. Odds Ratio for Improvement in WHO Functional Class Compared to Placebo by Dose Group in Study A1481131



There is some indication of an effect of sildenafil on WHO functional class improvement but it is limited to the high dose.

The table below shows the number of subjects who became worse by 1 functional class

Number of subjects

	sildenafil			placebo
	Low	Medium	high	
Number of subjects randomized	42	55	77	60
Number with data	31	34	55	35
Worse by 1 class	3	2	1	4

There are too few subjects who became worse to draw a conclusion about the efficacy of sildenafil.

6.1.6 Other Endpoints

Subject/Parent and Physician Global Assessments

With the subject/parent global assessment, improvements from baseline were observed with all treatment groups, including placebo. However, greater proportions of sildenafil-treated subjects had marked or moderate improvements compared to placebo-treated subjects (35.7%, 34.6% and 45.5% for the low, medium and high dose groups, respectively, compared to 21.6% in the placebo treatment group).

Similar results were observed with the physician global assessment, with most physicians reporting mild or better improvement in disease severity from baseline in all treatment groups.

Again greater proportions of sildenafil-treated subjects reported marked or moderate improvements (26.2%, 27.2% and 28.6% for the low, medium and high dose groups, respectively, compared to 10.0% in the placebo treatment group).

Quality of Life – CHQ-PF28 Questionnaire

Increases from baseline in the mean CHQ-PF28 physical and psychosocial scale scores were observed in all treatment groups, including placebo. There was no apparent difference between the sildenafil treatment groups and placebo.

6.1.7 Subpopulations

Subjects under 7 years of age had lower mean baseline values for mPAP and PVRI, and higher mean cardiac index, than the older subjects.

Table S8. Baseline Mean (SD, n) PVRI, mPAP and Cardiac Index Values and Functional Class by Age

Parameter	<7 years old N=63	≥7 years old N=171
PVRI (Wood units•m^2)	12.3 (8.0, 58)	20.7 (14.7, 164)
mPAP (mmHg)	54.2 (21.0, 61)	64.7 (21.5, 170)
Cardiac Index (L/min/m^2)	4.2 (1.8, 58)	3.2 (1.6, 168)
Functional Class I	27 (43%)	48 (29%)
Functional Class II	30 (48%)	90 (54%)
Functional Class III/IV	6 (10%)	30 (18%)

Source: Tables 29SL, 11.7.235A and 11.7.236A
Note: percentages do not add to 100% due to rounding

The table below shows the results of the hemodynamic analyses by age.

Table S9. Treatment Comparisons to Placebo for PVRI, Cardiac Index and mPAP by Age

Parameter	Treatment Group	Comparison to Placebo (95% CI) <7 years old	Comparison to Placebo (95% CI) ≥ 7 years old
PVRI (ratio to placebo)	Low Dose	0.97 (0.47, 2.00) (n=2)	0.97 (0.78, 1.21) (n=35)
	Medium Dose	0.77 (0.53, 1.10) (n=14)	0.83 (0.67, 1.03) (n=37)
	High Dose	0.74 (0.54, 1.02) (n=23)	0.72 (0.59, 0.89) (n=45)
Cardiac Index (ratio to placebo)	Low Dose	1.00 (0.63, 1.61) (n=2)	1.11 (0.96, 1.28) (n=35)
	Medium Dose	1.06 (0.84, 1.34) (n=14)	1.04 (0.90, 1.20) (n=37)
	High Dose	1.15 (0.93, 1.41) (n=23)	1.15 (1.01, 1.32) (n=46)
mPAP (difference in mmHg from placebo)	Low Dose	-3.30 (-26.26, 19.66) (n=2)	0.54 (-5.73, 6.81) (n=37)
	Medium Dose	-1.65 (-12.49, 9.20) (n=17)	-4.19 (-10.41, 2.04) (n=38)
	High Dose	- 0.76 (-10.72, 9.20) (n=25)	-9.79 (-15.73, -3.85) (n=46)

Note: as no subjects were randomized to the low dose treatment group in the 8-20 kg weight group only 2 subjects <7 years of age had evaluable hemodynamic values in this treatment group.
Source: Tables 11.7.59A, 11.7.60A and 11.7.61A
Placebo: PVRI <7 years old n=15; ≥7 years old n=37
Cardiac Index <7 years old n=15; ≥7 years old n=40
mPAP <7 years old n=15; ≥7 years old n=41

With the <7 year-old subjects there was an estimated 23% and 26% reduction in PVRI with the sildenafil medium and high dose groups, respectively. There were corresponding estimated increases in cardiac index of 6% and 15% for the medium and high dose groups respectively. With the ≥7 year-old subjects there was an estimated 17% and 28% reduction in PVRI and a corresponding 4% and 15% increase in cardiac index, indicating that the treatment effects on PVRI and cardiac index were similar in the 2 populations. For mPAP the <7 year-old subjects showed a smaller improvement over placebo for the medium and high dose groups compared to the ≥7 year-old subjects. The low dose group for the <7 year old had only 2 subjects.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The low dose group did not demonstrate clinically relevant efficacy with either VO2peak or hemodynamic endpoints and excess mortality was seen with the medium and high dose groups. Therefore, there is no dosing recommendation as a result of no proof of efficacy with the low dose and a higher than expected mortality rate with the medium and high doses.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Summary

Introduction
Safety information about the use of sildenafil in children with PAH was obtained primarily from study A1481131, a placebo controlled study using three dose levels of sildenafil, and study A1481156, an ongoing long-term extension study. Detailed reviews of these studies are located in the appendices.

The NDA contained combined A1481131 and A1481156 safety data using April 4, 2011 as the cut-off date for adverse events and June 20, 2011 for serious safety and survival analyses. The cut-off date for the safety update was November 15, 2011.

An independent Data Monitoring Committee (DMC) had been reviewing safety data from the two studies. It was disbanded following the completion of Study A1481131 and then re-instated in January 2009 when a numerical imbalance in mortality was observed by the sponsor across the treatment groups. The DMC was reconvened on July 26, 2011 to review the current safety data, following 4 newly reported deaths since their last meeting in November 2010. At this time, all subjects were at least 3 years post randomization with some as long as 7 years post randomization.

At the time of the cut-off for survival data of June 20, 2011 used for the DMC, 35 deaths had been reported. Of these 35 deaths, 26 had been reported as being on treatment or within 7 days of the last dose. Upon review of the mortality results, the DMC unanimously concluded, that in the context of this clinical trial, the high dose of sildenafil was associated with a harmful effect on survival when compared to the low dose. The DMC also expressed concern as to the potential dose-response relationship between increasing dose and mortality. Therefore, the DMC recommended discontinuation of the 40 mg and 80 mg TID doses, as well as the 20 mg TID dose in children with body weight <20 kg.

Both the study investigators and FDA were notified of the changes and recommendations. The study A1481156 continues with only the use of the low dose.

Safety Summary

There were no deaths reported in randomized subjects the 16-week controlled trial A1481131. There were two deaths reported in the screening phase of the study, however, and both deaths were associated with the right heart catheterization procedure.

There were 35 deaths reported in the ongoing, open label, uncontrolled trial A1481156. Of these deaths, 26 occurred when the subject was either on treatment or within 7 days of the last dose and 9 occurred for subjects who had been discontinued from study treatment for more than 7 days. The majority of deaths appear to be related to the underlying disease. However, there is a randomized[2] dose response relationship:

> The hazard ratio for mortality in the high dose group compared with the low dose group was 3.5 (1.29 to 9.51, 95% Confidence Interval).

The Data Monitoring Committee (DMC) that was following the studies unanimously concluded, as do I, that the high dose of sildenafil is associated with a harmful effect on survival when compared to the low dose.

The two month safety update reported 4 additional deaths (2 in the medium dose group and 2 in the high dose groups), of which 1 (medium dose) died on drug and the other 3 (1 medium, 2 high dose) died more than 7 days after their last dose of sildenafil.

My review of this application has found nothing to explain the imbalances in deaths in the high dose group. My conclusion, based on the mortality findings as well as the lack of effect with the low dose, is that there is no evidence of a dose of sildenafil that is both safe and effective for the treatment of children with PAH.

7.1 Methods

The safety evaluation was reviewed as presented by the sponsor. Also, many case reports for death and hospitalizations were examined by this reviewer.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Sildenafil tablets were studied in children with PAH in Study A1481131, a placebo controlled, double blind, randomized study and Study A1481156, an ongoing, uncontrolled long-term safety extension study. Only children who completed study the base study were eligible for the extension study.

[2] Survival analyses used the dose to which the subject was randomized to in the base study A1481131. Dose titration was allowed in the open label extension study A1481156

The clinical safety also includes supportive data from 2 pediatric studies of intravenous (IV) sildenafil in the treatment of pulmonary hypertension (A1481134 and A1481157). These studies were conducted in children with pulmonary hypertension (PH) or persistent pulmonary hypertension of the newborn (PPHN). Study A1481134[3] was terminated after 4 subjects because of poor recruitment and study A1481157[4] was terminated after 36 subjects, also for poor recruitment.

7.1.2 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

Data were pooled for two studies (a controlled study and its long-term extension). The base study A1481131 has been completed and the extension study A1481156 is still ongoing. Only subjects who were enrolled in the base study were eligible for the extension study.

All deaths in randomized subjects were reported after the subjects completed the 16-week study A1481131 and were either ongoing in study A1481156 or had been dropped from it.

7.2 Adequacy of Safety Assessments

The safety database for oral sildenafil in pediatric subjects includes 234 pediatric subjects in the base study (A1481131; 174 who received sildenafil and 60 who received placebo). Most of these subjects (220) entered the long term extension study A1481156 during which all were given sildenafil. As of the April 4, 2011 data cut-off, 133 subjects were still ongoing in the study.

An additional 53 pediatric subjects, 48 of whom received IV sildenafil, are included in the safety database: the 12 subjects who received sildenafil in Study A1481134, a study of IV sildenafil in the treatment of pulmonary hypertension and the 36 subjects who received sildenafil in Study A1481157, a study of IV sildenafil in the treatment of PPHN.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The pediatric clinical development program includes 234 treated subjects in the placebo controlled Study A1481131. The majority (228; 97%) completed 16 weeks of treatment in Study A1481131, and 220 of these subjects continued into the extension Study A1481156.

The total number of children who received oral sildenafil in studies A1481131 and/or A14891156 is 229.

[3] two of seventeen subjects reported serious adverse events (predominantly pulmonary hypertension). There was one death (placebo) and two subjects discontinued.

[4] there were six serious events, four of which occurred during treatment (severe hypotension, anomalous pulmonary venous connection, two pneumothorax) one occurred prior to the start of treatment (pneumothorax) and one more than seven days after treatment (cardiomyopathy).

Of the 234 treated subjects in Study A1481131, 60 received placebo. Subjects who received placebo in Study A1481131 were randomly assigned to a sildenafil dose level for the long-term extension Study A1481156. Of the 60 placebo-treated subjects, 55 received sildenafil treatment in Study A1481156.

As of the April 4, 2011, all subjects have been followed for a minimum of 3 years from the start of A148113.

- 206/234 subjects (88%) were ongoing in the study for ≥ 1 year (from the start of Study A1481131),
- 184/234 (79%) for ≥2 years of therapy, and
- 166/234 (71%) for ≥ 3 years of therapy.

Sildenafil doses were to be 10, 20, 40 and 80 mg TID with the exact dose based on subject body weight.

Table T2. Sildenafil Doses (TID) to Achieve Target Sildenafil Steady-State Maximum Concentrations of 47, 140 and 373 ng/mL at the Low, Medium and High doses, Respectively

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

Source: Appendix A1
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.

Subjects enrolled into A1481156 received 1 of 3 doses (low, medium, or high) of sildenafil. Study medication was taken 3 times daily, at least 6 hours apart. With the exception of the subjects who were randomized to placebo in A1481131, subjects remained on the same treatment group as in A1481131[5]. The subjects in the placebo group were randomized (stratified by weight) to 1 of the 3 active study treatment dose groups used in A1481131. To prevent treatment unblinding in A1481131, the treatment double-blind was maintained in A1481156 until the last subject had completed A1481131 and the database was locked (August 2, 2008). Since then A1481156 has continued as an open-label study. The number of subjects per dose is shown below

[5] *Subjects were stratified according to weight and developmental ability to perform the CPX 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. Sildenafil low, medium, and high doses were selected such that target maximum plasma concentrations (C_{max}) of 47, 140 and 373 ng/mL, respectively, would be achieved at steady-state. In subjects weighing from 8 to 20 kg, modeling of the plasma concentrations for each dose level showed that the low and medium doses were similar (i.e., subjects would receive the same dose because of the available tablet strengths); consequently, these subjects were randomized 1:2:1 to sildenafil medium and high doses, and placebo, respectively.*

- Low dose = 42 sildenafil subjects plus 13 placebo subjects from A1481131 = 55 subjects
- Medium dose = 55 sildenafil subjects plus 19 placebo subjects from A1481131 =74 subjects
- High dose = 77 sildenafil subjects plus 23 placebo subjects from A1481131 = 100 subjects

7.2.2 Explorations for Dose Response

There is dose response associated with mortality. As of June 20, 2011, 35 deaths had been reported. Of these 35 deaths, 26 had been reported as being on treatment or within 7 days of the last dose.

The number of deaths in each of the treatment groups was

- 20/100 (20%) in the high dose treatment group (sildenafil high/high dose and placebo/high dose),
- 10/74 (13.5%) in the medium dose treatment group (sildenafil medium/medium dose and placebo/medium dose), and
- 5/55 (9%) in the low dose treatment group (sildenafil low/low dose and placebo/low dose), respectively.

In a proportional hazards model stratified by weight class assuming a linear relationship among the doses, the estimated hazard ratio of mortality comparing middle dose to low dose is 1.89 [p=0.008; confidence interval = (1.18, 3.03)]. Because of the assumed linear relationship, this is the same estimate of the hazard ratio for high dose compared to low dose. The estimated hazard ratio of high dose compared to low dose is about 3.6.

7.2.3 Special Animal and/or In Vitro Testing

None

7.2.4 Routine Clinical Testing

The following safety data were collected:
adverse events, laboratory tests, parents or legal guardians of subjects who permanently discontinued study drug were asked for their consent for their children to be followed up every 3 months for the evaluation of survival status, a physical examination, blood pressure and heart rate measurements (sitting/resting), and ocular testing.

7.2.5 Metabolic, Clearance, and Interaction Workup

None

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Bleeding events
There were 20 sildenafil subjects (12%) in study A1481131 who reported a total of 23 bleeding events compared to 6 placebo subjects who reported 6 events (10%). The incidence of bleeding events did not increase with sildenafil dose. In the adult PAH study A1481140, the reported a bleeding rate was 17% with sildenafil and 16% with placebo.

Ocular Events
Age appropriate ocular assessments including funduscopy, visual acuity, and color vision were performed in studies A1481131 and A1481156. An ophthalmologist performed the following ocular tests:

- Clinical examination of the eye including external examination of the eye;
- Visual acuity (Snellen Chart). For younger children, a suitable alternative to the Snellen Chart, such as assessment of preferential looking using Teller cards, could be used. Visual acuity was measured with the child's current refractive corrections or a pinhole;
- Farnsworth-Munsell D15 Hue Test for color vision. For children <8 years old, a suitable alternative, such as color plates, could be used. If the Ishihara test was performed, the number of correctly identified plates and the number of plates tested were recorded as the numerator and denominator, respectively, in the comments section of the CRF;
- Funduscopy (if any abnormalities were detected during the funduscopy examination a photograph was taken);
- Slit Lamp Testing when appropriate (e.g. assessment of possible AE).

The majority of ocular adverse events (86/110) were mild in severity. Conjunctivitis (13/234) and visual acuity reduced (12/234) were the only adverse events reported in more than 5% of subjects.

There were two reported serious adverse events:

- Subject 11246 experienced corneal edema and keratoconus.
- Subject 11604 (AER number 2004053416) experienced vision blurred, gait disturbance, cyanosis, dizziness, and dyspepsia. These events occurred in conjunction with right heart catheterization.

Color vision monitoring in studies A1481131 and A1481156 combined (April 4, 2011 data-cut), revealed 5 subjects (Subjects 10416, 10419, 11224, 11602, and 11603) who reported a worsening from baseline.

Hypotension
There were four episodes (2 reported by the same subjects) of hypotension reported in 3 subjects as of April 4, 2011. Subject 11611 (sildenafil low/low) who reported hypotension (study day 850 to 853 and then day 860 to 861), loss of consciousness, cardiac failure and respiratory failure. The subject died and the cause of death was reported as pulmonary hypertension.

Hearing loss
There was one report in a 10 year old female (Mfr #2011302331) who reported mild to moderate neurosensory hearing loss in the right ear (40 mg TID, 2007-2011).

Major Safety Results

7.3.1 Deaths

Study A1481131 and A1481156 combined
At the time of the April 4, 2011 data cut-off, 57% of subjects treated in the base study A1481131 were still ongoing in the extension study A1481156 (133/234) and 43% of subjects had discontinued (101/234).

Dosing information: subjects randomized to high, medium, or low dose sildenafil in the base studyA1481131 continued the same dose regimen in the extension study A1481156. Subjects randomized to placebo in the base study were re-randomized to either the medium or high dose sildenafil groups according to weight.

Dose Titration was allowed in the extension study. Down titrations occurred in 8 subjects (3 in the base study and 5 in the extension study). Only 1 of the 5 down titrations in the extension study was the result of an adverse event (Subject 10844/high dose/headache). The other reasons for down titration included 1) to maintain their dose level when weight increase triggered an increase and 2) because of an error.

The majority of up titrations were in the low dose group with 28 subjects having at least 1 up titration, whereas 11 and 13 subjects had at least 1 up titration in the medium and high dose groups, respectively. The majority of up titrations occurred after the study was unblinded.

The mean subject year exposure by randomized sildenafil dose is shown below.

Table 5. Mean Subject Year Exposure by Randomized A1481131/A1481156 Treatment Sequence†

Treatment Sequence	Total number of subjects	Total sildenafil exposure for all subjects (years)	Mean sildenafil exposure (years)
Sildenafil low/low dose	42	157	3.7
Sildenafil medium/medium dose	55	215	3.9
Sildenafil high/high dose	77	285	3.7
Placebo/low dose	13	47	3.7
Placebo/medium dose	19	69	3.7
Placebo/high dose	23	81	3.5

† Only duration of treatment on sildenafil is counted.
Source: Table 3.4, A1481156 Supplemental Safety Report, Module 5.3.5.3

There were no reported deaths during the base study A1481131. However, 2 subjects[6] died before randomization (1 subject during preparation for right heart catheterization and 1 subject while undergoing right heart catheterization; both deaths were considered related to general anesthesia).

There were 35 deaths reported in the extension study A1481156, of which 26 were reported as being either on treatment or within 7 days of the last dose and 9 deaths were reported for subjects who had been discontinued from study treatment. The majority of deaths appeared to be the result of worsening pulmonary hypertension, cardiac failure, cardiogenic shock, and ventricular fibrillation. I reviewed the narratives for the 26 deaths that occurred on study treatment and at least part of the CRF for most. There is nothing that appears to be the cause of death other than what was stated in the narratives. Tables of the individual deaths are shown in the review of study A1481156.

Safety update
An additional 4 deaths have been reported between June 21, 2011 and the survival cut-off date of November 15, 2011[7]:

- 2 deaths were in the medium/medium dose group (Subjects 11243 worsening pulmonary hypertension and 10852), and
- 2 deaths were in the high/high dose group (Subjects 10434 and 10806).

Subject 11243 was reported as being on treatment (within 7 days of the last dose) and the 3 other deaths (10852, 10434 and 10806) occurred more than 7 days after their last study treatment.

The Kaplan-Meier survival estimates for the low, medium, and high dose groups at 3 years were 94%, 93%, and 88%.

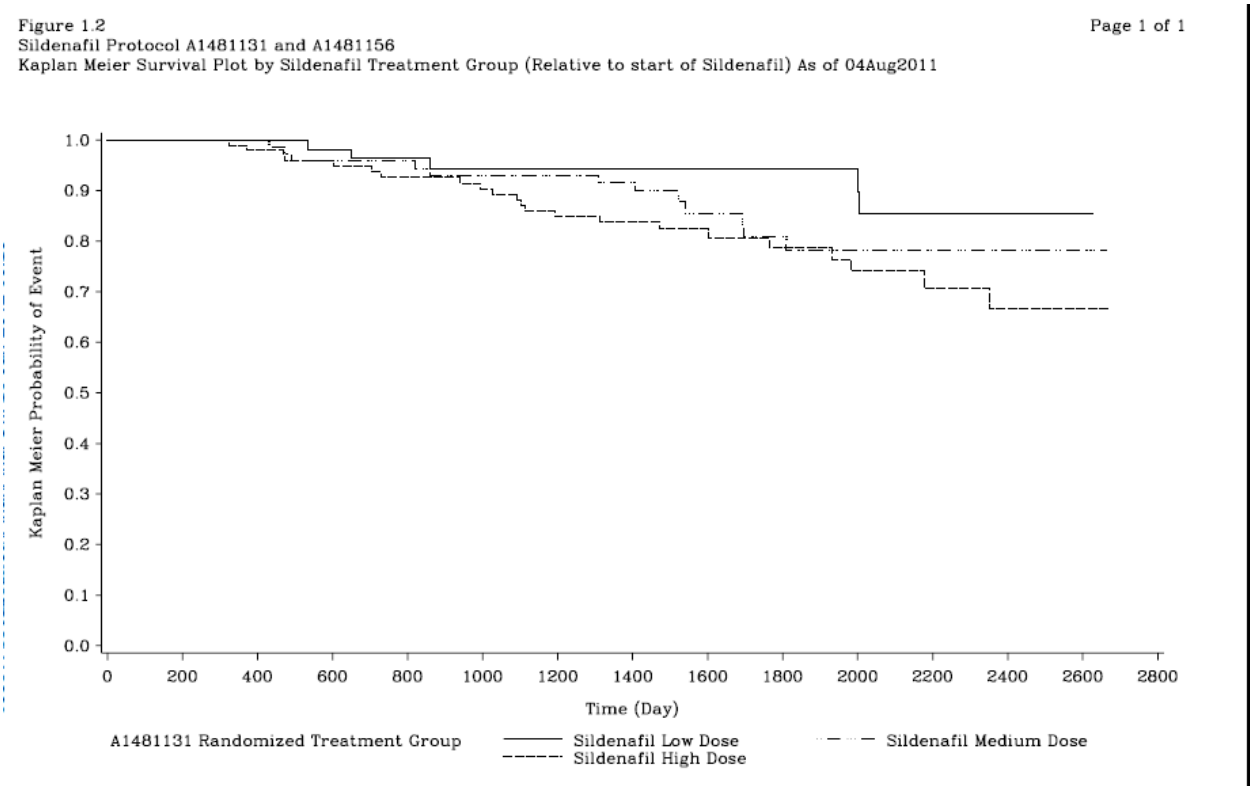
[6] (#1026S8034 and #1029S8174)
[7] This includes subject 10852 who died on Nov. 17, 2011

Table 13 Page 1 of 3
Sildenafil Protocol A1481131 and A1481156
Summary of Survival by Sildenafil Treatment Group (relative to start of Sildenafil) As of 04Aug2011
Subjects Randomized and Treated with Sildenafil in A1481131/1156

		Sildenafil Low Dose (N= 55)	Sildenafil Medium Dose (N= 74)	Sildenafil High Dose (N=100)
1 Year	Deaths (N (%))	0 (0.0)	0 (0.0)	1 (1.0)
	Life Table Estimates of deaths (by year 1)			
	Proportion Died*	0.000	0.000	0.010
	95% CI for proportion died*	(0.000, 0.000)	(0.000, 0.000)	(0.001, 0.070)
	Survived (N (%))	55 (100.0)	74 (100.0)	99 (99.0)
	Survived 1 year of study	49 (89.1)	69 (93.2)	87 (87.9)
	Discontinued before 1 year of study	6 (10.9)	5 (6.8)	12 (12.1)
	Ongoing for less than 1 year of study	0 (0.0)	0 (0.0)	0 (0.0)
2 Years	Deaths (N (%))	2 (3.6)	3 (4.1)	7 (7.0)
	Life Table Estimates of deaths (by year 2)			
	Proportion Died*	0.037	0.042	0.074
	95% CI for proportion died*	(0.009, 0.140)	(0.014, 0.124)	(0.036, 0.149)
	Survived (N (%))	53 (96.4)	71 (95.9)	93 (93.0)
	Survived 2 years of study	43 (81.1)	62 (87.3)	76 (81.7)
	Discontinued before 2 years of study	10 (18.9)	9 (12.7)	17 (18.3)
	Ongoing for less than 2 years of study	0 (0.0)	0 (0.0)	0 (0.0)
3 Years	Deaths (N (%))	3 (5.5)	5 (6.8)	11 (11.0)
	Life Table Estimates of deaths (by year 3)			
	Proportion Died*	0.056	0.070	0.118
	95% CI for proportion died*	(0.019, 0.165)	(0.030, 0.160)	(0.067, 0.203)
	Survived (N (%))	52 (94.5)	69 (93.2)	89 (89.0)
	Survived 3 years of study	38 (73.1)	55 (79.7)	70 (78.7)
	Discontinued before 3 years of study	14 (26.9)	14 (20.3)	18 (20.2)
	Ongoing for less than 3 years of study	0 (0.0)	0 (0.0)	1 (1.1)

Note: time is relative to the start of Sildenafil treatment.
* Kaplan-Meier estimate.
(1) P-value for comparison of three groups
Table 7.4 in submission Pediatric Data Cut, protocol A1481131_and_A1481156_2
Date of snapshot: 15NOV2011
PFIZER CONFIDENTIAL Date of Reporting Dataset Creation: 28NOV2011 Date of Table Generation: 09DEC2011 (02:10)

The figure below shows the Kaplan Meir survival plot by sildenafil dose group as of August 4, 2011.



Deaths and weight groups

The table below shows the observed and expected number of deaths for each of the 3 sildenafil groups.

Table 8. Summary of Deaths (All) by Weight Group and Sildenafil Treatment Group

	Low	Medium	High
Total	55	74	100
Observed	5	12	22
Expected 1	11.0	12.7	15.3
Expected 2	11.8	12.9	14.3
8 to 20 Kg			
N		20	44
Observed		1	5
Expected 1		1.9	4.1
Expected 2		1.8	4.2
>20 Kg			
N	55	54	56
Observed	5	11	17
Expected 1	11.0	10.8	11.2
Expected 2	11.8	11.1	10.1

Source: Table 14, Appendix 1

1. Taking account of the number of subjects in each treatment group in the ≤20 kg and >20kg weight groups (Expected 1).
2. As per (1), but also taking into account duration of observation. This has been achieved through the use of a log rank survival analysis. This analysis excludes the 5 subjects who received placebo and did not enter Study A1481156, as they never received sildenafil (Expected 2).

Overall, there were 22 observed deaths compared to 15 that were expected in the high dose group. Most of the imbalance was seen in the high dose group who weighed over 20 kg.

The hazard ratio comparisons for survival from the start of sildenafil by sildenafil dose groups as well as from the start of dosing (start of study A1481131) by the randomized groups are shown below.

Table 9. Treatment Group Comparisons for Survival from the Start of A1481131 and the Start of Sildenafil

Comparison	Stratified HR (95% CI)		
	Low Dose Group	Medium Dose Group	High Dose Group
Start of A1481131			
Comparison with Placebo	1.38 (0.37, 5.18)	2.95 (0.94, 9.26)	4.79 (1.62, 14.15)
Comparison with Low dose		2.13 (0.74, 6.16)	3.46 (1.26, 9.47)
Comparison with Medium dose			1.63 (0.77, 3.45)
Start of Sildenafil			
Comparison with Low dose	-	2.31 (0.81, 6.59)	4.02 (1.49, 10.83)
Comparison with Medium dose	-	-	1.74 (0.85, 3.55)

Source: Table 14 and Table 17, Appendix 1

The high dose group exhibits hazard ratios with 95% confidence intervals that exclude 1 (equivalence) for comparisons with low dose and placebo.

Subjects were grouped according to low, medium and high concentrations. The hazard ratio comparisons for these 3 groups are shown in the table below.

Table 11. Concentration Group Comparisons for Survival from the Start of Sildenafil

Comparison	Stratified HR (95% CI)	
	Medium Concentration Group	High Concentration Group
Start of Sildenafil		
Comparison with Low Concentration Group	1.48 (0.62, 3.52)	2.37 (1.06, 5.30)
Comparison with Medium Concentration Group	-	1.61 (0.77, 3.34)

Concentration groups covered the following concentration ranges:
Low Concentration Group: 17 to 44 ng/ml
Medium Concentration Group; 44 to 99 ng/ml
High Concentration Group: 100 to 227 ng/ml
Source: Table 20, Appendix 1

This supports the hypothesis that there is an increase in mortality with increasing sildenafil exposure.

Baseline characteristics and mortality[8] (from Table 7 Safety Update)
Those subjects who died tended to have poor hemodynamic variables:

- 77% (30/39) of the subjects who died had baseline PVRI above or equal to the median (15.1 Wood unitsm2),
- 67% (26/39) had mPAP greater than or equal to the median (62 mmHg), and
- 72% (28/39) had RAP greater than or equal to the median (7.0 mmHg).

Those subjects who died tended to have been classified as WHO functional class III or IV at baseline compared with of the overall study population (39% (15/39) and 17% (39/234), respectively).

While the majority of subjects (67%) had secondary as opposed to primary pulmonary hypertension (33%) as the etiology of their disease, the majority of deaths (77%, 30/39 were reported in subjects with primary pulmonary arterial hypertension).

The country of origin showed an imbalance in mortality rate. The 3 countries with the highest rates were India (44%, 12/27), Mexico (36%, 5/14), and Poland (21%, 7/33). The mortality rate in the United States was 5% (2/39). (Table 7).

[8] from Table 7 Safety Update

In addition to the above, there were 2 deaths in subjects prior to randomization in study A1481131. Both deaths were associated with the right heart catheterization procedure which required general anesthesia.

7.3.2 Nonfatal Serious Adverse Events

A1481131
The non fatal serious events reported by eleven subjects in study A1481131 are shown in the table below.

Table T29. Treatment-Emergent Serious Adverse Events

Subject	Age/ Sex	Sildenafil Dose	Adverse Event	Severity	Treatment Related	Outcome
Sildenafil Low Dose						
11604	12 years/F	10 mg	Dyspnea	Severe	No	Resolved
		10 mg	Cyanosis	Severe	No	Resolved
		10 mg	Syncope	Severe	No	Resolved
		10 mg	Haematochezia	Mild	No	Resolved
Sildenafil Medium Dose						
10445	2 years/F	10 mg	Pneumonia	Severe	No	Resolved
		10 mg	Upper respiratory tract infection	Severe	No	Resolved
Sildenafil High Dose						
10415	6 years/M	20 mg	Gastroenteritis	Mild	No	Resolved
		20 mg	Pyrexia	Mild	No	Resolved
10417	22 months/M	20 mg	Upper respiratory tract infection	Moderate	No	Resolved
10420	20 months/M	10 mg	Stridor [a]	Severe	Yes	Resolved
10427	3 years/M	20 mg	Bronchospasm	Moderate	No	Resolved
		20 mg	Bradycardia	Moderate	No	Resolved
10446	5 years/M	20 mg	Pneumonia	Moderate	No	Resolved
10831	13 years/M	40 mg	Pneumonia	Severe	No	Resolved
		40 mg	Cardiac failure congestive	Severe	No	Resolved
12001[b]	14 years/M	80 mg	Ventricular arrhythmia	Mild	Yes	Resolved
Placebo						
10426	31 months/F		Diarrhea	Moderate	No	Resolved
11247	5 years/F		Pneumonia	Moderate	No	Resolved

Source: Table 6.4 and Appendix B, Table 3
[a] Subject was discontinued for the adverse event; the treatment code was unblinded.
[b] The sponsor's internal Safety Surveillance and Reporting Group requested unblinded treatment details for Subject 12001 on 25 August 04. The investigator and the study team were not provided with the unblinded treatment data.

These events do not appear to be unexpected in this population.

A1481131 and A1481156 combined

As of the April 4, 2011 data cut-off, 92/229 subjects (40.2%) who received sildenafil at some point had experienced at least one serious adverse event. The most commonly reported serious adverse events (sae) are shown in the table below.

No. and (percent) of subjects

	Randomized to sildenafil in base study			Randomized to placebo in base study			
	Low	Med	high	Low	Med	high	Non-randomized
No. randomized	42	55	77	13	19	23	5
No. of subjects with sae	12	31	35	1	4	9	0
Cardiac	5 (12)	7 (13)	12 (16)	0	1 (5)	1 (4)	0
Cardiac failure	3 (7)	2 (4)	6 (8)	0	0	0	0
infections	4 (10)	11 (20)	19 (25)	0	3 (16)	4 (17)	0
Respiratory	2 (5)	9 (16)	12 (16)	1(8)	1 (5)	4 (17)	0

Table 4.25

Considering the underlying disease of the subject population, these are not unexpected serious adverse events.

7.3.3 Dropouts and/or Discontinuations

Studies A1481131 and A1481156 combined:
Overall, 16 subjects permanently discontinued from Studies A1481131 and A1481156 combined because of a non fatal adverse event.

Table 29. Studies A1481131 and A1481156 Combined: Summary of Discontinuations† due to Adverse Events by A1481131/A1481156 Treatment Sequence

Subject Number	Sex/Age	Weight (kg)	Dose at Onset of AE (mg)	Preferred Term	Start Day/ Stop Day	Severity	Outcome	Causality
Sildenafil Low/Low Dose								
11201*	F/7 years	26.5	10	Weight decreased	37/127	Mild	Unknown	Study drug
			Post	Weight decreased	1/>6[a]	Mild	Unknown	Study drug
11604	F/12 years	62	40	Cardiac failure	1968/1976	Moderate	Resolved	Disease under study
Sildenafil Medium/Medium Dose								
10432	F/5 years	14.6	10	Convulsion	358/370	Moderate	Resolved	Study drug
			Post	Convulsion	1/56[a]	Moderate	Resolved	Study drug
10442	M/4 years	14	10	Cardiac operation	476/483	Severe	Resolved	Disease under study
			Post	Cardiac operation	1/17[a]	Severe	Resolved	Disease under study
10860	F/16 years	42.5	20	Drug exposure during pregnancy	607/>787	Mild	Still present	Other
11248	M/13 years	39	20	Right ventricular failure	451/>462	Severe	Still present	Disease under study
11605	F/10 years	60.3	40	Syncope	531/531	Moderate	Resolved	Other[b]
Sildenafil High/High Dose								
10417	M/20 months	10.5	20	Cardiac failure congestive	201/>202	Severe	Still present	Disease under study
10420*	M/20 months	10	10	Stridor	10/10	Severe	Resolved	Study drug
10434	F/5 years	14	20	Cardiac failure	282/293	Severe	Resolved	Disease under study
11202	F/9 years	25	40	Dyspnoea	495/515	Moderate	Resolved	Study drug
			Post	Dyspnoea	1/2[a]	Moderate	Resolved	Study drug
			40	Hypoxia	379/515	Severe	Resolved	Study drug
			Post	Hypoxia	1/39[a]	Severe	Resolved	Study drug
Placebo/Low Dose								
10807	M/12 years	42.9	10/0	Rash macular	113/114	Mild	Resolved	Study drug
Placebo/Medium Dose								
10857	F/13 years	32	20	Mitral valve stenosis	1114/ >1120	Moderate	Still present	Disease under study
11210	F/16 years	37.5	0	Malaise	89/368	Moderate	Still present	Disease under study
			Post	Malaise	1/>29[a]	Moderate	Still present	Disease under study
Placebo/High Dose								
10402	F/6 years	14.2	40	Pulmonary hypertension	2060/ >2127	Severe	Still present	Disease under study
11203	F/9 years	26	40	Dyspnoea exertional	1566/1595	Moderate	Resolved	Disease under study

7.3.4 Significant Adverse Events

- There were two deaths in subjects prior to randomization associated with right heart catheterization (1 subject during preparation for right heart catheterization and 1 subject while undergoing right heart catheterization; both deaths were considered related to general anesthesia) in study A1481131. There were several serious adverse events association with the right heart catheterization in subjects prior to randomization in this study.

- There were an addition 2 serious adverse events also associated with catheterization (Subject 11604 (AER number 2004053416) experienced vision blurred, gait disturbance, cyanosis, dizziness, and dyspepsia. These events occurred in conjunction with right heart catheterization. Subject 0427 developed bronchospasm, respiratory arrest, bradycardia, and 60% oxygen level during right heart catheterization. These were reported during study A1481156.

7.3.5 Submission Specific Primary Safety Concerns

There is an increased mortality with increasing sildenafil exposure. 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).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The table below shows the reported adverse events reported by at least 3% of subjects in any treatment group in the placebo controlled study A1481131. The columns marked AC include all reported events.

Table 16. Study A1481131: Incidence of Treatment-Emergent Adverse Events Reported in ≥3% of Subjects in Any Treatment Group

	Sildenafil									
Dose	Low		Medium		High		Combined		Placebo	
Subjects evaluable for AEs	42		55		77		174		60	
	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR
Number of AEs	77	23	129	31	142	48	348	102	114	39
Number (%) of subjects with AEs[f]	29 (69.0)	11 (26.2)	44 (80.0)	13 (23.6)	54 (70.1)	22 (28.6)	127 (73.0)	46 (26.4)	40 (66.7)	14 (23.3)
Number (%) of subjects with MedDRA (v11.0) preferred term[a]:										
Headache	5 (11.9)	4 (9.5)	6 (10.9)	5 (9.1)	12 (15.6)	8 (10.4)	23 (13.2)	17 (9.8)	8 (13.3)	7 (11.7)
URTI[b]	5 (11.9)	0	9 (16.4)	0	7 (9.1)	0	21 (12.1)	0	4 (6.7)	0
Pyrexia	3 (7.1)	1 (2.4)	8 (14.5)	0	9 (11.7)	2 (2.6)	20 (11.5)	3 (1.7)	1 (1.7)	0
Vomiting	3 (7.1)	2 (4.8)	5 (9.1)	3 (5.5)	11 (14.3)	4 (5.2)	19 (10.9)	9 (5.2)	4 (6.7)	1 (1.7)
Spontaneous penile erection or Erection increased[c,d]	0	0	3 (12.5)	3 (12.5)	3 (11.5)	3 (11.5)	6 (9.0)	6 (9.0)	0	0
Diarrhoea	2 (4.8)	0	3 (5.5)	0	7 (9.1)	2 (2.6)	12 (6.9)	2 (1.1)	5 (8.3)	1 (1.7)
Bronchitis[e]	2 (4.8)	0	5 (9.1)	0	3 (3.9)	0	10 (5.7)	0	1 (1.7)	0
Cough	2 (4.8)	1 (2.4)	4 (7.3)	0	2 (2.6)	2 (2.6)	8 (4.6)	3 (1.7)	3 (5.0)	0
Nausea	0	0	4 (7.3)	1 (1.8)	4 (5.2)	1 (1.3)	8 (4.6)	2 (1.1)	0	0
Nasopharyngitis	3 (7.1)	0	3 (5.5)	0	2 (2.6)	0	8 (4.6)	0	4 (6.7)	0
Pharyngitis	3 (7.1)	0	3 (5.5)	0	1 (1.3)	0	7 (4.0)	0	0	0
Dizziness	2 (4.8)	0	2 (3.6)	2 (3.6)	2 (2.6)	1 (1.3)	6 (3.4)	3 (1.7)	2 (3.3)	1 (1.7)
Epistaxis	1 (2.4)	1 (2.4)	2 (3.6)	0	3 (3.9)	3 (3.9)	6 (3.4)	4 (2.3)	2 (3.3)	1 (1.7)
Abdominal pain upper	0	0	3 (5.5)	0	3 (3.9)	2 (2.6)	6 (3.4)	2 (1.1)	1 (1.7)	0
Rhinorrhoea	0	0	4 (7.3)	0	2 (2.6)	1 (1.3)	6 (3.4)	1(0.6)	0	0
Chest pain	2 (4.8)	1 (2.4)	1 (1.8)	0	2 (2.6)	0	5 (2.9)	1 (0.6)	2 (3.3)	1 (1.7)
Rhinitis	1 (2.4)	0	3 (5.5)	0	1 (1.3)	0	5 (2.9)	0	1 (1.7)	0
Pneumonia	0	0	3 (5.5)	0	2 (2.6)	0	5 (2.9)	0	0	0
Fatigue	2 (4.8)	1 (2.4)	0	0	2 (2.6)	0	4 (2.3)	1 (0.6)	1 (1.7)	1 (1.7)
Abdominal pain lower	0	0	0	0	3 (3.9)	2 (2.6)	3 (1.7)	2 (1.1)	0	0
Abdominal pain	1 (2.4)	0	0	0	2 (2.6)	2 (2.6)	3 (1.7)	2 (1.1)	3 (5.0)	3 (5.0)
Dyspnoea	2 (4.8)	0	1 (1.8)	1 (1.8)	0	0	3 (1.7)	1 (0.6)	1 (1.7)	1 (1.7)
Haemoptysis	1 (2.4)	0	2 (3.6)	0	0	0	3 (1.7)	0	1 (1.7)	0
Rash macular	0	0	2 (3.6)	0	1 (1.3)	0	3 (1.7)	0	0	0
Dyspepsia	0	0	2 (3.6)	1 (1.8)	0	0	2 (1.1)	1 (0.6)	1 (1.7)	0
Anaemia	0	0	2 (3.6)	0	0	0	2 (1.1)	0	1 (1.7)	0
Conjunctivitis	0	0	0	0	2 (2.6)	0	2 (1.1)	0	2 (3.3)	0
Influenza	0	0	2 (3.6)	0	0	0	2 (1.1)	0	0	0
Pain in extremity	2 (4.8)	2 (4.8)	0	0	0	0	2 (1.1)	2 (1.1)	2 (3.3)	1 (1.7)
Flushing	1 (2.4)	1 (2.4)	1 (1.8)	1 (1.8)	0	0	2 (1.1)	2 (1.1)	3 (5.0)	3 (5.0)
Enuresis	0	0	2 (3.6)	1 (1.8)	0	0	2 (1.1)	1 (0.6)	0	0
Laryngitis	1 (2.4)	0	0	0	1 (1.3)	0	2 (1.1)	0	2 (3.3)	0
Nasal congestion	0	0	0	0	0	0	0	0	2 (3.3)	2 (3.3)
Pneumonia bacterial	0	0	0	0	0	0	0	0	2 (3.3)	0

Of all these events, only pyrexia, vomiting, nausea, and erection increased/spontaneous penile erection seem to be dose related.

7.4.2 Laboratory Findings

The placebo controlled study A1481131 and the long term study A1481156 showed little change from baseline at endpoint in median laboratory values. There were no discontinuations because of laboratory abnormalities during the studies.

7.4.3 Vital Signs

There were small and inconsistent changes in heart rate, sitting diastolic and systolic blood pressure regardless of treatment group in the placebo controlled study A1481131.

Table 35. Study A1481131: Vital Signs - Mean (SD) Baseline and Change from Baseline at Week 16

	Sildenafil									
Dose	Low		Medium		High		Combined		Placebo	
	N		N		N		N		N	
Sitting heart rate, bpm										
Baseline	41	86.2 (12.3)	55	86.5 (17.2)	76	91.7 (14.7)	172	88.7 (15.2)	60	87.1 (16.9)
Change from baseline at Week 16	40	-2.9 (14.2)	54	-0.8 (15.9)	75	-2.4 (14.4)	169	-2.0 (14.8)	58	-3.5 (14.8)
Sitting diastolic BP, mmHg										
Baseline	41	60.8 (8.6)	55	63.7 (10.8)	76	62.6 (12.0)	172	62.5 (10.9)	60	59.7 (10.0)
Change from baseline at Week 16	40	-0.8 (11.2)	54	-1.6 (12.5)	75	-1.3 (13.0)	169	-1.3 (12.4)	58	3.7 (13.6)
Sitting systolic BP, mmHg										
Baseline	41	98.9 (11.2)	55	103.0 (14.6)	76	99.6 (12.5)	172	100.5 (13.0)	60	98.9 (12.7)
Change from baseline at Week 16	40	3.8 (11.3)	54	0.9 (12.1)	75	0.6 (14.6)	169	1.4 (13.1)	58	3.7 (13.0)

Source: A1481131 CSR Table 8.2
SD=standard deviation; bpm=beats per minute; BP=blood pressure

There were two subjects who reported serious heart rate/rhythm event:

- Subject 11218 (sildenafil medium/medium dose) reported paroxysmal tachycardia on Days 406-422; this resolved following administration of treatment.
- Subject 11621 (sildenafil low/low dose) reported supraventricular tachycardia on Days 448-449, 471 and 564.

There were two subjects who reported serious hypotensive events.

- Subject 11611 (sildenafil low/low dose) reported a serious adverse event of severe hypotension on Days 850-853 associated with right heart catheterization which resolved following parenteral fluid intake, and an adverse event of moderate hypotension on Days 860-861.
- Subject 10427 (sildenafil high/high dose) experienced a serious adverse event of moderate bradycardia on Day 115 in conjunction with right heart catheterization.

7.4.4 Electrocardiograms (ECGs)

The ECG findings were similar regardless of treatment group and were expected considering the underlying disease.

7.4.5 Special Safety Studies/Clinical Trials

7.4.6 Immunogenicity

Subject 10420 (US) reporting stridor was rechallenged before he was permanently discontinued from sildenafil. On study day 2, the subject experienced stridor, which lasted for 2 to 3 hours. The study treatment was stopped. On study day 10, sildenafil treatment was restarted, with 1/100 of the required dose without any event. Eight hours later, 1/10 of the dose was administered. The subject developed stridor within 15 minutes, which lasted for 3 to 4 hours and required treatment. Sildenafil treatment was permanently discontinued.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See previous part of review for complete discussion of dose and mortality.

7.5.2 Time Dependency for Adverse Events

See previous part of review for complete discussion of time on drug and mortality. There were no deaths reported in randomized subjects in the 16-week base study A1481131. In the extension study, the subject whose death occurred earliest had started drug 471 days before dying. Many subjects had been on drug 1000 days or more before dying.

7.5.3 Drug-Demographic Interactions

Those subjects who died tended to have been classified as WHO functional class III or IV at baseline compared with of the overall study population (39% (15/39) and 17% (39/234), respectively).

While the majority of subjects (67%) had secondary as opposed to primary pulmonary hypertension (33%) as the etiology of their disease, the majority of deaths (77%, 30/39 were reported in subjects with primary pulmonary arterial hypertension).

The country of origin showed an imbalance in mortality rate. The 3 countries with the highest rates were India (44%, 12/27), Mexico (36%, 5/14), and Poland it was 21% (7/33). The mortality rate in the United States was 5% (2/39).

7.5.4 Drug-Disease Interactions

None investigated.

7.5.5 Drug-Drug Interactions

Drug-drug interaction studies have only been performed in adults.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See package insert for Revatio.

7.6.2 Human Reproduction and Pregnancy Data

See package insert for Revatio.

7.6.3 Pediatrics and Assessment of Effects on Growth

Pediatric Cognitive and Motor Development Assessment
The majority of subjects for all treatment sequences were not limited in their cognitive or motor development at baseline and Week 52. Few subjects had changes in cognitive or motor development from baseline to Week 52.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no new information available for this submission. Please refer to the data included in the original REVATIO submission (NDA 21-845).

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Post-marketing data from Pfizer's safety database has been reviewed during 9 periods since the approval of REVATIO. The results from these reviews are summarized below.

Table 37. Summary of Post-Marketing Adverse Events Reported to the Pfizer from 03 June 2005 through 30 October 2009

	All Ages			Age 17 and under		
Reporting Period†	Number of Cases (Number of events)	Number (%) of serious cases	Deaths (%)	Number of Cases (Number of events)	Number (%) of serious cases	Deaths (%)
03 June 2005 through 30 November 2005	39 (140)	23 (59%)	9 (23%)	4 (19)	3 (75%)	2 (50%)
01 December 2005 through 31 May 2006	88 (232)	47 (53%)	11 (12%)	8 (16)	6 (75%)	1 (12%)
01 June 2006 through 30 November 2006	63 (157)	39 (62%)	3* (5%)	13 (22)	10 (77%)	0
01 December 2006 through 31 May 2007	82 (194)	65 (79%)	7 (9%)	8 (13)	8 (88%)	1 (12%)
01 June 2007 through 31 October 2007	76 (160)	53 (70%)	16 (21%)	6 (9)	6 (100%)	0
01 November 2007 through 31 May 2008	127 (228)	75 (59%)	10 (8%)	17 (42)	6 (35%)	0
01 June 2008 through 31 May 2009	207 (335)	127 (61%)	49 (24%)	39 (54)	16 (42%)	3 (8%)
01 June 2009 through 27 February 2010	238 (448)	201 (85%)	127 (53%)	19 (41)	14 (74%)	5 (26%)
28 February 2010 through 31 May 2011‡	451 (894)	340 (75%)	188 (42%)	45 (97)	32 (71%)	9 (20%)

† Line listings for each post-marketing period are provided in Module 5.3.6.
*Follow-up for one of these cases later confirmed that the patient had received sildenafil for erectile dysfunction, not PAH.
‡ Please note that the overall number of cases and events for the period 28 February 2010 through 31 May 2011 represents PeriodicSafety Update Report (PSUR) medically confirmed events and non-serious listed medically confirmed events to reflect the data as provided in the PSUR, wheeras the figures for all other reporting periods reflect PSUR medically confirmed events.

Review of pediatric cases from the 9 periodic reviews of post-marketing data revealed nothing unexpected in this patient population.

9 Appendices

1) Listing of all studies

2) Review of study A1481131

3) Review of study A1481156

4) Review of study A1481134

5) Review of study A1481157

9.1 Literature Review/References

Articles which were pertinent to this indication were reviewed.

9.2 Labeling Recommendations

Approval for pediatric patients with PAH is not being recommended. The results of studies A1481131 and A1481156 will be added to the package label for Revatio.

9.3 Advisory Committee Meeting

None

Apendix 1

Section 5.2 Table 1. Listing of All Studies

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics (No. of Subjects)	Duration of Treatment	Study Start/Status	Study Report Location
Efficacy Studies of Oral Sildenafil in the Treatment of PAH in Pediatric Subjects							
A1481131 Brazil, 1 Canada, 1 Chile, 1 Colombia, 3 Guatemala, 1 Hungary, 2 India, 2 Italy, 1 Japan, 1 Malaysia, 1 Mexico, 1 Poland, 3 Russia, 1 Sweden, 1 Taiwan, 3 United States, 9 **Total: 32**	Randomised, DB, PC, PG 16-week dose ranging study of oral sildenafil in the treatment of children, aged 1-17 years with PAH	***All subjects***	Randomized: 235 Treated: 234 Completed: 228	All Treated subjects: Sex: 89 M/145 F Age (min/max): (1-17) years Race: W/B/O: 97/5/132	Planned duration 16 weeks	28 August 2003/ Complete	Study Report Synopsis A1481131
		Low dose sildenafil Target sildenafil steady-state 47ng/ml	Planned 51[a] Randomized: 42 Treated: 42 Completed: 40	Sex: 17 M/25 F Mean Age (min/max): 11.6 (5/17) years Race: W/B/O: 19/1/22	Median (days): 113 Range (days): 3-130		Supplemental Study Report A1481131
		Medium dose sildenafil Target sildenafil steady-state 140 ng/ml	Planned 51[a] Randomized: 56 Treated: 55 Completed: 55	Sex: 24 M/31 F Mean Age (min/max): 9.9 (2/17) years Race: W/B/O: 26/1/28	Median (days): 113 Range (days): 106-150		Supplemental Addendum A1481131
		High dose sildenafil Target sildenafil steady-state 373 ng/ml	Planned 51[a] Randomized: 77 Treated: 77 Completed: 75	Sex: 26 M/51 F Mean Age (min/max):8.5 (1/17) years Race: W/B/O: 28/1/48	Median (days): 113 Range (days): 8-144		
		Placebo	Planned 51[a] Randomized: 60 Treated: 60 Completed: 58	Sex: 22 M/38 F Mean Age (min/max):9.4 (2/16) years Race: W/B/O: 24/2/34	Median (days): 113 Range (days): 27-151		

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Section 5.2 Table 1. Listing of All Studies

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics (No. of Subjects)	Duration of Treatment	Study Start/Status	Study Report Location
A1481156 Brazil, 1 Chile, 1 Colombia, 3 Guatemala, 1 Hungary, 2 India, 2 Italy, 1 Japan, 1 Malaysia, 1 Mexico, 1 Poland, 3 Russia, 1 Sweden, 1 Taiwan, 3 United States, 9 **Total: 31**	M/C, long-term extension study of subjects who completed Study A1481131	**A1481131/ A1481156 Treatment Sequence** Includes all subjects from Study A1481131	Assigned: 235 Treated: 234 Entered Study A1481156: 220 Discontinued as of interim data cutoff: 75	All Treated subjects: Sex: 89 M/145 F Age (min/max): (1/17) years Race: W/B/O: 97/5/132		13 January 2004 Ongoing; CSR includes Interim clinical data as of 15 May 2009	Study Report Synopsis A1481156
	Sildenafil-treated subjects from A1481131 were assigned to the same dose group in A1481156	***Low dose/ Low dose sildenafil***	Assigned: 42 Treated: 42 Discontinued as of interim data cutoff: 13	Sex: 17 M/25 F Mean/Median Age (min/max): 11.6 (5/17) years Race: W/B/O: 19/1/22			
		Medium dose/ Medium dose sildenafil	Assigned: 56 Treated: 55 Discontinued as of interim data cutoff: 17	Sex: 24 M/31 F Mean/Median Age (min/max): 9.9 (2/17) years Race: W/B/O: 26/1/28			
		High dose/ High dose sildenafil	Assigned: 77 Treated: 77 Discontinued as of interim data cutoff: 26	Sex: 26 M/51 F Mean/Median Age (min/max): 8.5 (1/17) years Race: W/B/O: 28/1/48			
	Placebo-treated subjects from A1481131 were stratified by weight and randomized to receive sildenafil in A1481156 as per 1 of the active	***Placebo/ Low dose sildenafil***	Assigned: 13 Treated: 13 Discontinued as of interim data cutoff: 4	Sex: 4 M/9 F Mean/Median Age (min/max): 9.7 (4/16) years Race: W/B/O: 4/0/9			
		Placebo/ Medium dose sildenafil	Assigned: 19 Treated: 19 Discontinued as of interim data cutoff: 4	Sex: 8 M/11 F Mean/Median Age (min/max): 9.3 (2/16) years Race: W/B/O: 7/2/10			

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Section 5.2 Table 1. Listing of All Studies

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics (No. of Subjects)	Duration of Treatment	Study Start/Status	Study Report Location
A1481156 con't	treatment groups in A1481131	***Placebo/ High dose sildenafil***	Assigned: 23 Treated: 23 Discontinued as of interim data cutoff: 6	Sex: 8M/15 F Mean/Median Age (min/max): 9.3 (2/15) years Race: W/B/O: 12/0/11			
		Placebo/ Non-Randomised	Assigned: 5 Treated: 5 Discontinued as of interim data cutoff: 5	Sex: 2 M/3 F Mean/Median Age (min/max): 10.0 (3/16) years Race: W/B/O: 1/0/4			
Studies of Intravenous Sildenafil in Pediatric Subjects							
A1481134 Denmark, 2 France, 3 Netherlands, 2 Switzerland, 1 United Kingdom, 2 United States, 18 **Total: 28**	Randomised, DB,PG, PC, multi-centre study assess IV sildenafil as treatment of PH post-corrective surgery for congenital heart disease in children aged 0-17 years.	***Low IV sildenafil*** Loading dose targeting plasma concentration of 40 ng/ml followed by maintenance infusion for 24-72 hours.	Randomized: 4 Treated: 4 Completed: 4	Sex: 2 M/2 F Mean Age (min/max):21.8 (3/77) months Race: W/B/O: 2/0/2	One single dose followed by 24-72 hour infusion	14 September 2003 /Terminated due to lack of recruitment	Study Report **A1481134** Cross Reference NDA 22-473 Sequence 0000 Section 5.3.5.4
		Medium IV sildenafil Loading dose targeting plasma concentration of 120 g/ml followed by maintenance infusion for 24-72 hours	Randomized: 5 Treated: 4 Completed: 3	Sex: 2 M/2 F Mean Age (min/max):11.3 (3/25) months Race: W/B/O: 2/0/2			Pharmacokinetic Results Study Report A1481134
		High IV sildenafil Loading dose	Randomized: 4 Treated: 4 Completed: 4	Sex: 1 M/3 F Mean Age (min/max):8 (3/17) months			

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Section 5.2 Table 1. Listing of All Studies

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics (No. of Subjects)	Duration of Treatment	Study Start/Status	Study Report Location
A1481134 con't		targeting plasma concentration of 360 g/ml followed by maintenance infusion for 24-72 hours		Race: W/B/O: 3/1/0			
		Placebo Route: Intravenous	Randomized: 5 Treated: 5 Completed: 4	Sex: 4 M/1 F Mean Age (min/max):38.8 (3/178) months Race: W/B/O: 3/0/2			
A1481157 France, 2 United Kingdom, 2 United States, 6 **Total: 10**	(Part1) M/C, OL, PC dose ranging study to evaluate the pharmaco-kinetics of IV sildenafil in near term and term newborns with PPHN	***Sildenafil*** Route: Intravenous Dose Regimen: Target plasma concen-tration up to 150ng/mL (Loading dose followed by infusion for 48-168 hours)	Enrolled: 36 Treated: 36 Completed: 31	Sex: 17 M/19 F Mean Age (min/max): 34.3 (11/71) hours from birth to first dose. Race: W/B/O: 10/11/15	Single dose. Loading dose followed by infusion for 7 days	02 Nov 2003/ Terminated due to lack of recruitment	Study Report **A1481157** Cross Reference NDA 22-473 Sequence 0000 Section 5.3.5.4

Section 5.2 Table 1. Listing of All Studies

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics (No. of Subjects)	Duration of Treatment	Study Start/Status	Study Report Location
Bioavailability (BA) and Bioequivalence (BE) Study Reports							
A1481275 Belgium, 1	3-way, 3-period XO PK Study to evaluate the relative bioequi-alence of pediatric use formulations to Revatio® 20 mg intact tablet	Oral Revatio® intact tablet Revatio® 20 mg crushed tablet mixed with apple sauce Revatio® 20 mg extemporaneously prepared formulation	Planned 18 Randomized: 18 Treated: 18 Completed: 18	Sex: 9 M/9 F Mean Age: 37.4 (min/max): 25-51 Race: W/B/O: 16/2/0	Subjects received a single dose of each of three formulations	16 September 2009 /Completed	Study Report Synopsis A1481275
A1481261 United States, 1	SB study in healthy adult volunteers to investigate the palatability of different oral suspension formulations of sildenafil citrate.	***Sildenafil*** 4 prototype suspension formulations containing 10 mg sildenafil citrate, sweeteners and proprietary flavor agents ***Placebo (control) formulation***	Planned 8 Treated: 4 Completed: 4	Sex: 3 M/1 F Mean Age: 45.5 (min/max): 40-50 Race: W/B/O: 4/0/0	All formulations were expectorated not swallowed	11 August 2008/Completed	Study Report Synopsis A1481261

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Section 5.2 Table 1. Listing of All Studies

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics (No. of Subjects)	Duration of Treatment	Study Start/Status	Study Report Location
A1481293 Belgium, 1	3-way, 3-period XO PK 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	REVATIO® 20 mg IR oral tablet 2 x 10 mg sildenafil citrate IR oral tablet 2 mL of the sildenafil citrate 10 mg/mL POS (provided as a powder in a bottle for constitution with water).	Planned 42 Treated: 42 Completed: 42	Sex: 14 M/28 F Mean Age: 37.0 (min/max): 20-54 Race: W/B/O: 42/0/0	Subjects received a single dose of each of three formulations	17 January 2011/Completed	Study Report Synopsis A1481293
Other Study Reports							
A1481140	A multi-national, M/C, randomised, DB, double-dummy, PC, PG study to assess the efficacy and safety of 20, 40 and 80mg sildenafil TID in	Tmt Grp Placebo: (Route: Oral; Dose Regimen: multiple doses three times a day) Tmt Grp 20mg sildenafil: (Route: Oral;	Randomized: 70 Treated: 70 Completed: 68 Randomized: 69 Treated: 69 Completed: 67	Sex: 13 M/57 F Mean Age (min/max): 49.1 (18/78) years Race: W/B/O: 61/1/8 Sex: 20 M/49 F Mean Age (min/max): 47.2 (19/78) years	12 weeks multiple dose (sildenafil)	October 2nd 2002/Completed	Study Report **A1481140** Cross Reference NDA 21-845 Section 5.3.5.1

Section 5.2 Table 1. Listing of All Studies

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics (No. of Subjects)	Duration of Treatment	Study Start/Status	Study Report Location
	treatment of pulmonary arterial hypertension.	Dose Regimen: multiple doses three times a day) Tmt Grp 40mg sildenafil: (Route: Oral; Dose Regimen: multiple doses three times a day) Tmt Grp 80mg sildenafil: (Route: Oral; Dose Regimen: multiple doses three times a day)	 Randomized: 68 Treated: 67 Completed: 65 Randomized: 71 Treated: 71 Completed: 65	Race: W/B/O: 59/0/10 Sex: 20 M/47 F Mean Age (min/max): 51.4 (23/81) years Race: W/B/O: 58/4/5 Sex: 15 M/56 F Mean Age (min/max): 48.1 (20/81) years Race: W/B/O: 58/1/12			
A1481141	A multi-national, M/C, randomised, DB, PC, PG study to assess the safety and efficacy of a subject-optimised dose of sildenafil based on toleration, when used in combination with intravenous prostacyclin (epoprostenol) in patients with	Tmt Grp Placebo: (Route: Oral; Dose Regimen: multiple doses three times a day) Tmt Grp Sildenafil: (Route: Oral; Dose Regimen: subject-optimised dose of 20,40 or 80mg tablets TID)	Randomized: 133 Treated: 131 Completed: 108 Randomized: 134 Treated: 134 Completed: 122	Sex: 29 M/102 F Mean Age (min/max): 47.7 (18/75) years Race: W/B/O: 106/7/18 Sex: 24 M/110 F Mean Age (min/max): 47.8 (20/75) years Race: W/B/O: 105/10/19	16 weeks multiple dose (sildenafil)	July 3rd 2003/Completed	Study Report **A1481141** Cross Reference NDA 21-845 Sequence 0013 Section 5.3.5.1

Section 5.2 Table 1. Listing of All Studies

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics (No. of Subjects)	Duration of Treatment	Study Start/Status	Study Report Location
	pulmonary arterial hypertension.						
A1481142	A multi-centre, multinational, long-term extension study, to assess the safety and toleration of subject optimized treatment regimens of oral sildenafil for pulmonary arterial hypertension in subjects who have completed study A1481140.	Patients were up-titrated from A1481140 treatment group to receive 20 mg, 40 mg or 80 mg sildenafil: (Route: Oral; Dose Regimen: multiple doses three times a day)	Treated: 259 Completed: 170	Sex: 64 M/195 F Mean Age (min/max): 48.7 (19/78) years Race: W/B/O: 219/5/35	Median duration in study was 1171 days.	December 24th 2002/Completed	Study Report Synopsis A1481142
A1481153	A M/C, multi-national, long-term, OL extension study, to assess the safety of subject-optimised treatment regimens of oral sildenafil when used in combination with	Tmt Grp Sildenafil (subjects who received placebo in A1481141 only): (Route: Oral; Dose Regimen: subject-optimised dose of 20,40 or 80mg tablets TID plus subject-	Randomized and treated in A1481141: 131 Treated: 115 Discontinued: 62 Completed: 53	Sex: 23 M/92 F Mean Age (min/max): 48.3 (18/75) years Race: W/B/O: 93/6/16	Median duration of treatment: 1294 days	November 28th 2003/Completed	Study Report Synopsis A1481153

Section 5.2 Table 1. Listing of All Studies

Protocol No. (Country)	Study Design and Objective	Treatment Groups	No. of Subjects	Demographics (No. of Subjects)	Duration of Treatment	Study Start/Status	Study Report Location
	intravenous prostacyclin (epoprostenol) for pulmonary arterial hypertension in subjects who have completed study A1481141.	optimised dose of IV epoprostenol) Tmt Grp Sildenafil: (Route: Oral; Dose Regimen: subject-optimised dose of 20,40 or 80mg tablets TID plus subject-optimised dose of IV epoprostenol)	Randomized and treated in A1481141: 134 Treated: 134 (including 7 subjects who received sildenafil in Study A1481141, but did not continue to Study A1481153) Discontinued: 78 Completed: 56	Sex: 24 M/110 F Mean Age (min/max): 47.8 (20/75) years Race: W/B/O: 105/10/19	Median duration of treatment: 1154.5 days		

Notes: B = Black; DB = Double-blind; F = Female; Grp = Group; IV= Intravenous; M = Male; M/C = Multi-centre; No. = Number; PC = Placebo-controlled; PG = Parallel-group; PAH = Pulmonary Arterial Hypertension; PH = Pulmonary Hypertension; PK= Pharmacokinetic; PPHN = Persistent Pulmonary Hypertension of the Newborn; O = Other; OL = Open-label; TID = Three times daily; Tmt = Treatment; XO = Cross-over; W = White
* Planned enrollment in Study A1481131 is the sample size estimated prior to study initiation.

Appendix 2
Study review

Protocol number: A1481131

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

Study start/completion dates: August 2003/June 2008

Study Center locations (total 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.

Indication:
Pulmonary Arterial Hypertension

Amendments
There were 6 global, 3 country-specific and 3 center-specific amendments to the protocol.

Objectives
The objective of this study is to assess the efficacy, safety and pharmacokinetics of 16 weeks of chronic treatment with oral sildenafil in pediatric subjects with pulmonary hypertension.
Number of Subjects
A minimum of 200 subjects randomized including at least 90 subjects who were developmentally able to exercise).
Study Population
Pediatric subjects aged 1 to 17 years with pulmonary arterial hypertension (PAH) including primary pulmonary hypertension or pulmonary arterial hypertension associated with congenital heart disease or collagen vascular disease.
Inclusions
-Male or female subjects aged from 1 to 17 years (for Russia only, aged from 3 to 17 years [country-specific Protocol Amendment No. 2]; for center 1017 (US) only, aged from 5 to 17 years old [center-specific Protocol Amendment No. 2]). Females of child bearing potential who were sexually active must have been practicing a suitable method of birth control so tha,t in the opinion of the investigator, they would not become pregnant during the study;
-Subjects weighing $\geq$8 kg;
-Subjects who had symptomatic PAH because of 1 of the following conditions:
    -Primary PAH;

-PAH in the presence of a small or hemodynamically insignificant congenital systemic to pulmonary shunt lesion that in the opinion of the investigator was not the cause of PH;

-PAH associated with collagen vascular disease (eg, scleroderma);

-PAH associated with congenital systemic-to-pulmonary shunts with a baseline resting room air oxygen saturation (SaO2) ≥88%. If the defect was repaired, it should have been repaired ≥6 months prior to screening (repairs could be either surgical or via interventional cardiac catheterization (eg, atrial septal defect closure device or coil of patent ductus arteriosus);

-PAH associated with d-transposition of the great arteries repaired within the first 30 days of life;

-PAH in subjects who had undergone surgical repair of other congenital heart lesions ≥6 months prior to screening and did not have clinically significant residual left-sided heart disease consistent with the exclusion criteria.

-Subjects with a mean pulmonary artery pressure ≥ 25 mmHg[9] at rest, pulmonary capillary wedge pressure (PCWP) ≤15 mmHg, and pulmonary vascular resistance index (PVRI) ≥3 Wood units.m2. If PCWP was not available, then mean left atrial pressure ≤15 mmHg or left ventricular end-diastolic pressure (LVEDP) ≤15 mmHg in the absence of left atrial obstruction;

-Subjects, developmentally able to exercise, whose functional capacity measured by CPX test was within the following parameters: Peak VO2 ≥10 mL/kg/minute and ≤ 28 mL/kg/minute during the screening CPX test;

-The investigator must have obtained written informed consent and assent where applicable before the subject was screened for the study. The inclusion of a subject more than once in the same clinical study was not permissible;

-Subjects who would undergo a large shift[10] in altitude in order to participate in the study (eg, live at altitude and shift to sea level in order to participate) must have resided at the "in study" altitude for ≥90 days prior to baseline and during the study period.

Exclusions summarized

Subjects were excluded from the study if they had PH secondary to other diseases, left-sided heart disease and other similar heart-related diseases, or had treatment with off-label sildenafil, an endothelin-A receptor antagonists or prostacyclin/prostacyclin analogue within 30 days prior to randomization, or who were taking medications such as parenteral inotropic medication, parenteral vasodilators within 3 months prior to screening, alpha-blockers or cytochrome P450 (CYP) 3A4 inhibitors.

Study Design

[9] Hemodynamic measurements could be performed within 21 days prior to randomization for study purposes.

[10] A "large shift" was defined as approximately 5000 feet or 1524 m.

This study is a 16-week, randomized, double-blind, placebo controlled, dose ranging, parallel group study with subjects aged 1 to 17 years, receiving placebo or 1 of 3 doses of sildenafil (low, medium or high doses). The study planned to randomize a minimum of 90 subjects who are developmentally able to perform the CPX test to evaluate the primary objective. In addition, subjects who are not developmentally able to perform the CPX test will be randomized into the study for an evaluation of safety and growth and development.

All potential subjects were to have a diagnosis of increased pulmonary artery pressures that had been confirmed by right heart catheterization. At the baseline visit, eligible subjects were randomized according to weight and developmental ability to perform the cardiopulmonary exercise (CPX) test.

Following the baseline visit, the treatment phase consisted of a telephone contact at 1 week and 3 additional clinic visits during which efficacy and safety data were collected. Subjects were to be treated for 16 weeks. Blood samples for the determination of pharmacokinetics were to be collected during the study. After completion of the study, subjects were to have the option of enrolling in an extension study, A1481156. Subjects electing not to participate in the extension study were to be followed up for safety assessments 30-40 days after the end of the study treatment.

All subjects who have permanently withdrawn from study drug, regardless of the duration of participation, were to perform all the Week 16/End of Treatment visit scheduled assessments if the subject's safety was not compromised.

Legal guardians or parents of all A1481131 subjects who do not enter A1481156 were to be asked for permission for their children to be followed up on a yearly basis for the evaluation of survival status.

Treatments
Subjects were randomized in a double-blind fashion to placebo or sildenafil (low, medium or high dose) TID for a maximum of 16 weeks. Sildenafil doses were to be 10, 20, 40 and 80 mg TID with the exact dose based on subject body weight. See table below.

Table T2. Sildenafil Doses (TID) to Achieve Target Sildenafil Steady-State Maximum Concentrations of 47, 140 and 373 ng/mL at the Low, Medium and High doses, Respectively

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

Source: Appendix A1
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.

Dose was titrated up from low (10 mg TID) to the randomized dose at 1 week for the medium and high dose groups.

Endpoints

Primary Endpoint
-Percent change in peak VO2 normalized to body weight from baseline to Week 16 assessed by CPX testing (bicycle ergometry) for those who perform the procedure.
Secondary Endpoint(s):
-Mean pulmonary artery pressure (mPAP); and
-Pulmonary Vascular Resistance Index (PVRI)

The following endpoints were also evaluated:
Percent change from baseline to Week 16 in:
-Respiratory Exchange Ratio (RER);
-Time to maximum VO2.
Change from baseline to Week 16 in:
-Pulmonary Vascular Resistance (PVR);
-Cardiac Index (CI);
-Right atrial pressure (RAP);
-Child Health Questionnaire Parent Form (CHQ-PF28), physical and psychosocial scales;
- WHO PH functional class

Evaluations

Efficacy: All endpoints, except hemodynamics, were evaluated at screening, baseline, Week 8 (peak plasma levels) and Week 16/end-of-study. In addition, the World Health Organization (WHO) PH functional class was evaluated at Week 4. Hemodynamics were evaluated at baseline and Week16/end of study.
Pharmacokinetic: 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.
Safety: Adverse events (AEs) were monitored throughout the study.
Laboratory tests (hematology, chemistry and urinalysis) on blood and urine samples were performed at screening, baseline, and Weeks 4, 8 and 16/end-of-treatment. Vital sign measurements (blood pressure and pulse rate) were recorded at screening, baseline, and Weeks 4, 8 and 16/end-of-treatment, end-of-study and follow-up (if the subject did not enter the extension study). Electrocardiogram measurements (ECG) and ocular safety tests were recorded at baseline and Week 16/end-of-treatment. Physical examinations were performed at screening and Week 16/end-of-treatment.

RESULTS

Subject Disposition

Of the 324 subjects screened, 235 subjects were randomized to 1 of 4 treatment groups. The table below shows, by treatment group, the number of subjects randomized, the number treated, the number who completed, and for those who did not complete the reason for discontinuation. The table also shows the number of subjects who were analyzed for safety and/or efficacy.

Table T7. Disposition

	Sildenafil				
Dose	Low	Medium	High	Combined	Placebo
Number (%) of subjects:					
Randomized	42	56	77	175	60
Treated	42	55[a]	77	174[a]	60
Completed	40 (95.2)	55 (98.2)	75 (98.7)	170 (97.1)	58 (96.7)
Entered Study A1481156	38 (90.5)	53 (94.6)	74 (96.1)	165 (94.3)	55 (91.7)
Had follow-up visit and did not enter Study A1481156	1 (2.4)	1 (1.8)	1 (1.3)	3 (1.7)	3 (5.0)
Did not have follow-up visit and did not enter Study A1481156	1 (2.4)	1 (1.8)	0	2 (1.1)	0
Discontinued prior to treatment	0	1 (1.8)	0	1 (0.6)	0
Discontinued[b]	2 (4.8)	0	2 (2.60)	4 (2.3)	2 (3.3)
Had follow-up visit	1 (2.4)	0	1 (1.3)	2 (1.1)	0
Did not have follow-up visit	1 (2.4)	0	1 (1.3)	2 (1.1)	2 (3.3)
Reason for Discontinuation					
Adverse event	1 (2.4)	0	1 (1.3)	2 (1.1)	0
Lost to follow-up	0	0	0	0	1 (1.7)
Other	1 (2.4)	0	1 (1.3)	2 (1.1)	0
No longer willing to participate	0	0	0	0	1 (1.7)
Analyzed for efficacy					
ITT[c]	42 (100)	55 (98.2)	77 (100)	174 (99.4)	60 (100)
Per Protocol	23 (54.8)	23 (41.1)	27 (35.1)	73 (41.7)	24 (40.0)
Aged ≥5 years	42 (100)	46 (82.1)	58 (75.3)	146 (83.4)	53 (88.3)
CHQ-PF28[d]	37 (88.1)	34 (60.7)	48 (62.3)	119 (68.0)	46 (76.7)
Developmentally able	28 (66.7)	28 (50.0)	29 (37.7)	85 (48.6)	30 (50.0)
Analyzed for safety					
Adverse events	42 (100)	55 (98.2)	77 (100)	174 (99.4)	60 (100)
Laboratory data	42 (100)	55 (98.2)	76 (98.7)	173 (98.9)	60 (100)
Visual safety	42 (100)	55 (98.2)	75 (97.4)	172 (98.3)	60 (100)

Source: Table 1.1 and Table 4.1
CHQ-PF28=Child Health Questionnaire-Parent Report
[a] Subject 10463 was randomized but not treated
[b] Discontinuations occurring >7 days after the last dose of study treatment were attributed to the last study treatment received
[c] Subjects who were randomized to study treatment and received ≥1 dose of study treatment
[d] Subjects who fulfilled the criteria for the ITT were ≥5 years old and had CHQ-PF28 assessments in their first language

Of the 235 subjects randomized, 228 subjects completed the trial and 6 subjects discontinued early (2 sildenafil low dose, 2 sildenafil high dose and 2 placebo). The majority of subjects (96%, 220/235) who completed the study entered the extension study A14811565.

The allocation to treatment groups by weight is shown below.

Table T8. Allocation to Treatment Groups by Weight

	Sildenafil						Placebo	
	Low		Medium[a]		High			
Body weight, kg	N (n)	Dose	N (n)	Dose	N (n)	Dose	N (n)	Dose
≥8-20	NA	NA	15 (0)	10 mg	35 (1)	20 mg	18 (1)	NA
>20-45	31 (19)	10 mg	30 (20)	20 mg	31 (18)	40 mg	32 (21)	NA
>45	11 (9)	10 mg	10 (9)	40 mg	11 (9)	80 mg	10 (8)	NA

Source: Appendix B, Tables 15.1 and 16
N=total number of subjects; n=number of developmentally able subjects; NA=not applicable
[a] Subject 11612 (medium dose) was misallocated to high weight and should have received sildenafil dose appropriate for medium weight (actual weight 44.6 kg)

Subjects excluded from the analyses

Of the 235 randomized subjects, 234 were treated and included in the ITT population. A total of 115 subjects (49%, 115/235) were developmentally able to perform the CPX test.

Table T9. Subjects Excluded from Efficacy Analyses

	Sildenafil				
Dose	Low	Medium	High	Combined	Placebo
Number (%) of subjects:					
Randomized	42	56	77	175	60
Treated	42	55[a]	77	174[a]	60
Analyzed for efficacy					
ITT population[b]	42 (100)	55 (98.2)	77 (100)	174 (99.4)	60 (100)
Developmentally able (peak VO_2)	28 (66.7)	28 (50.0)	29 (37.7)	85 (48.6)	30 (50.0)
Analyzed for primary analysis	24 (57.1)	26 (46.4)	27 (35.1)	77 (44)	29 (48.3)
PP population	23 (54.8)	23 (41.1)	27 (35.1)	73 (41.7)	24 (40.0)
Reason for exclusion from primary analysis[c]					
Discontinued	1 (3.6)	0	1 (3.4)	2 (2.4)	0
Machine failure/damage	1 (3.6)	0	1 (3.4)	2 (2.4)	1 (3.3)
Too ill	1 (3.6)	0	0	1 (1.2)	0
Other[d]	1 (3.6)	2 (7.1)	0	3 (3.5)	0
Reason for exclusion from PP population					
Failed inclusion/exclusion criteria	1 (3.6)	1 (3.6)	1 (3.4)	3 (3.5)	1 (3.3)
Non compliance	0	0	0	0	0
Prohibited concomitant medication	0	0	0	0	0
No baseline or Week 16 VO_2	5 (17.9)	4 (14.3)	2 (6.9)	11 (12.9)	5 (16.7)
Received incorrect medication	0	1 (3.6)	0	1 (1.2)	0

Source: Tables 1.1, 5.1.1 and 5.1.2, and Appendix A, Item 8
ITT=intention-to-treat; PP=per protocol
[a] Subject 10463 was randomized but not treated
[b] Subjects who were randomized to study treatment and received ≥1 dose of study treatment
[c] All subjects were excluded from the primary analysis because they had a missing Week 16 assessment. The denominator used for percentages was the number of subjects developmentally able to perform the CPX test. Reasons for exclusion from primary analysis are documented in various sources including CRFs
[d] Other category included inadequate CPX test result, no staff available at site to run the CPX test or the test was erroneously not done

Most subjects were part of the efficacy analyses.

Demographics

Demographics of the subjects are shown in the table below.

Table T10. Demography – All Subjects

	Sildenafil				
Dose	Low	Medium	High	Combined	Placebo
Number of subjects	42	55	77	174	60
Male, n (%)	17 (40.5)	24 (43.6)	26 (33.8)	67 (38.5)	22 (36.7)
Female, n (%)	25 (59.5)	31 (56.4)	51 (66.2)	107 (61.5)	38 (63.3)
Age (years), n (%):					
1-4	0	9 (16.4)	19 (24.7)	28 (16.1)	7 (11.7)
5-12	25 (59.5)	28 (50.9)	36 (46.8)	89 (51.1)	37 (61.7)
13-17	17 (40.5)	18 (32.7)	22 (28.6)	57 (32.8)	16 (26.7)
≥18	0	0	0	0	0
Race, n (%):					
White	19 (45.2)	26 (47.3)	28 (36.4)	73 (42.0)	24 (40.0)
Black	1 (2.4)	1 (1.8)	1 (1.3)	3 (1.7)	2 (3.3)
Asian	6 (14.3)	13 (23.6)	15 (19.5)	34 (19.5)	7 (11.7)
Other	18 (38.1)	15 (27.3)	33 (42.9)	64 (36.8)	27 (45.0)
Region, n (%):					
America[a]	10 (23.8)	11 (20.0)	16 (20.8)	37 (21.3)	17 (28.3)
Asia	6 (14.3)	13 (23.6)	15 (19.5)	34 (19.5)	7 (11.7)
Europe	16 (38.1)	18 (32.7)	22 (28.6)	56 (32.2)	16 (26.7)
South America	10 (23.8)	13 (23.6)	24 (31.2)	47 (27.0)	20 (33.3)
Mean weight (range), kg	38.2 (20.0-105.0)	32.1 (8.6-106.0)	25.8 (8.2-61.0)	30.8 (8.2-106.0)	29.3 (9.1-60.0)
Mean height (range), cm	141.6 (111.0-172.0)	130.5 (77.0-192.5)	120.8 (72.0-180.0)	128.9 (72.0-192.5)	128.4 (78.0-173.0)
Mean BMI (SD), kg/m^2	18.2 (4.8)	17.6 (3.9)	16.3 (3.4)	17.2 (4.0)	16.9 (3.6)

n=number of subjects; BMI=body mass index; SD=standard deviation
[a] America=includes USA, Canada and Mexico

Overall, there were more females (145/234, 62%) than males (89/234, 38%) and the majority of subjects were between the ages of 5 and 12 years. Body weights were greater than 8 kg. Considering the small number of subjects per group, the demographics between groups were fairly similar.

PAH diagnoses

The number and percent of subjects with primary or secondary PAH are shown below.

	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	Sildenafil Combined Doses	Placebo
Number of Subjects	42	55	77	174	60
Primary Diagnosis MedDRA (v11.0) Lower Level Term					
PRIMARY PULMONARY HYPERTENSION					
Number of Subjects	12	19	26	57	21
Duration Since First Diagnosis (yrs)					
Mean	1.122	1.671	1.460	1.459	2.225
Range	0.005-7.042	0.003-7.280	0.008-8.290	0.003-8.290	0.027-12.422
Unspecified (N)	0	0	0	0	0
SECONDARY PULMONARY ARTERIAL HYPERTENSION					
Number of Subjects	30	36	51	117	39
Duration Since First Diagnosis (yrs)					
Mean	7.468	6.412	5.099	6.110	5.663
Range	0.005-16.255	0.085-16.079	0.003-15.699	0.003-16.255	0.038-16.958
Unspecified (N)	0	0	0	0	0

Most subjects were diagnosed with secondary PAH (67%, 156/234).

The diseases associated with secondary PAH are shown below.

	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	Sildenafil Combined Doses	Placebo
Number of subjects	42	55	77	174	60
Primary Diagnosis					
Primary pulmonary hypertension					
Number of Subjects	12	19	26	57	21
Duration Since First Diagnosis (yrs)					
Mean	1.122	1.671	1.460	1.459	2.225
Range	0.005-7.042	0.003-7.280	0.008-8.290	0.003-8.290	0.027-12.422
Unspecified (N)	0	0	0	0	0
Secondary pulmonary arterial hypertension					
Surgical Repair					
Atrial Septal Defect					
Number of Subjects		2	5	7	1
Duration Since First Diagnosis (yrs)					
Mean		1.589	5.693	4.520	3.159
Range		1.574-1.604	1.426-15.075	1.426-15.075	3.159-3.159
Unspecified (N)		0	0	0	0
Ventricular Septal Defect					
Number of Subjects	5	6	10	21	10
Duration Since First Diagnosis (yrs)					
Mean	9.178	4.521	4.888	5.805	4.863
Range	0.005-16.175	1.079-10.716	0.022-10.924	0.005-16.175	0.038-12.734
Unspecified (N)	0	0	0	0	0
Patent Ductus Arteriosis					
Number of Subjects	4	4	3	11	
Duration Since First Diagnosis (yrs)					
Mean	7.632	8.040	7.650	7.785	
Range	0.575-12.813	0.652-12.893	0.118-13.692	0.118-13.692	
Unspecified (N)	0	0	0	0	

The secondary PAH etiologies included (number of subjects):
-surgical repair of
- atrial septal defect (8),
-ventricular septal defect (31),
-patent ductus arteriosis (11),
-aorto pulmonary window (1),
-other, not specified (16)
-congenital systemic to pulmonary shunt (85),
-D-transposition of the great arteries (4).

The means and ranges for the durations since first diagnosis for subjects with secondary PAH were greater than those for subjects with primary PAH (6 to 7 years, compared to 1 to 2 years, respectively).

World Health Organization (WHO) Functional Class
The WHO functional class at baseline is shown below.

Table T18. World Health Organization (WHO) Functional Class at Baseline

	Sildenafil				
	Low	Medium	High	Combined	Placebo
Class, n (%)[a]					
I	9 (22.5)	20[b] (37.0)	21 (27.6)	50 (29.4)	25 (41.7)
II	22[b] (55.0)	25 (46.3)	43 (56.6)	90 (52.9)	29 (48.3)
III	9 (22.5)	8 (14.8)	12 (15.8)	29 (17.1)	6 (10.0)
IV	0	1 (1.9)	0	1 (0.6)	0
Missing	2	1	1	4	0

Source: Table 5.11.1
WHO=world health organization
[a] The number of subjects with known WHO functional class has been used as the denominator for the calculation of percentages
[b] Subjects 11620 (sildenafil low dose) and 11221 (sildenafil medium dose) recorded baseline functional class on Day 2. The investigators confirmed that there was no significant change in functional class from pre-treatment and therefore these records were used as the baseline value.

At baseline, more than 80% of subjects were Class I or II. There were 4 subjects (all sildenafil) who did not report WHO class.

Concomitant Medication

The majority of concomitant medications were associated with non-specific background therapy for PAH, and the right heart catheterization procedure. The most commonly taken individual concomitant drugs were midazolam, fentanyl and heparin. During the study, 39 subjects received calcium channel blockers, 54 subjects received diuretics and 28 subjects received oral anticoagulants.

Efficacy

Changes in the Planned Analyses

The following changes were made to certain analyses:

1. Baseline peak VO2 was included as a covariate in the primary analysis, as it was found to be correlated to percent change in peak VO2 from baseline. This would make adjustments in the analyses for random baseline differences between the treatments and account for some of the variability in the primary analysis.
2. The lowest weight category (≥8 to 20 kg) was combined with the middle weight category for the primary analysis. It was not suitable to use the lowest weight category alone as, at the time of the blinded review, there were only 3 developmentally able subjects in the lowest weight category (≥8 to 20 kg).
3. Baseline was defined as the average of the screening and baseline assessment data. There was no consistent difference observed between the screening and baseline assessment data and hence this was an appropriate approach to reduce the variability in the baseline measurement.

Percentage Change from Baseline in Peak Volume of Oxygen Consumed (VO2) at Week 16

There were 115 subjects deemed to be developmentally able to perform the CPX test (cycle ergometry). The baseline value was the average of the screening and baseline readings. There were 8 subjects randomized to a sildenafil dose and 1 subject randomized to placebo who were excluded from the primary analysis (missing week 16 assessment). The reasons given were the following: subject discontinued study (2 sildenafil), machine problems (2 sildenafil, 1 placebo), too ill to perform test (1 sildenafil), and other (3 sildenfail).

See the results in the table and figure.

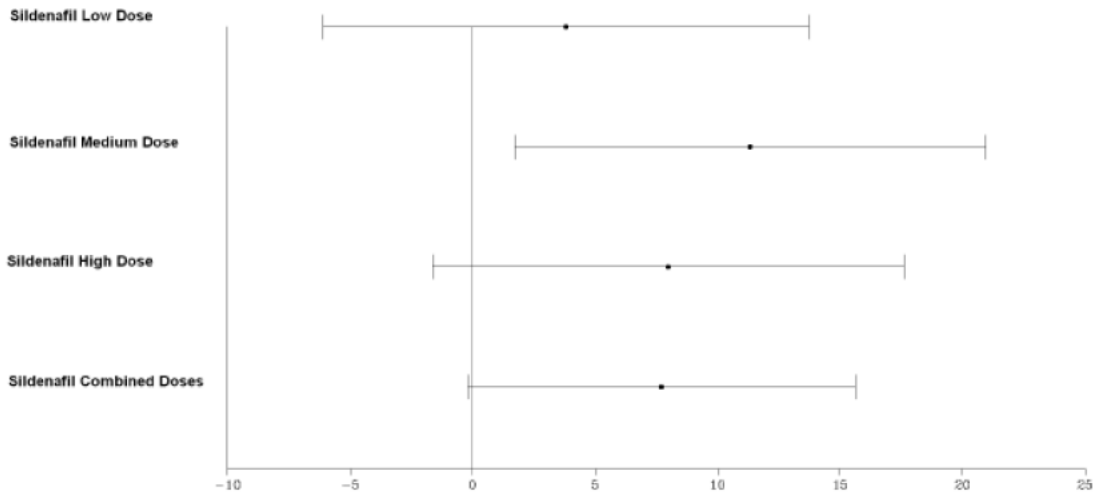
Table T14. Percentage Change from Baseline in Peak Volume of Oxygen Consumed (VO2) at Week 16 (LOCF) – ITT

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

Source: Tables 5.2.1.1 and 5.2.2
VO_2=volume of oxygen consumed; LOCF=last observation carried forward; ITT=intention-to-treat population; SD=standard deviation; SE=standard error; NA=not applicable
[a] ITT subset of developmentally able subjects
[b] Baseline was the average of all assessments on or before the first day of study treatment
[c] Analyses were performed using analysis of covariance with etiology, weight and baseline peak VO_2 as the covariates

Mean baseline peak VO2 values were somewhat higher for the placebo treatment group. The mean percentage change from baseline for the sildenafil treatment groups were 6.44% (low dose), 13.40% (medium dose), and 10.58% (high dose), and 0.53% for placebo. The mean difference for the sildenafil combined group versus placebo was not statistically significant.

Figure F2. Treatment Difference in Percentage Change from Baseline in Peak VO_2 at Week 16 (LOCF): Mean and 95% Confidence Intervals - ITT



Other endpoints

Cardiac output (and hence derivation of PVRI) was assessed by either the thermodilution or Fick methods. When the Fick method was used oxygen consumption was either measured or estimated. A large proportion of subjects had their hemodynamic assessment done by the Fick method; 73% (147/202) of subjects who had a valid PVRI measurement at Baseline and Week 16 were assessed using the Fick method. Post hoc analyses were conducted using a standardized approach to estimating oxygen consumption for those subjects who had their cardiac output determined by the Fick method.

Pulmonary vascular resistance index (PVRi).

Of the 234 subjects randomized, 202 subjects (152 sildenafil, 50 placebo) were evaluated for this secondary endpoint. Therefore, 32 subjects are not included in the analyses.

The subject number and reason for exclusion are shown below.

Subject Number	Reason
10405	Subject had shunt, but had cardiac output assessed by thermodilution at Baseline
10412	Missing PCWP at Week 16
10415[2]	Subject had shunt, but had cardiac output assessed by thermodilution
10420	RHC not done at Week 16 (Discontinued due to AE)
10427	RHC not completed at Week 16 (Subject has SAE whilst having RHC)

Subject Number	Reason
10429	Different methods used for measuring cardiac output at Baseline and Week 16
10435	Different methods used for measuring cardiac output at Baseline and Week 16
10443	Baseline more than 21 days before start of study treatment
10453	RHC not done at Week 16 (Discontinued)
10459	Baseline more than 21 days before start of study treatment
10465[1]	Missing Oxygen Consumption at Baseline and Week 16
10466[1]	Missing Oxygen Consumption at Baseline and Week 16
10813	RHC not done at Week 16 (Discontinued)
10840[2]	Missing PCWP at Baseline and Week 16
10854	RHC not done at Week 16 (Parent would not allow RHC assessment)
10858	Baseline more than 21 days before start of study treatment
10863	Pulmonary Arterial Oxygen Saturation = Pulmonary Venous Oxygen Saturation at Baseline; resulting in zero in denominator for calculating cardiac output
10872[1]	Missing Oxygen Consumption at Baseline and Week 16
10873	Missing Pulmonary Arterial Oxygen Saturation at Baseline Missing Oxygen Consumption at Baseline and Week 16
10875	Missing Pulmonary Arterial Oxygen Saturation at Baseline
11201	RHC not done at Week 16 (Discontinued due to AE)
11208	Week 16 RHC performed after start of A1481156
11213[2]	Subject had shunt, but had cardiac output assessed by thermodilution.
11240	RHC not done at Week 16 (Discontinued)
11246	Week 16 RHC performed after start of A1481156
11247[1]	Missing Oxygen Consumption at Baseline and Week 16
11248[1]	Missing Oxygen Consumption at Baseline and Week 16
11606[1]	Missing Oxygen Consumption at Week 16
11620	RHC not done at Week 16 (Discontinued)
11621	Different methods used for measuring cardiac output at Baseline and Week 16
11624[2]	Missing Hb at Baseline and Week 16
11625	Different methods used for measuring cardiac output at Baseline and Week 16

[1] Subjects excluded from original analyses, but included in analyses with standardized data
[2] Subjects excluded from sensitivity analyses using multiple imputation
AE – Adverse Event, SAE – Serious AE
Hb - Haemoglobin
PCWP – Pulmonary Capillary Wedge Pressure

The results for the remaining subjects are shown in the table below.

Table 20. Change from Baseline in PVRI (CRF Data) at Week 16 – ITT Population

	Sildenafil				
Treatment Group	Low	Medium	High	Combined	Placebo
Number of subjects	36	49	67	152	50
Mean (SD) PVRI, dyne.s.cm^{-5}.m^2					
Baseline[a]	1877.7 (1214.5)	1518.1 (1102.6)	1669.9 (1518.1)	1669.9 (1326.3)	1286.4 (958.8)
Week 16	1885.6 (1278.4)	1278.4 (878.9)	1262.4 (1078.7)	1414.2 (1094.6)	1414.2 (1102.6)
Change from baseline	8.0 (870.9)	-231.7 (918.9)	-407.5 (1174.5)	-255.7 (1038.7)	127.8 (735.1)
Mean difference versus placebo (SE)	-47.9 (215.7)	-359.6 (191.8)	-575.3 (183.8)	-327.6 (159.8)	NA
95% Confidence interval[b]	-471.4, 375.5	-743.1, 24.0	-934.8,-215.7	-639.2, -16.0	NA
P-value[b]	NA	NA	NA	0.041	NA

Source: Study A1481131 CSR Tables 5.4.1 and 5.4.2.1 (Module 5.3.5.1)
ITT=intention-to-treat population; SE=standard error; SD=Standard Deviation; NA=not applicable
[a] Baseline was the last PVRI assessment up to 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 covariates

Mean values at baseline were similar across treatment groups. At week 16, mean difference versus placebo were minimal for the low dose group (-47.9 dynes.s.cm-5.m). The medium and high dose groups showed greater effects (-359.6 and -575.3 dynes.s.cm-5.m, respectively) and showed a dose response.

Table 21. Change from Baseline in PVRI (Standardized Data) at Week 16 – ITT Population

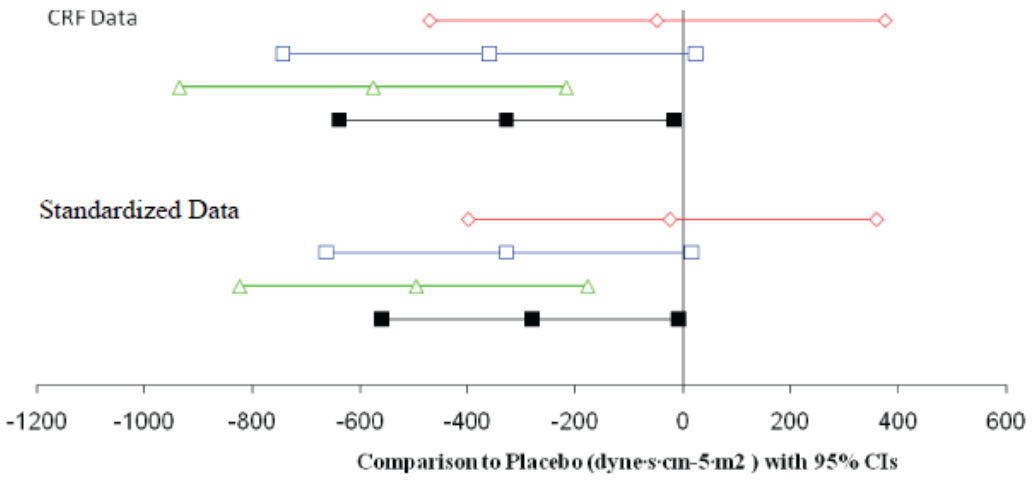
	Sildenafil				
Treatment Group	Low	Medium	High	Combined	Placebo
Number of subjects	37	51	68	156	52
Mean (SD) PVRI, dyne.s.cm^{-5}.m^2					
Baseline[a]	1741.8 (1022.7)	1510.1 (1142.6)	1630.0 (1302.4)	1622.0 (1182.5)	1222.5 (775.0)
Week 16	1725.8 (1134.6)	1246.4 (779.0)	1238.5 (974.8)	1358.3 (982.8)	1294.4 (815.0)
Change from baseline	-16.0 (767.0)	-263.7 (958.8)	-391.5 (1070.7)	-311.6 (974.8)	71.9 (511.4)
Mean difference versus placebo (SE)	-24.0 (191.8)	-327.6 (175.8)	-495.4 (159.8)	-279.7 (143.8)	NA
95% Confidence interval[b]	-399.5, 359.6	-663.2, 16.0	-823.0, -175.8	-559.3, -8.0	NA
P-value[b]	NA	NA	NA	0.047	NA

Source: Study A1481131_AddHaem Table 5.4.1 and A1481131 Hemodynamic Supplemental Report Table 11.7.27A (Module 5.3.5.1)
ITT=intention-to-treat population; SE=standard error; SD=Standard Deviation; NA=not applicable
[a] Baseline was the last PVRI assessment up to 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 covariates

Mean baseline PVRI values ranged from 1510.1 to 1630.0 dyne.s.cm^{-5}.m^2 across the sildenafil treatment groups; baseline value for the placebo group was 1222.5 dyne.s.cm^{-5}.m^2. At week 16, the placebo group showed an increase from baseline (71.9 dyne.s.cm^{-5}.m^2) while the 3 sildenafil groups showed decreases in a dose related manner (-16, -263.7, -391.5 dyne.s.cm-5.m2, respectively).

The figure below shows the results with the original data (CSR) as well as for the standardized data.

Figure 8. Treatment Comparisons for PVRI Changes from Baseline: Mean and 95% Confidence Intervals



Dose groups: Red – Low, Blue – Medium, Green – High, Black – Combined
Note: PVRI was analysed on the natural scale
Source: A1481131 CSR Table 5.4.2.1 and A1481131 AddHaem Table 5.4.2 (Module 5.3.5.1)

The results from the standardized data for PVRI were similar to those presented in the original CSR, with similar improvements over placebo for the 3 dose groups.

Log Transformed Analysis

The table below shows the results of the analyses of the standardized PVRI data, using a natural log transformation of the data.

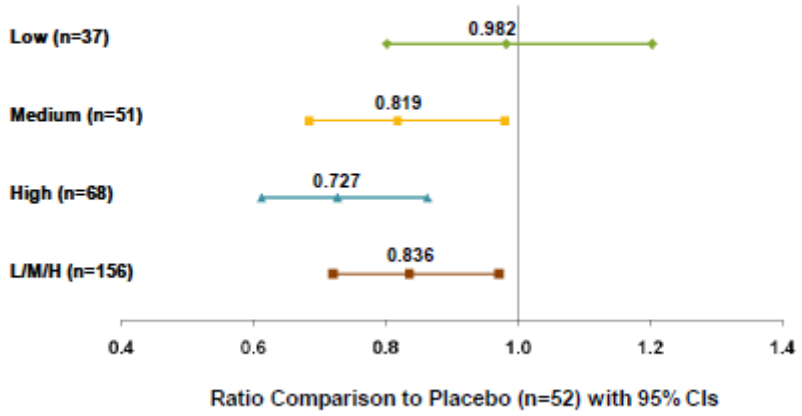
Table 22. Treatment Comparisons to Placebo for PVRI

Parameter	Treatment Group	Comparison to Placebo (95% CI)
PVRI (ratio to placebo)	Low Dose	0.98 (0.80, 1.20) (n=37)
	Medium Dose	0.82 (0.68, 0.98) (n=51)
	High Dose	0.73 (0.61, 0.86) (n=68)
	Combined Doses	0.84 (0.72,0.97) (n=156)

Source: Study A1481131 Hemodynamic Supplemental Report Table 11.7.27A (Module 5.3.5.1)
Placebo: PVRI n=52
Analyses were performed using ANCOVA with etiology, weight, ability to perform an exercise test and log transformed baseline PVRI as covariates. Baseline is the last PVRI assessment in the period from 21 days before treatment to the first day of treatment. Treatment comparisons are in the form of ratios as the analyses were conducted on log transformed data.

The results are shown in the figure below.

Figure 9. Proportional Comparisons in Study A1481131 for PVRI at Week 16



Source: Study A1481131 Hemodynamic Supplemental Report Table 11.7.27A (Module 5.3.5.1)

Pulmonary Artery pressure (mPAP)

The results are shown below.

Table T16. Change from Baseline in Mean Pulmonary Artery Pressure (mPAP) at Week 16 (LOCF) – ITT

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

Source: Tables 5.3.1 and 5.3.2.1
mPAP=mean pulmonary artery pressure; LOCF=last observation carried forward; ITT=intention-to-treat population; SD=standard deviation; SE=standard error; 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

Mean baseline mPAP values were similar across treatment. Decreases from baseline in mean mPAP were observed for the sildenafil medium and high groups and ranged from -3.9 to -7.4 mmHg. The placebo group showed a small (0.4 mmHg) decrease.

Cardiac Index

The table below shows the means at baseline, week 16 and change from baseline at week 16 for cardiac index by treatment group.

Table T22. Change from Baseline in Cardiac Index at Week 16 (LOCF) – ITT

	Sildenafil				
Dose	Low	Medium	High	Combined	Placebo
Number of subjects	37	49	68	154	52
Mean (SD) cardiac index, L/minute/m^2					
Baseline[a]	2.95 (1.16)	3.40 (1.85)	3.73 (2.09)	3.44 (1.84)	4.08 (2.31)
Week 16	3.15 (1.37)	3.42 (1.94)	3.97 (2.23)	3.60 (1.98)	3.48 (1.41)
Change from baseline	0.20 (1.17)	0.02 (1.44)	0.24 (2.19)	0.16 (1.76)	-0.60 (2.12)
Mean difference versus placebo (SE)[b]	0.71 (0.41)	0.61 (0.37)	0.89 (0.35)	0.74 (0.30)	NA
95% Confidence interval[b]	-0.10, 1.52	-0.12, 1.35	0.21, 1.58	0.14, 1.34	NA
P-value[b]	NA	NA	NA	0.015	NA

Source: Tables 5.8.1 and 5.8.2
VO_2=volume of consumed oxygen LOCF=last observation carried forward; ITT=intention-to-treat population; SD=standard deviation; SE=standard error; NA=not applicable
[a] Baseline was the last cardiac index 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

The sildenafil treatment groups had mean increases from baseline in cardiac index compared to placebo which had a mean decrease.

World Health Organization (WHO) Functional Class At Week 16 (LOCF) Class.
The table below shows the WHO functional class at baseline by treatment group.

Table T18. World Health Organization (WHO) Functional Class at Baseline

	Sildenafil				
	Low	Medium	High	Combined	Placebo
Class, n (%)[a]					
I	9 (22.5)	20[b] (37.0)	21 (27.6)	50 (29.4)	25 (41.7)
II	22[b] (55.0)	25 (46.3)	43 (56.6)	90 (52.9)	29 (48.3)
III	9 (22.5)	8 (14.8)	12 (15.8)	29 (17.1)	6 (10.0)
IV	0	1 (1.9)	0	1 (0.6)	0
Missing	2	1	1	4	0

Source: Table 5.11.1
WHO=world health organization
[a] The number of subjects with known WHO functional class has been used as the denominator for the calculation of percentages
[b] Subjects 11620 (sildenafil low dose) and 11221 (sildenafil medium dose) recorded baseline functional class on Day 2. The investigators confirmed that there was no significant change in functional class from pre-treatment and therefore these records were used as the baseline value.

Most subjects were in class II or III with only one rated as class IV. The placebo treatment group had the highest proportion of subjects with PAH Class I.

The table below shows the functional class at baseline and week 16 by treatment class.

Functional class worsened from Class I to Class II (7.1%, 3.6% and 1.3%, for sildenafil low, medium, high dose, respectively, compared to 6.7% in the placebo).

Functional class improved from Class II to Class I (4.8%, 3.6%, 10.4% for sildenafil low, medium, and high doses, respectively, and 3.3% for placebo.

Functional class improved from Class III to Class II (9.5%, 12.7% and 10.4%, sildenafil low, medium, and high doses, respectively, compared to 3.3% in the placebo treatment group).

One subject (1.3%) in the sildenafil high group functional class improved from Class III to Class I. The subject with Class IV at baseline, in the sildenafil medium group, improved to Class III.

The table below summarizes the changes in WHO class from baseline at week 16 by treatment group.

Table 5.11.2 Page 3 of 4
Sildenafil Protocol A1481131
WHO Pulmonary Hypertension Functional Class Summary of Changes by Visit - ITT Population

			Functional Class at Baseline									
			I		II		III		IV		Missing	
Visit	Treatment	Functional Class Post-Baseline	N	(%)	N	(%)	N	(%)	N	(%)	N	(%)
Week 16	Sildenafil Low Dose	I	6	(14.3)	2	(4.8)	0	(0.0)	0	(0.0)	0	(0.0)
		II	3	(7.1)	19	(45.2)	4	(9.5)	0	(0.0)	1	(2.4)
		III	0	(0.0)	0	(0.0)	5	(11.9)	0	(0.0)	0	(0.0)
		IV	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		Missing	0	(0.0)	1	(2.4)	0	(0.0)	0	(0.0)	1	(2.4)
	Sildenafil Medium Dose	I	18	(32.7)	2	(3.6)	0	(0.0)	0	(0.0)	0	(0.0)
		II	2	(3.6)	23	(41.8)	7	(12.7)	0	(0.0)	1	(1.8)
		III	0	(0.0)	0	(0.0)	1	(1.8)	1	(1.8)	0	(0.0)
		IV	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		Missing	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Sildenafil High Dose	I	20	(26.0)	8	(10.4)	1	(1.3)	0	(0.0)	1	(1.3)
		II	1	(1.3)	34	(44.2)	8	(10.4)	0	(0.0)	0	(0.0)
		III	0	(0.0)	0	(0.0)	2	(2.6)	0	(0.0)	0	(0.0)
		IV	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		Missing	0	(0.0)	1	(1.3)	1	(1.3)	0	(0.0)	0	(0.0)
	Sildenafil Combined Doses	I	44	(25.3)	12	(6.9)	1	(0.6)	0	(0.0)	1	(0.6)
		II	6	(3.4)	76	(43.7)	19	(10.9)	0	(0.0)	2	(1.1)
		III	0	(0.0)	0	(0.0)	8	(4.6)	1	(0.6)	0	(0.0)
		IV	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		Missing	0	(0.0)	2	(1.1)	1	(0.6)	0	(0.0)	1	(0.6)
	Placebo	I	20	(33.3)	2	(3.3)	0	(0.0)	0	(0.0)	0	(0.0)
		II	4	(6.7)	26	(43.3)	2	(3.3)	0	(0.0)	0	(0.0)
		III	0	(0.0)	0	(0.0)	4	(6.7)	0	(0.0)	0	(0.0)
		IV	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
		Missing	1	(1.7)	1	(1.7)	0	(0.0)	0	(0.0)	0	(0.0)

Baseline is the last assessment from 4 days before, to the first day of study treatment.

The table below shows the number and percent of subjects who had no change or improved in their functional class. Subjects with PAH Class I at baseline are not included.

Table T19. Improvements from Baseline in World Health Organization (WHO) Functional Class for Subjects with PAH Class II to IV at Baseline

	Sildenafil				
	Low	Medium	High	Combined	Placebo
Number of subjects	31	34	55	120	35
No change, n (%)	25 (80.6)	24 (70.6)	38 (69.1)	84 (70.0)	31 (88.6)
Improved by 1 class, n (%)	6 (19.4)	10 (29.4)	16 (29.1)	32 (26.7)	4 (11.4)
Improved by 2 classes, n (%)	0	0	1 (1.8)	1 (0.8)	0

Source: Table 5.11.2

According to these data, the sildenafil groups were more likely to show improvement in their functional class compared to the placebo group.

Worsening in functional class

There were 10 subjects who had a worse WHO functional class at endpoint compared to baseline. All had started in class I and had slipped to class II, either at week 4, 8, or 16.

Number of subjects

	sildenafil			placebo
	Low	Medium	high	
Number of subjects randomized	42	55	77	60
Number with data	31	34	55	35
Worse by 1 class	3	2	1	4

The table below shows the 10 individual subjects.

Table 1 Subjects Whose WHO Functional Class Worsened during A1481131

Subject	Baseline	Week 4	Week 8	Week 16	Last known (Study Day) Status[1]
Placebo[2]					
10438	I	I	I	II	I (1752)
10441	I	I	I	II	I (1708)
10466	I	I	II	II	I (1224)
10856	I	I	I	II	I (785) Died (815)^
Sildenafil Low Dose					
10810	I	I	II	II	II (449) Discontinued
10825	I	II	II	II	II (2214)
10842	I	I	I	II	I (1477)
Sildenafil Medium Dose					
10405	I	II	II	II	I (2420)
10410	I	I	II	II	II (113) Did not enter A1481156
Sildenafil High Dose					
10853	I	I	I	II	I (1456)

Source: Section 13 Table 2.3 A1481131 CSR, Table 4.2 and Section 13 Table 5, A1481156 Supplemental Safety Report, Module 5.3.5.3
[1]Date of data cut-off: April 2011 (June 2011 for deaths), ie same as NDA submission
[2] Subjects 10438, 10441, 10466 and 10856 were randomized to high, medium, high and high dose sildenafil respectively in Study A1481156.
^probable penicillin reaction resulting in death.

Pulmonary Vascular Resistance (PVR)

The table below shows the mean PVR at baseline and week 16, as well as change from baseline at week 16.

Table 5.7.1 Page 1 of 1
Sildenafil Protocol A1481131
Pulmonary Vascular Resistance (Wood units) by Visit - ITT Population

			Week 16			Week 16 LOCF		
Treatment	Statistic	Baseline All Subjects	Baseline	Value	Change from Baseline	Baseline	Value	Change from Baseline
Sildenafil Low Dose	N	40	36	36	36	36	36	36
	Mean	20.4	20.3	20.2	-0.1	20.3	20.2	-0.1
	95% CI of Mean	(16.5,24.4)	(16.1,24.5)	(15.4,25.0)	(-3.6,3.4)	(16.1,24.5)	(15.4,25.0)	(-3.6,3.4)
	Std. Dev	12.3	12.5	14.3	10.4	12.5	14.3	10.4
	Median	19	19	14	-1	19	14	-1
	Min, Max	4,53	4,53	4,64	-26,32	4,53	4,64	-26,32
Sildenafil Medium Dose	N	50	49	49	49	49	49	49
	Mean	17.6	17.9	14.5	-3.3	17.9	14.5	-3.3
	95% CI of Mean	(14.1,21.2)	(14.3,21.4)	(12.2,16.8)	(-6.4,-0.3)	(14.3,21.4)	(12.2,16.8)	(-6.4,-0.3)
	Std. Dev	12.4	12.4	7.9	10.5	12.4	7.9	10.5
	Median	16	16	14	-2	16	14	-2
	Min, Max	4,80	4,80	5,36	-54,15	4,80	5,36	-54,15
Sildenafil High Dose	N	72	67	67	67	67	67	67
	Mean	21.6	22.3	17.1	-5.2	22.3	17.1	-5.2
	95% CI of Mean	(17.6,25.6)	(18.0,26.6)	(13.9,20.3)	(-9.0,-1.4)	(18.0,26.6)	(13.9,20.3)	(-9.0,-1.4)
	Std. Dev	17.2	17.5	13.3	15.7	17.5	13.3	15.7
	Median	17	17	12	-4	17	12	-4
	Min, Max	2,78	3,78	1,62	-65,48	3,78	1,62	-65,48
Sildenafil Combined Doses	N	162	152	152	152	152	152	152
	Mean	20.1	20.4	17.0	-3.4	20.4	17.0	-3.4
	95% CI of Mean	(17.8,22.4)	(18.0,22.8)	(15.0,19.0)	(-5.5,-1.3)	(18.0,22.8)	(15.0,19.0)	(-5.5,-1.3)
	Std. Dev	14.7	14.9	12.2	13.1	14.9	12.2	13.1
	Median	17	17	13	-2	17	13	-2
	Min, Max	2,80	3,80	1,64	-65,48	3,80	1,64	-65,48
Placebo	N	55	50	50	50	50	50	50
	Mean	16.1	16.9	16.9	0.1	16.9	16.9	0.1
	95% CI of Mean	(12.2,20.0)	(12.6,21.1)	(13.9,20.0)	(-3.3,3.4)	(12.6,21.1)	(13.9,20.0)	(-3.3,3.4)
	Std. Dev	14.5	15.0	10.7	11.8	15.0	10.7	11.8
	Median	12	13	13	0	13	13	0
	Min, Max	3,93	3,93	3,45	-63,23	3,93	3,45	-63,23

Baseline is the last PVR assessment in the period from 21 days before treatment to the first day of treatment
PFIZER CONFIDENTIAL Source Data: Section 11, Item 11, Table 3.3 Date of Reporting Dataset Creation: 02AUG2008 Date of Table Generation: 04AUG2008 (09:28)

The sildenafil groups showed a decrease in PVR compared to an increase for the placebo group.

Right Atrial Pressure (RAP)
Mean baseline RAP values were similar across treatment groups.

Table 5.9.1 Page 1 of 1
Sildenafil Protocol A1481131
Right Atrial Pressure (mmHg) by Visit - ITT Population

Treatment	Statistic	Baseline All Subjects	Week 16 Baseline	Week 16 Value	Week 16 Change from Baseline	Week 16 LOCF Baseline	Week 16 LOCF Value	Week 16 LOCF Change from Baseline
Sildenafil Low Dose	N	42	39	39	39	39	39	39
	Mean	7.93	7.69	7.92	0.23	7.69	7.92	0.23
	95% CI of Mean	(6.56,9.30)	(6.31,9.07)	(7.00,8.85)	(-1.05,1.51)	(6.31,9.07)	(7.00,8.85)	(-1.05,1.51)
	Std. Dev	4.39	4.26	2.85	3.95	4.26	2.85	3.95
	Median	7.5	7.0	8.0	1.0	7.0	8.0	1.0
	Min, Max	2.0,22.0	2.0,22.0	3.0,14.0	-12.0,7.0	2.0,22.0	3.0,14.0	-12.0,7.0
Sildenafil Medium Dose	N	55	55	55	55	55	55	55
	Mean	7.98	7.98	8.05	0.07	7.98	8.05	0.07
	95% CI of Mean	(6.61,9.36)	(6.61,9.36)	(6.86,9.25)	(-1.04,1.18)	(6.61,9.36)	(6.86,9.25)	(-1.04,1.18)
	Std. Dev	5.09	5.09	4.42	4.10	5.09	4.42	4.10
	Median	7.0	7.0	7.0	0.0	7.0	7.0	0.0
	Min, Max	1.0,32.0	1.0,32.0	1.0,25.0	-15.0,11.0	1.0,32.0	1.0,25.0	-15.0,11.0
Sildenafil High Dose	N	75	71	71	71	71	71	71
	Mean	8.61	8.70	7.75	-0.96	8.70	7.75	-0.96
	95% CI of Mean	(7.51,9.72)	(7.54,9.87)	(6.77,8.73)	(-1.91,-0.01)	(7.54,9.87)	(6.77,8.73)	(-1.91,-0.01)
	Std. Dev	4.81	4.91	4.14	4.01	4.91	4.14	4.01
	Median	7.0	7.0	7.0	0.0	7.0	7.0	0.0
	Min, Max	1.0,25.0	1.0,25.0	1.0,25.0	-13.0,7.0	1.0,25.0	1.0,25.0	-13.0,7.0
Sildenafil Combined Doses	N	172	165	165	165	165	165	165
	Mean	8.24	8.22	7.89	-0.33	8.22	7.89	-0.33
	95% CI of Mean	(7.52,8.96)	(7.48,8.96)	(7.28,8.50)	(-0.95,0.29)	(7.48,8.96)	(7.28,8.50)	(-0.95,0.29)
	Std. Dev	4.79	4.82	3.95	4.04	4.82	3.95	4.04
	Median	7.0	7.0	7.0	0.0	7.0	7.0	0.0
	Min, Max	1.0,32.0	1.0,32.0	1.0,25.0	-15.0,11.0	1.0,32.0	1.0,25.0	-15.0,11.0
Placebo	N	59	56	56	56	56	56	56
	Mean	7.98	7.88	8.11	0.23	7.88	8.11	0.23
	95% CI of Mean	(6.77,9.20)	(6.61,9.14)	(7.14,9.07)	(-0.97,1.43)	(6.61,9.14)	(7.14,9.07)	(-0.97,1.43)
	Std. Dev	4.66	4.71	3.61	4.48	4.71	3.61	4.48
	Median	8.0	7.5	8.0	0.0	7.5	8.0	0.0
	Min, Max	1.0,28.0	1.0,28.0	3.0,20.0	-15.0,16.0	1.0,28.0	3.0,20.0	-15.0,16.0

Baseline is the last right atrial pressure assessment in the period from 21 days before treatment to the first day of treatment
PFIZER CONFIDENTIAL Source Data: Section 11, Item 11, Table 3.3 Date of Reporting Dataset Creation: 02AUG2008 Date of Table Generation: 04AUG2008 (10:21)

The table below shows small decreases from baseline in mean RAP in the sildenafil groups compared to placebo.

Table 5.9.2 Page 1 of 1
Sildenafil Protocol A1481131
Treatment Comparisons of Change from Baseline in Right Atrial Pressure (mmHg) at Week 16 (LOCF) - ITT Population

	Treatment difference (Sildenafil - Placebo)			
Statistic	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	Sildenafil Combined Doses
Mean Difference (SE)	-0.17(0.88)	-0.19(0.78)	-1.14(0.75)	-0.50(0.64)
N (Sildenafil)	39	55	71	165
N (Placebo)				56
p-value				0.440
95% Confidence Interval	(-1.91,1.57)	(-1.73,1.36)	(-2.61,0.33)	(-1.77,0.77)

Baseline is the last right atrial pressure assessment in the period from 21 days before treatment to the first day of treatment
Significance tests of peak VO2 are performed using ANCOVA with etiology, weight, ability to perform an exercise test and baseline right atrial pressure as the c
variates.
PFIZER CONFIDENTIAL Source Data: Section 11, Item 11, Table 2.7 Date of Reporting Dataset Creation: 02AUG2008 Date of Table Generation: 08AUG2008 (11:09)

Respiratory Exchange Ratio (RER)

Mean baseline RER values were similar across treatment groups. Changes from baseline in mean RER compared to placebo are shown below.

Table 5.5.2 Page 1 of 1
Sildenafil Protocol A1481131
Treatment Comparisons of Percent Change from Baseline in Respiratory Exchange Ratio at Week 16 (LOCF) - ITT Population*

	Treatment difference (Sildenafil - Placebo)			
Statistic	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose	Sildenafil Combined Doses
Mean Difference (SE)	2.62(2.99)	-1.29(2.92)	0.52(2.90)	0.61(2.36)
N (Sildenafil)	24	26	27	77
N (Placebo)				29
p-value				0.795
95% Confidence Interval	(-3.31,8.54)	(-7.09,4.50)	(-5.24,6.28)	(-4.07,5.30)

* ITT Population for this table refers only to the subset of the ITT population who are developmentally able.
Baseline is the average of all assessments on or before the first day of study treatment.
Significance tests are performed using ANCOVA with etiology and weight as the covariates.
PFIZER CONFIDENTIAL Source Data: Section 11, Item 11, Table 2.3 Date of Reporting Dataset Creation: 02AUG2008 Date of Table Generation: 12AUG2008 (05:28)

Time to Peak Volume of Oxygen Consumed (VO2)
The table below shows mean time to peak VO2 values at baseline, week 16 and change from baseline at week 16 by treatment group.

Table T21. Percentage Change from Baseline in Time to Peak Volume of Oxygen Consumed (VO_2) at Week 16 (LOCF) – ITT

	Sildenafil				
Dose	Low	Medium	High	Combined	Placebo
Number of subjects[a]	24	26	27	77	29
Mean (SD) time to peak VO_2, seconds					
Baseline[b]	414.54 (123.13)	452.27 (141.88)	433.81 (108.69)	434.04 (124.44)	466.43 (139.14)
Week 16	479. 38 (183.02)	516.69 (185.73)	465.15 (104.51)	486.99 (160.34)	475.28 (166.82)
Change from baseline	64.83 (103.69)	64.42 (102.70)	31.33 (107.04)	52.95 (104.40)	8.84 (96.09)
Percentage change from baseline	15.21 (26.28)	15.97 (22.92)	11.16 (28.62)	14.04 (25.82)	4.56 (34.85)
Mean difference versus placebo (SE)[c]	10.34 (7.84)	11.43 (7.67)	5.96 (7.62)	9.24 (6.20)	NA
95% Confidence interval[c]	-5.21, 25.90	-3.78, 26.64	-9.16, 21.08	-3.05, 21.54	NA
P-value[c]	NA	NA	NA	0.139	NA

Source: Tables 5.6.1.1a and 5.6.2a
VO_2=volume of oxygen consumed; ITT=intention-to-treat population; SD=standard deviation; 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 to the first day of study treatment
[c] Analyses were performed using analysis of covariance with etiology and weight as the covariates

The sildenfil groups had a larger increase from baseline at week 16 in the time to peak VO_2 compared to the placebo group.

Quality of Life (QoL)
Mean baseline CHQ-PF28 physical scale and psychosocial scale scores were similar across treatment groups. Changes were similar for sildenafil and placebo groups.

Subject (Parent) and Physician Global Assessments
At Week 16 (LOCF), most subjects/parents reported mild or better improvement in disease severity from baseline in all treatment. At Week 16 (LOCF), most physicians reported mild or better improvement in disease severity from baseline in all treatment.

Background Therapy
Approximately half the subjects in any treatment group were not receiving any background therapy (including anticoagulants, oxygen, diuretics, calcium channel blockers or digoxin) at baseline. Very few subjects had additions or discontinuations of medications to their background therapy during the trial.

Clinical Worsening
There were 3 subjects who met the criteria for clinical worsening (lung transplantation, hospitalization because of PAH, initiation of prostacyclin or bosentan therapy): 1 subject in the sildenafil low treatment group (hospitalization/11604) and 2 subjects in the sildenafil high treatment group (hospitalization/10831 and initiation of bosentan/10420). The latter subject started treatment with bosentan after discontinuation from the study one month before because of a reported allergic reaction (stridor).

Subpopulations

Hemodynamic parameters
Age
The table below shows the baseline PVRi, mPAP, cardiac index, and functional class for two age groups (< 7 years and ≥ 7 years).

Table S8. Baseline Mean (SD, n) PVRI, mPAP and Cardiac Index Values and Functional Class by Age

Parameter	<7 years old N=63	≥7 years old N=171
PVRI (Wood units•m^2)	12.3 (8.0, 58)	20.7 (14.7, 164)
mPAP (mmHg)	54.2 (21.0, 61)	64.7 (21.5, 170)
Cardiac Index (L/min/m^2)	4.2 (1.8, 58)	3.2 (1.6, 168)
Functional Class I	27 (43%)	48 (29%)
Functional Class II	30 (48%)	90 (54%)
Functional Class III/IV	6 (10%)	30 (18%)

Source: Tables 29SL, 11.7.235A and 11.7.236A
Note: percentages do not add to 100% due to rounding

The younger children had lower PVRI, mPAP, and higher cardiac index as well as more likely to have functional class I at baseline than their older colleagues.

Overall, with the <7 year-old subjects there was an estimated 23% and 26% reduction in PVRI with the sildenafil medium and high dose groups, respectively. There were corresponding estimated increases in cardiac index of 6% and 15% for the medium and high dose groups respectively. With the ≥7 year-old subjects there was an estimated 17% and 28% reduction in PVRI and a corresponding 4% and 15% increase in cardiac index. For mPAP the <7 year-old subjects showed a smaller improvement over placebo for the medium and high dose groups compared to the ≥7 year-old subjects.

Weight

The table below shows the baseline functional class and hemodynamic characteristics for the 3 weight groups .

Table S10. Baseline Mean (SD, n) PVRI, mPAP and Cardiac Index Values and Functional Class by Weight

Parameter	8-20kg N=68	>20-45kg N=125	>45kg N=41
PVRI (Wood units•m^2)	13.3 (8.2, 64)	20.5 (15.4, 119)	21.1 (13.9, 39)
mPAP (mmHg)	56.8 (21.0, 66)	65.2 (22.3, 124)	60.2 (20.3, 41)
Cardiac Index (L/min/m^2)	4.1 (1.9, 64)	3.3 (1.5, 123)	3.1 (1.4, 39)
Functional Class I	28 (42%)	37 (30%)	10 (25%)
Functional Class II	33 (49%)	63 (51%)	24 (60%)
Functional Class III/IV	6 (9%)	24 (19%)	6 (15%)

Source: Tables 29SL, 11.7.238A, 11.7.239A and 11.7.240A

Baseline characteristics split by treatment group are presented in Tables 5SL, 6SL and 7SL for the 3 weight groups.

There was a higher proportion of subjects in the 8-20kg weight group who had functional class I at baseline and mean PVRI and mPAP baseline values were lower for the 8-20kg weight group than the 2 heavier weight groups and mean cardiac index values were correspondingly higher.

The table below shows the treatment comparisons to placebo for the selected hemodynamic variables.

Table S11. Treatment Comparisons to Placebo for PVRI, Cardiac Index and mPAP by Weight

Parameter	Treatment Group	Comparison to Placebo (95% CI) 8-20kg	>20-45kg	>45kg
PVRI (ratio to placebo)	Low Dose	-	0.99 (0.79, 1.25) (n=28)	0.86 (0.55, 1.35) (n=9)
	Medium Dose	0.81 (0.55, 1.19) (n=13)	0.84 (0.67, 1.06) (n=30)	0.79 (0.50, 1.24) (n=8)
	High Dose	0.81 (0.59, 1.11) (n=30)	0.81 (0.64, 1.03) (n=27)	0.42 (0.27, 0.64) (n=11)
Cardiac Index (ratio to placebo)	Low Dose	-	1.16 (0.97, 1.38) (n=29)	0.91 (0.71, 1.16) (n=8)
	Medium Dose	1.17 (0.94, 1.46) (n=13)	1.02 (0.85, 1.21) (n=30)	0.96 (0.75, 1.23) (n=8)
	High Dose	1.11 (0.92, 1.33) (n=30)	1.19 (1.00, 1.42) (n=28)	1.09 (0.87, 1.38) (n=11)
mPAP (difference in mmHg from placebo)	Low Dose	-	0.4 (-7.2, 8.0) (n=29)	-4.8 (-16.7, 7.0) (n=10)
	Medium Dose	3.3 (-6.8,13.5) (n=15)	-4.7 (-12.1, 2.8) (n=31)	-8.9 (-21.1, 3.3) (n=9)
	High Dose	2.8 (-5.7, 11.4) (n=32)	-11.6 (-19.3, -4.0) (n=28)	-16.5 (-28.0, -4.9) (n=11)

Note: no subjects were randomized to the low dose treatment group in the 8-20 kg weight group.
Source: Tables 11.7.2A, 11.7.19A and 11.7.29A
Placebo: PVRI 8-20kg n=15; >20-45kg n=28; >45kg n=9
Cardiac Index 8-20kg n=16; >20-45kg n=30; >45kg n=9
mPAP 8-20kg n=16; >20-45kg n=30; >45kg n=10

Etiology

The table below shows the baseline functional class and hemodynamic characteristics for 3 etiology groups.

Table S14. Baseline Mean (SD, n) PVRI, mPAP and Cardiac Index Values and Functional Class by Etiology

Parameter	Primary PAH N=78	Secondary PAH Surgical Repair N=71	Secondary PAH Unrepaired CHD N=85
PVRI (Wood units•m^2)	20.3 (14.7, 75)	16.7 (13.3, 67)	18.4 (13.2, 80)
mPAP (mmHg)	59.7 (23.1, 77)	55.3 (23.9, 70)	69.4 (16.0, 84)
Cardiac Index (L/min/m^2)	3.4 (1.5, 77)	3.5 (1.8, 67)	3.5 (1.7, 82)
Functional Class I	20 (26%)	27 (38%)	28 (34%)
Functional Class II	38 (49%)	37 (52%)	45 (54%)
Functional Class III/IV	19 (25%)	7 (10%)	10 (12%)

Note: surgical repair group also includes the 3 subjects with D-transposition of the great arteries
Source: Tables 29SL,11.7.72A, 9.1.464O and 9.1.465O

Baseline mPAP was higher with the unrepaired CHD subjects. This could be the result of
the subjects having a systemic-to-pulmonary shunt.

The table below shows the results of the hemodynamic analyses by etiology.

Table S15. Treatment Comparisons to Placebo for PVRI, Cardiac Index and mPAP by Etiology

Parameter	Treatment Group	Comparison to Placebo (95% CI)		
		Primary PAH	Secondary PAH Surgical Repair	Secondary PAH Unrepaired CHD
PVRI (ratio to placebo)	Low Dose	0.95 (0.67 1.36) (n=11)	1.12 (0.73, 1.72) (n=12)	0.81 (0.61, 1.07) (n=14)
	Medium Dose	0.75 (0.55, 1.02) (n=18)	0.95 (0.64, 1.40) (n=15)	0.82 (0.64, 1.07) (n=18)
	High Dose	0.69 (0.52, 0.92) (n=24)	0.59 (0.41, 0.84) (n=22)	0.90 (0.70, 1.16) (n=22)
Cardiac Index (ratio to placebo)	Low Dose	1.10 (0.90, 1.35) (n=12)	1.12 (0.83, 1.51) (n=11)	1.12 (0.89, 1.41) (n=14)
	Medium Dose	1.26 (1.05, 1.53) (n=18)	0.98 (0.75, 1.28) (n=15)	0.95 (0.77, 1.17) (n=18)
	High Dose	1.37 (1.14, 1.65) (n=24)	1.04 (0.81, 1.33) (n=22)	1.11 (0.91, 1.36) (n=23)
mPAP (difference in mmHg from placebo)	Low Dose	0.7 (-9.9, 11.3) (n=12)	7.5 (-6.0, 21.0) (n=13)	-3.6 (-11.9, 4.6) (n=14)
	Medium Dose	-1.2 (-10.3, 8.0) (n=19)	-2.3 (-14.9, 10.2) (n=16)	-5.2 (-12.6, 2.2) (n=20)
	High Dose	-5.1 (-13.8, 3.5) (n=25)	-14.1 (-25.7, -2.4) (n=23)	-2.9 (-10.0, 4.3) (n=23)

Source: Tables 5.4, 11.7.21A and 11.7.31A.
Placebo: PVRI Primary PAH n=18; Surgical Repair n=13; Unrepaired CHD n=21
Cardiac Index Primary PAH n=19; Surgical Repair n=13; Unrepaired CHD n=23
mPAP Primary PAH n=20; Surgical Repair n=13; Unrepaired CHD n=23

Functional Class
The table below shows the baseline hemodynamic characteristics for the 3 functional class groups.

Table S16. Baseline Mean (SD, n) PVRI, mPAP and Cardiac Index Values by Functional Class

Parameter	I N=75	II N=120	III/IV N=36
PVRI (Wood units•m^2)	13.3 (8.1, 72)	19.5 (14.8, 114)	26.8 (15.8, 34)
mPAP (mmHg)	54.6 (21.4, 74)	63.1 (21.4, 118)	73.0 (19.4, 36)
Cardiac Index (L/min/m^2)	3.6 (1.5, 72)	3.4 (1.6, 117)	3.3 (2.0, 34)

Source: Tables 16SL, 17SL, 18SL and 29SL

As expected, baseline hemodynamics are worse with increasing functional class.

The table below shows the results of the hemodynamic analyses by functional class.

Table S17. Treatment Comparisons to Placebo for PVRI, Cardiac Index and mPAP by Functional Class

Parameter	Treatment Group	Comparison to Placebo (95% CI) I	II	III/IV
PVRI (ratio to placebo)	Low Dose	1.14 (0.78,1.67) (n=9)	0.89 (0.66, 1.21) (n=19)	1.03 (0.55, 1.92) (n=9)
	Medium Dose	0.82 (0.61, 1.10) (n=19)	0.83 (0.62, 1.09) (n=23)	0.93 (0.50, 1.74) (n=8)
	High Dose	0.67 (0.50, 0.91) (n=19)	0.72 (0.56, 0.93) (n=38)	0.74 (0.39, 1.40) (n=10)
Cardiac Index (ratio to placebo)	Low Dose	0.94 (0.70, 1.25) (n=9)	1.26 (1.07, 1.49) (n=19)	1.13 (0.75, 1.72) (n=8)
	Medium Dose	1.04 (0.84, 1.30) (n=19)	1.08 (0.93, 1.26) (n=23)	1.07 (0.71, 1.62) (n=8)
	High Dose	1.28 (1.03, 1.60) (n=19)	1.11 (0.97, 1.28) (n=39)	1.22 (0.81, 1.84) (n=10)
mPAP (difference in mmHg from placebo)	Low Dose	0.96 (-10.72, 12.63) (n=9)	0.35 (-8.65, 9.34) (n=20)	7.85 (-3.41, 19.12) (n=9)
	Medium Dose	0.05 (-8.76,8.86) (n=20)	-5.74 (-14.03, 2.55) (n=25)	-0.59 (-11.82, 10.63) (n=9)
	High Dose	-1.44 (-10.18, 7.29) (n=21)	-11.21 (-18.77, -3.65) (n=39)	-9.58 (-20.76, 1.60) (n=10)

Source: Tables 11.7.56A, 11.7.57A and 11.7.58A
Placebo: PVRI FC I n=21; FC II n=26; FC III/IV n=5
Cardiac Index FC I n=22; FC II n=27; FC III/IV n=6
mPAP FC I n=22; FC II n=28; FC III/IV n=6

Reductions in PVRI compared with placebo were observed in the medium and high doses (but not the low dose) groups across all baseline functional classes. There were no obvious effects with the other parameters.

SAFETY

Serious safety

No randomized subject was reported to have died during the trial.

There were 2 subjects who died during screening (one during the preparation for catheterization and one while being catheterized) and there other subjects who reported serious adverse events that were associated with catheterization[11].

Discontinuations for safety reasons

[11] Subjects 8072, 8191, 8034 (died), 8174 (died)

There were 2 subjects who were permanently discontinued from study medication because of adverse events. Details regarding these 2 subjects are shown in the tables below.

Table 4.2.1 Page 1 of 2
Sildenafil Protocol A1481131
Discontinuations Due to Adverse Events

Treatment Group: Sildenafil Low Dose

Body System	meddra Preferred Term/ INVESTIGATOR ENTRY	Trt Phase	Treatment At Onset	Adverse Event Start Day++/ Stop Day++	SEVERITY/ Outcome	ACTION/ Causality	SAE
11201 (F/ 7(YEARS)/ OTHER (MIDDLE EASTERN)/ 26.5(kg))							
INVESTIGATIONS	Weight decreased*/ WEIGHT LOSS	Active	Sildenafil Low Dose	37/ 121	MILD/ Unknown	STUDY DRUG ACTION: (PERMANENTLY DISCONTINUED) SUBJECT ACTION: (D/C STUDY)/ Study drug	NO

Age and weight are at screening
* Treatment-emergent
++ Day relative to first day of each treatment period. First day of each treatment period = day 1
[] Values in brackets are imputed from incomplete dates and times.
SAE = Serious Adverse Event (according to Investigators assessment).
Treatment (Trt) column gives study treatment at time of adverse event.
PFIZER CONFIDENTIAL Source Data: Section 13, Table 3 Date of Reporting Dataset Creation: 02AUG2008 Date of Table Generation: 02AUG2008 (09:04)

Table 4.2.1 Page 2 of 2
Sildenafil Protocol A1481131
Discontinuations Due to Adverse Events

Treatment Group: Sildenafil High Dose

Body System	meddra Preferred Term/ INVESTIGATOR ENTRY	Trt Phase	Treatment At Onset	Adverse Event Start Day++/ Stop Day++	SEVERITY/ Outcome	ACTION/ Causality	SAE
10420 (M/ 20(MONTHS)/ OTHER (HISPANIC)/ 10(kg))							
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Stridor*/ STRIDOR	Active	Sildenafil High Dose	10/ 10	SEVERE/ Resolved (09FEB2005)	STUDY DRUG ACTION: (PERMANENTLY DISCONTINUED) SUBJECT ACTION: (TREATMENT GIVEN,D/C STUDY)/ Study drug	YES

Age and weight are at screening
* Treatment-emergent
++ Day relative to first day of each treatment period. First day of each treatment period = day 1
[] Values in brackets are imputed from incomplete dates and times.
SAE = Serious Adverse Event (according to Investigators assessment).
Treatment (Trt) column gives study treatment at time of adverse event.
PFIZER CONFIDENTIAL Source Data: Section 13, Table 3 Date of Reporting Dataset Creation: 02AUG2008 Date of Table Generation: 02AUG2008 (09:04)

Table T27. Discontinuations Due to Adverse Events

Subject	Age/Sex	Sildenafil Dose	Adverse Event	Severity	Treatment Related	Outcome
Sildenafil low dose						
11201	7 years/F	10 mg	Weight loss (from 26.5 kg to 25.0 kg after 70 days of treatment)	Mild	Yes	Unknown
Sildenafil high dose						
10420[a]	20 months/M	10 mg	Stridor[b]	Severe	Yes	Resolved

Source: Table 4.2.1 and Appendix B, Table 3
M=male; F=female
[a] Subject was receiving sildenafil 10 mg during the up-titration period
[b] Adverse event was a serious adverse event

Subject 11201 (US) reported vomiting and weight loss. She was discontinued on day 114.

Subject 10420 (US) reporting stridor was rechallenged before he was permanently discontinued from sildenafil. On study day 2, the subject experienced stridor, which lasted for 2 to 3 hours. The study treatment was stopped. On study day 10, sildenafil treatment was restarted, with 1/100 of the required dose without any event. Eight hours later, 1/10 of the dose was administered. The subject developed stridor within 15 minutes, which lasted for 3 to 4 hours and required treatment. Sildenafil treatment was permanently discontinued.

Serious adverse events
There were eleven subjects reporting serious events. These are shown below.

Table T29. Treatment-Emergent Serious Adverse Events

Subject	Age/ Sex	Sildenafil Dose	Adverse Event	Severity	Treatment Related	Outcome
Sildenafil Low Dose						
11604	12 years/F	10 mg	Dyspnea	Severe	No	Resolved
		10 mg	Cyanosis	Severe	No	Resolved
		10 mg	Syncope	Severe	No	Resolved
		10 mg	Haematochezia	Mild	No	Resolved
Sildenafil Medium Dose						
10445	2 years/F	10 mg	Pneumonia	Severe	No	Resolved
		10 mg	Upper respiratory tract infection	Severe	No	Resolved
Sildenafil High Dose						
10415	6 years/M	20 mg	Gastroenteritis	Mild	No	Resolved
		20 mg	Pyrexia	Mild	No	Resolved
10417	22 months/M	20 mg	Upper respiratory tract infection	Moderate	No	Resolved
10420	20 months/M	10 mg	Stridor [a]	Severe	Yes	Resolved
10427	3 years/M	20 mg	Bronchospasm	Moderate	No	Resolved
		20 mg	Bradycardia	Moderate	No	Resolved
10446	5 years/M	20 mg	Pneumonia	Moderate	No	Resolved
10831	13 years/M	40 mg	Pneumonia	Severe	No	Resolved
		40 mg	Cardiac failure congestive	Severe	No	Resolved
12001[b]	14 years/M	80 mg	Ventricular arrhythmia	Mild	Yes	Resolved
Placebo						
10426	31 months/F		Diarrhea	Moderate	No	Resolved
11247	5 years/F		Pneumonia	Moderate	No	Resolved

Source: Table 6.4 and Appendix B, Table 3
[a] Subject was discontinued for the adverse event; the treatment code was unblinded.
[b] The sponsor's internal Safety Surveillance and Reporting Group requested unblinded treatment details for Subject 12001 on 25 August 04. The investigator and the study team were not provided with the unblinded treatment data.

More subjects in the sildenafil high dose group reported serious events compared to the other groups. All events were reported to have resolved with one discontinuation.

There was one report of syncope, 2 reports of breathing difficulties, 1 report of stridor (see study discontinuations), 4 reports of pneumonia (one with congestive heart failure), bronchospasm and bradycardia, 1 ventricular arrhythmia (reported as a change from class Lown 4 to Lown 4B, with salvos of ventricular contractions. The subject remained asymptomatic and in the study).

Subject 10427 was hospitalized for right heart catheterization as part of Week 16 assessments in accordance with the study protocol. For the right heart catheterization, the subject was sedated with ketamine and midazolam, after which the subject desaturated with 60% oxygen level. The subject developed bronchospasm, respiratory distress and bradycardia, and was treated with oxygen, hydrocortisone injection, Asthalin® (salbutamol) nebulization, and bag and mask ventilation. The subject

recovered within 20 minutes and oxygen saturation reached 100%. The right heart catheterization was postponed. The study treatment continued unchanged.

Dose Reductions or Temporary Discontinuations Due to Adverse Events
The following 11 subjects had either dose reductions or were temporarily discontinued from study drug.

Table T28. Temporary Discontinuations (or Dose Reductions) Due to Adverse Events

Subject	Age/Sex	Sildenafil Dose	Adverse Event	Severity	Treatment Related	Outcome
Sildenafil Low Dose						
11631	10 years/F	10 mg	Upper respiratory tract infection	Mild	No	Resolved
Sildenafil Medium Dose						
11238	9 years/M	20 mg	Upper respiratory tract infection	Mild	No	Resolved
11603	12 years/F	10 mg	Dizziness[a]	Mild	Yes	Resolved
		40 mg	Headache[a]	Severe	Yes	Resolved
		40 mg	Dyspnea[a]	Moderate	Yes	Resolved
11605	10 years/F	10 mg	Gastroenteritis viral	Moderate	No	Resolved
Sildenafil High Dose						
10415	6 years/M	20 mg	Nausea	Mild	No	Resolved
		20 mg	Pyrexia[b]	Moderate	No	Resolved
		20 mg	Gastroenteritis[b]	Moderate	No	Resolved
10420	20 months/M	10 mg	Stridor	Moderate	Yes	Resolved
10443	18 months/M	20 mg	Lethargy	Mild	Yes	Resolved
10448	30 months/F	20 mg	Right ventricular failure	Moderate	No	Resolved
		20 mg	Ecchymosis	Mild	No	Resolved
10451	32 months/F	20 mg	Diarrhea	Mild	Yes	Resolved
		20 mg	Vomiting	Moderate	Yes	Resolved
		20 mg	Vomiting	Mild	No	Resolved
Placebo						
10418	3 years/F	NA	Irritability[a]	Moderate	Yes	Ongoing
		NA	Weight loss[a]	Moderate	Yes	Ongoing
		NA	Decreased appetite[a]	Moderate	Yes	Resolved
		NA	Disturbance in social behavior[a]	Moderate	Yes	Ongoing
		NA	Insomnia[a]	Moderate	Yes	Resolved
10815	13 years/M	NA	Cyanosis	Mild	No	Resolved
		NA	Dizziness	Mild	No	Resolved
		NA	Headache	Mild	No	Resolved
		NA	Hypotension	Mild	No	Resolved
11240	7 years/F	NA	Headache[a, c]	Severe	Yes	Resolved

Source: Table 4.2.2 and Appendix B, Table 3
M=male; F=female; NA=not applicable
[a] Dose reduction rather than temporary discontinuation
[b] Adverse event was a serious adverse event
[c] The AE is recorded in the database with no action taken (see Appendix A13)

The most temporary discontinuations (or reductions) occurred in the high dose group. Many of these adverse reactions can be attributed to minor childhood infections. All but a few resolved.

All reported adverse events

The adverse events reported by at least 3% of subjects are shown in the table below.

Table T25. Incidence of Treatment-Emergent Adverse Events Reported in ≥3% of Subjects in Any Treatment Group

	Sildenafil									
Dose	Low		Medium		High		Combined		Placebo	
Subjects evaluable for AEs	42		55		77		174		60	
	AC	TR	AC	TR	AC	TR	AC	TR	AC	TR
Number of AEs	77	23	129	31	142	48	348	102	114	39
Number (%) of subjects with AEs	28 (66.7)	11 (26.2)	44 (80.0)	13 (23.6)	54 (70.1)	22 (28.6)	126 (72.4)	46 (26.4)	40 (66.7)	14 (23.3)
Number (%) of subjects with MedDRA (v11.0) preferred term[a]:										
Headache	5 (11.9)	4 (9.5)	6 (10.9)	5 (9.1)	12 (15.6)	8 (10.4)	23 (13.2)	17 (9.8)	8 (13.3)	7 (11.7)
URTI	4 (9.5)	0	9 (16.4)	0	7 (9.1)	0	20 (11.5)	0	4 (6.7)	0
Pyrexia	3 (7.1)	1 (2.4)	8 (14.5)	0	9 (11.7)	2 (2.6)	20 (11.5)	3 (1.7)	1 (1.7)	0
Vomiting	3 (7.1)	2 (4.8)	5 (9.1)	3 (5.5)	11 (14.3)	4 (5.2)	19 (10.9)	9 (5.2)	4 (6.7)	1 (1.7)
Diarrhea	2 (4.8)	0	3 (5.5)	0	7 (9.1)	2 (2.6)	12 (6.9)	2 (1.1)	5 (8.3)	1 (1.7)
Cough	2 (4.8)	1 (2.4)	4 (7.3)	0	2 (2.6)	2 (2.6)	8 (4.6)	3 (1.7)	3 (5.0)	0
Nausea	0	0	4 (7.3)	1 (1.8)	4 (5.2)	1 (1.3)	8 (4.6)	2 (1.1)	0	0
Bronchitis[b]	1 (2.4)	0	5 (9.1)	0	2 (2.6)	0	8 (4.6)	0	1 (1.7)	0
Nasopharyngitis	3 (7.1)	0	3 (5.5)	0	2 (2.6)	0	8 (4.6)	0	4 (6.7)	0
Pharyngitis	3 (7.1)	0	3 (5.5)	0	1 (1.3)	0	7 (4.0)	0	0	0
Dizziness	2 (4.8)	0	2 (3.6)	2 (3.6)	2 (2.6)	1 (1.3)	6 (3.4)	3 (1.7)	2 (3.3)	1 (1.7)
Epistaxis	1 (2.4)	1 (2.4)	2 (3.6)	0	3 (3.9)	3 (3.9)	6 (3.4)	4 (2.3)	2 (3.3)	1 (1.7)
Abdominal pain upper	0	0	3 (5.5)	0	3 (3.9)	2 (2.6)	6 (3.4)	2 (1.1)	1 (1.7)	0
Chest pain	2 (4.8)	1 (2.4)	1 (1.8)	0	2 (2.6)	0	5 (2.9)	1 (0.6)	2 (3.3)	1 (1.7)
Rhinitis	1 (2.4)	0	3 (5.5)	0	1 (1.3)	0	5 (2.9)	0	1 (1.7)	0
Pneumonia	0	0	3 (5.5)	0	2 (2.6)	0	5 (2.9)	0	0	0
Fatigue	2 (4.8)	1 (2.4)	0	0	2 (2.6)	0	4 (2.3)	1 (0.6)	1 (1.7)	1 (1.7)
Spontaneous penile erection[c]	0	0	2 (3.6)	2 (3.6)	1 (1.3)	1 (1.3)	3 (1.7)	3 (1.7)	0	0
Erection increased[c,d]	0	0	1 (1.8)	1 (1.8)	2 (2.6)	2 (2.6)	3 (1.7)	3 (1.7)	0	0

Source: Tables 6.1.1, 6.2.1, 6.1.3 and 6.2.3

AE=Adverse event; AC=all causality; TR=treatment-related NA=not available; URTI=upper respiratory tract infection

[a] AEs that occurred in ≥3% of subjects in any treatment group, including the sildenafil combined group, listed in descending order according to incidence in the sildenafil combined group

[b] Subjects 10853 and 11245 had bronchitis but the AEs were not recorded in the database (see Appendix A13)

[c] Percentages calculated from total number of subjects (ie, male and female) in each treatment group

[d] Does not occur in ≥3% of subjects in any treatment group, but considered in combination with spontaneous penile erection increased

Upper respiratory tract infection, pyrexia and vomiting were reported 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). Additionally, nausea, bronchitis, pharyngitis were reported by more subjects in the sildenafil combined group than the

placebo treatment group.

Erection increased and spontaneous penile erection combined were reported by 9.0% of male subjects in the sildenafil combined group and none by the placebo treatment group. Pyrexia, vomiting and nausea were observed with increased incidence at increased sildenafil dose.

Clinical laboratory tests

There were no observed clinically significant median changes from baseline to last observation in laboratory test data, and no clinically significant variation in median changes from baseline between the treatment groups.

Table 7.4 Page 1 of 2
Sildenafil Protocol A1481131
Laboratory Test Data: Median Changes from Baseline to Last Observation

		Sildenafil Low Dose			Sildenafil Medium Dose			Sildenafil High Dose		
PARAMETER	UNITS	N	BASELINE MEDIAN	MEDIAN CHANGE FROM BASELINE	N	BASELINE MEDIAN	MEDIAN CHANGE FROM BASELINE	N	BASELINE MEDIAN	MEDIAN CHANGE FROM BASELINE
Hemoglobin (HGB)	G/DL	40	17.3	-0.2	53	16.5	0.3	75	16.4	-0.4
Hematocrit (HCT)	%	40	51.9	-0.1	53	50.4	1.1	74	51.3	-1.1
RBC Count	10**6/MM**3	40	5.48	-0.02	53	5.3	0.09	74	5.25	-0.05
Platelets	10**3/MM**3	40	197	2	53	199	-7	73	193	-3
WBC Count	10**3/MM**3	40	7.5	-0.3	53	7.4	0.3	74	7.2	-0.9
Lymphocytes (Abs)	10**3/MM**3	39	1.79	0	51	2	-0.01	72	2.24	-0.16
Total Neutrophils (Abs)	10**3/MM**3	39	4.41	-0.2	51	4.19	-0.11	72	4.05	-0.46
Basophils (Abs)	10**3/MM**3	39	0.07	0	51	0.06	0	72	0.07	0
Eosinophils (Abs)	10**3/MM**3	39	0.08	0.01	51	0.11	0.01	72	0.1	-0.01
Monocytes (Abs)	10**3/MM**3	39	0.39	-0.02	51	0.32	0	72	0.34	-0.07
Total Bilirubin	MG/DL	41	0.6	0	54	0.5	-0.1	75	0.6	0
AST (SGOT)	IU/L	41	29	0	52	29	-1	75	28	1
ALT (SGPT)	IU/L	41	36	0	52	34	2	76	37	-1
Alkaline Phosphatase	IU/L	41	53	-1	53	54	1	76	49	1
Total Protein	G/DL	41	7.3	0.1	54	7.1	0.1	76	7.2	0.2
Albumin	G/DL	41	4.4	0.1	53	4.4	0.1	76	4.4	0.1
BUN	MG/DL	41	34.5	0	54	36.5	0.5	76	36.3	1.4
Creatinine	MG/DL	41	1	0	53	0.9	0	76	0.9	0
Sodium	MEQ/L	41	139	1	54	141	-1	76	140	1
Potassium	MEQ/L	41	4.2	0	52	4.2	-0.2	76	4.2	-0.1
Urine RBC	/HPF	3	0	0	4	0	1	5	1	0
Urine WBC	/HPF	3	1	0	3	1	0	4	1	0

		Sildenafil Combined Doses			Placebo		
PARAMETER	UNITS	N	BASELINE MEDIAN	MEDIAN CHANGE FROM BASELINE	N	BASELINE MEDIAN	MEDIAN CHANGE FROM BASELINE
Hemoglobin (HGB)	G/DL	168	16.6	-0.2	60	16.9	0.3
Hematocrit (HCT)	%	167	51.3	0	60	50.9	1.3
RBC Count	10**6/MM**3	167	5.39	0	60	5.31	0.17
Platelets	10**3/MM**3	166	197	-4	60	190	16
WBC Count	10**3/MM**3	167	7.4	-0.3	60	7.4	0.2
Lymphocytes (Abs)	10**3/MM**3	162	2	-0.06	56	1.85	0.2
Total Neutrophils (Abs)	10**3/MM**3	162	4.16	-0.2	56	4.13	-0.06
Basophils (Abs)	10**3/MM**3	162	0.07	0	56	0.07	0
Eosinophils (Abs)	10**3/MM**3	162	0.09	0.01	56	0.11	0
Monocytes (Abs)	10**3/MM**3	162	0.35	-0.03	56	0.35	-0.01
Total Bilirubin	MG/DL	170	0.6	0	60	0.5	0
AST (SGOT)	IU/L	168	29	0	60	30	0
ALT (SGPT)	IU/L	169	36	0	60	36	2
Alkaline Phosphatase	IU/L	170	53	1	60	59	1
Total Protein	G/DL	171	7.2	0.1	60	7.3	0.2
Albumin	G/DL	170	4.4	0.1	60	4.4	0.1
BUN	MG/DL	171	35.6	0	60	33.9	0
Creatinine	MG/DL	170	0.9	0	60	0.9	0
Sodium	MEQ/L	171	140	0	60	140	1
Potassium	MEQ/L	169	4.2	-0.1	60	4.3	0
Urine RBC	/HPF	12	0	0	6	0	0
Urine WBC	/HPF	10	1	0	6	1	1

Last observation is defined as last observation while on study drug or during the lag.
Normalized data has been used in the computations.
PFIZER CONFIDENTIAL Source Data: Section 13, Table 17 Date of Reporting Dataset Creation: 02AUG2008 Date of Table Generation: 02AUG2008 (10:18)

Individual Subject Changes

The tables below show the number and percent of subjects with reported laboratory abnormalities by treatment group. The first table includes subjects who had a normal baseline and the second table includes subjects who had an abnormal baseline.

Table T30. Incidence of Laboratory Test Abnormalities (Normal Baseline)

	Sildenafil									
Dose	Low		Medium		High		Combined		Placebo	
	N		N		N		N		N	
Number (%) of subjects with abnormalities		18 (43)		31 (56)		31 (41)		80 (46)		22 (37)
Number (%) of subjects with[a]:										
Basophils ($10^3/mm^3$) <1.2xULN	35	9 (26)	47	11 (23)	58	15 (26)	140	35 (25)	47	12 (26)
Total Neutrophils ($10^3/mm^3$) >1.2xULN	33	2 (6)	48	4 (8)	65	6 (9)	146	12 (8)	48	3 (6)
Monocytes ($10^3/mm^3$) >1.2xULN	37	5 (14)	49	3 (6)	70	2 (3)	156	10 (6)	55	2 (4)
Urine Blood/Hgb (Qual) ≥1	41	2 (5)	55	4 (7)	73	3 (4)	169	9 (5)	56	1 (2)
Lymphocytes ($10^3/mm^3$) >1.2xULN	34	1 (3)	41	5 (12)	59	3 (5)	134	9 (7)	46	3 (7)
Total Neutrophils ($10^3/mm^3$) <0.8xLLN	33	0	48	5 (10)	65	3 (5)	146	8 (5)	48	0
Eosinophils ($10^3/mm^3$) >1.2xULN	41	1 (2)	50	3 (6)	68	3 (4)	159	7 (4)	57	0
Lymphocytes ($10^3/mm^3$) <0.8xLLN	34	2 (6)	41	2 (5)	59	0	134	4 (3)	46	0
Hemoglobin (g/dL) <0.8xbaseline	20	1 (5)	38	2 (5)	51	0	109	3 (3)	37	0
Potassium (MEQ/L) >1.1xULN	40	1 (3)	53	1 (2)	71	1 (1)	164	3 (2)	57	3 (5)

Source: Table 7.1
Abs=absolute; Qual=qualitative; ULN=upper limit of normal; LLN=lower limit of normal; N=total number of subjects with abnormal baseline with ≥1 observation of the given laboratory test while on study
[a] Abnormalities that occurred in ≥5% of subjects in any treatment group

Table T31. Incidence of Laboratory Test Abnormalities (Abnormal Baseline)

Dose	Sildenafil								Placebo	
	Low		Medium		High		Combined			
	N		N		N		N		N	
Number of subjects with abnormalities		9		13		11		33		12
Number of subjects with[a]:										
Hemoglobin (g/dL) <0.8xbaseline	21	1	16	0	25	1	62	2	23	1
Hematrocit (%) <0.8xbaseline	16	0	17	1	23	1	56	2	22	2
RBC (10^6/mm^3) <0.8xbaseline	8	1	9	1	19	1	36	3	16	1
Platelets (10^3/mm^3) <0.8xbaseline	9	1	15	2	23	1	47	4	16	2
Lymphocytes (10^3/mm^3) <0.8xLLN	7	2	12	6	15	2	34	10	13	0
Lymphocytes (10^3/mm^3) >1.2xULN	7	0	12	1	15	2	34	3	13	0
Total Neutrophils (10^3/mm^3) >1.2xULN	8	1	5	0	9	1	22	2	11	2
Basophils (10^3/mm^3) >1.2xULN	6	2	6	2	16	3	28	7	12	3
Monocytes (10^3/mm^3) >1.2xULN	4	1	4	1	4	0	12	2	4	1
Total Bilirubin (mg/dL) >1.5xbaseline	5	3	4	1	4	0	13	4	3	0

Source: Table 7.2
Abs=absolute; Qual=qualitative; LLN=lower limit of normal; ULN=upper limit of normal; N=total number of subjects with abnormal baseline with ≥1 observation of the given laboratory test while on study
[a] Abnormalities that occurred in ≥2 of subjects in any treatment group

Individual Clinically Significant Abnormalities

-Subject 11628 (sildenafil medium) reported bilirubin increased which was reported as an adverse event on Day 112. The subject had an elevated bilirubin value of 1.7 mg/dL at screening. During the study, bilirubin values of 2.0 mg/dL, 2.1 mg/dL and 2.7 mg/dL were reported on Days 29, 57 and 112, respectively. ALT, AST and AP remained within normal limits throughout the study. No action was taken with respect to the study treatment.

-Subject 10417 (sildenafil high) reported decreased platelet count on Days 55 to 63 although the counts were within normal range (lowest reported was 204x10^3/mm$_3$.

Vital signs

Mean baseline and change from baseline at week 16 for blood pressure and heart rate are shown in the table below.

Table T32. Vital Signs - Mean (SD) Baseline and Change from Baseline at Week 16

	Sildenafil									
Dose	Low		Medium		High		Combined		Placebo	
	N		N		N		N		N	
Sitting heart rate, bpm										
Baseline	23	87.9 (14.0)	26	88.1 (22.6)	40	92.4 (15.3)	89	90.0 (17.4)	26	85.4 (20.9)
Change from baseline at Week 16	40	-2.9 (14.2)	54	-0.8 (15.9)	75	-2.4 (14.4)	169	-2.0 (14.8)	58	-3.5 (14.8)
Sitting diastolic BP, mmHg										
Baseline	23	59.8 (8.1)	26	62.5 (11.2)	40	62.8 (13.7)	89	62.0 (11.7)	26	59.3 (10.3)
Change from baseline at Week 16	40	-0.8 (11.2)	54	-1.6 (12.5)	75	-1.3 (13.0)	169	-1.3 (12.4)	58	3.7 (13.6)
Sitting diastolic BP, mmHg										
Baseline	23	100.8 (10.3)	26	98.8 (14.0)	40	100.2 (15.1)	89	99.9 (13.6)	26	97.2 (11.3)
Change from baseline at Week 16	40	3.8 (11.3)	54	0.9 (12.1)	75	0.6 (14.6)	169	1.4 (13.1)	58	3.7 (13.0)

Source: Table 8.2
SD=standard deviation; bpm=beats per minute; BP=blood pressure

Overall, there were small changes in all treatment groups. There seems to be no influence of sildenafil on vital signs.

Electrocardiogram

Ten subjects had abnormal ECG findings that were labeled as clinically significantly at Week 16. Of these ten subjects, two (10428, sildenafil medium and 10423 (sildenafil high) had an abnormality that was reported as an adverse event.

Table T33. Electrocardiogram – Changes from Screening

Subject	Age/Sex	Significantly more/less abnormal	Change from screening
Sildenafil Medium Dose			
10428	3 years/Female	More abnormal[a]	Electrocardiogram was more abnormal with widening of QRS-interval to right bundle branch block.
10454	9 years/Male	More abnormal	Right ventricle hypertrophy, right axis deviation, right auricle enlargement, left deviation axes.
10845	10 years/Male	More abnormal	Right ventricle hypertrophy.
Sildenafil High Dose			
10423	4 years/Female	More abnormal[a]	Right atrial overload, right axis deviation.
10451	32 months/ Female	More abnormal	Increased right ventricle hypertrophy, left axis deviation.
10819	10 years/Female	Less abnormal	Precordial leads QRS-interval voltage decreased.
11212	5 years/Female	Less abnormal	Improved repolarization, signs of right ventricular hypertrophy, ST-T-changes in myocardium.
11618	13 years/Female	Less abnormal	Slight improvement in right ventricular hypertrophy.
Placebo			
10408	4 years/Male	More abnormal	Right atrium and ventricular enlarged with right systolic pressure overloaded.
10811	10 years/Male	More abnormal	Incomplete right bundle branch block.
10843	7 years/ Male	More abnormal	Right ventricle hypertrophy.
11247	5 years/Female	More abnormal	Same findings as baseline plus PR-interval of 0.18 seconds.
11623	10 years/Male	More abnormal	Right axis deviation, biauricular and right ventricular growth.
10850	10 years/Male	Less abnormal	Sinus rhythm, complete right ventricular blockage.

Source: Appendix B, Table 19.1 and Appendix B, Table 6
[a] Reported as an adverse event

Development assessments

Pediatric Cognitive Development Assessment

The table below shows the cognitive development assessment at baseline and week 16.

Table 11.1 Page 1 of 1
Sildenafil Protocol A1481131
Paediatric Cognitive Development Assessment - ITT Population

Paediatric Cognitive Development Assessment			Paediatric Cognitive Development at Baseline							
		Paediatric Cognitive Development	Severely Limited		Moderately Limited		Mildly Limited		Not Limited	
Visit	Treatment	Post-Baseline	N	(%)	N	(%)	N	(%)	N	(%)
Week 16	Sildenafil Low Dose	Severely Limited	1	(2.4)	1	(2.4)	0	(0.0)	0	(0.0)
		Moderately Limited	0	(0.0)	2	(4.8)	2	(4.8)	1	(2.4)
		Mildly Limited	0	(0.0)	1	(2.4)	3	(7.1)	2	(4.8)
		Not Limited	0	(0.0)	0	(0.0)	1	(2.4)	26	(61.9)
	Sildenafil Medium Dose	Severely Limited	2	(3.6)	2	(3.6)	0	(0.0)	0	(0.0)
		Moderately Limited	0	(0.0)	4	(7.3)	2	(3.6)	0	(0.0)
		Mildly Limited	0	(0.0)	0	(0.0)	4	(7.3)	3	(5.5)
		Not Limited	0	(0.0)	1	(1.8)	1	(1.8)	36	(65.5)
	Sildenafil High Dose	Severely Limited	2	(2.6)	0	(0.0)	0	(0.0)	0	(0.0)
		Moderately Limited	0	(0.0)	6	(7.8)	2	(2.6)	0	(0.0)
		Mildly Limited	0	(0.0)	6	(7.8)	5	(6.5)	1	(1.3)
		Not Limited	0	(0.0)	0	(0.0)	4	(5.2)	50	(64.9)
	Sildenafil Combined Doses	Severely Limited	5	(2.9)	3	(1.7)	0	(0.0)	0	(0.0)
		Moderately Limited	0	(0.0)	12	(6.9)	6	(3.4)	1	(0.6)
		Mildly Limited	0	(0.0)	7	(4.0)	12	(6.9)	6	(3.4)
		Not Limited	0	(0.0)	1	(0.6)	6	(3.4)	112	(64.4)
	Placebo	Severely Limited	1	(1.7)	1	(1.7)	0	(0.0)	0	(0.0)
		Moderately Limited	2	(3.3)	6	(10.0)	1	(1.7)	0	(0.0)
		Mildly Limited	0	(0.0)	1	(1.7)	2	(3.3)	0	(0.0)
		Not Limited	0	(0.0)	0	(0.0)	2	(3.3)	41	(68.3)

The ITT population for Paediatric Cognitive Development Assessment includes all subjects randomized
to study treatment and have received at least one dose of study medication.
This is then used as the denominator in the calculation of the percentages by treatment.
PFIZER CONFIDENTIAL Source Data: Section 13, Table 2.7 Date of Reporting Dataset Creation: 02AUG2008 Date of Table Generation: 19AUG2008 (11:17)

16.

Most of the subjects were not deemed to be limited in their cognitive assessment at either baseline or endpoint. There were 16 reports of deterioration and 19 reports of improvement in the sildenafil groups. There were 2 reports of deterioration and 5 reports of improvement in the placebo treatment group.

Pediatric Motor Development Assessment

The table below shows the motor development assessment at baseline and week 16.

Table 11.2 Page 1 of 1
Sildenafil Protocol A1481131
Paediatric Motor Development Assessment - ITT Population

Paediatric Motor Development Assessment			Paediatric Motor Development at Baseline			
		Paediatric Motor Development	Severely Limited	Moderately Limited	Mildly Limited	Not Limited
Visit	Treatment	Post-Baseline	N (%)	N (%)	N (%)	N (%)
Week 16	Sildenafil Low Dose	Severely Limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Moderately Limited	0 (0.0)	2 (4.8)	2 (4.8)	1 (2.4)
		Mildly Limited	1 (2.4)	2 (4.8)	4 (9.5)	3 (7.1)
		Not Limited	0 (0.0)	0 (0.0)	3 (7.1)	22 (52.4)
	Sildenafil Medium Dose	Severely Limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Moderately Limited	0 (0.0)	4 (7.3)	1 (1.8)	0 (0.0)
		Mildly Limited	0 (0.0)	0 (0.0)	8 (14.5)	3 (5.5)
		Not Limited	2 (3.6)	1 (1.8)	2 (3.6)	34 (61.8)
	Sildenafil High Dose	Severely Limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Moderately Limited	0 (0.0)	3 (3.9)	4 (5.2)	0 (0.0)
		Mildly Limited	0 (0.0)	6 (7.8)	10 (13.0)	4 (5.2)
		Not Limited	0 (0.0)	0 (0.0)	2 (2.6)	47 (61.0)
	Sildenafil Combined Doses	Severely Limited	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
		Moderately Limited	0 (0.0)	9 (5.2)	7 (4.0)	1 (0.6)
		Mildly Limited	1 (0.6)	8 (4.6)	22 (12.6)	10 (5.7)
		Not Limited	2 (1.1)	1 (0.6)	7 (4.0)	103 (59.2)
	Placebo	Severely Limited	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
		Moderately Limited	0 (0.0)	4 (6.7)	2 (3.3)	0 (0.0)
		Mildly Limited	0 (0.0)	0 (0.0)	7 (11.7)	1 (1.7)
		Not Limited	0 (0.0)	0 (0.0)	5 (8.3)	37 (61.7)

The ITT population for Paediatric Motor Development Assessment includes all subjects randomized
to study treatment and have received at least one dose of study medication.
This is then used as the denominator in the calculation of the percentages by treatment.
PFIZER CONFIDENTIAL Source Data: Section 13, Table 2.7 Date of Reporting Dataset Creation: 02AUG2008 Date of Table Generation: 19AUG2008 (11:19)

Most subjects in all treatment groups were not deemed to be limited in their motor development at baseline and Week 16. There were 22 reports of deterioration and 24 reports of improvement in the sildenafil groups. There were 4 reports of deterioration and 5 reports of improvement subjects in the placebo group.

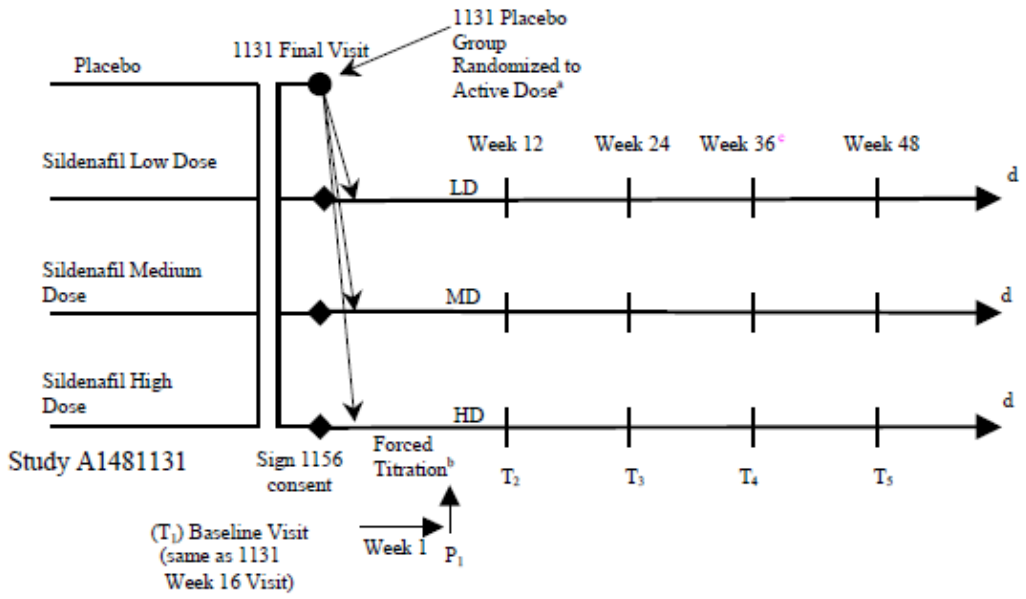
Ocular Measurements
There was one subject (10419, sildenafil medium) who reported color vision tests abnormal (Week 16).

Appendix 3
CLINICAL STUDY REVIEW
A1481156

Study Design
A1481156 is a multicenter, long-term extension study enrolling all subjects with PAH who completed a 16-week, placebo-controlled study (Study A1481131) and consented to participate in this extension study. A1481131 was to recruit a minimum of 200 subjects (including a minimum of 104 subjects who were developmentally able to exercise; an increase from the 90 subjects stated in the protocol for A1481156, as a consequence of a sample size re-estimation performed during A1481131). All subjects, including those who were not developmentally able to exercise in A1481131, could enter A1481156; these subjects were not expected to perform exercise tests in the extension study.

Dosing
Subjects enrolled into A1481156 received 1 of 3 doses (low, medium, or high) of sildenafil. Study medication was taken 3 times daily, at least 6 hours apart. With the exception of the subjects who were randomized to placebo in A1481131, subjects remained on the same treatment group as in A1481131. The subjects in the placebo group were randomized (stratified by weight) to 1 of the 3 active study treatment dose groups used in A1481131. To prevent treatment unblinding in A1481131, the treatment double-blind was maintained in A1481156 until the last subject had completed A1481131 and the database was locked (August 2, 2008). Since then A1481156 has continued as an open-label study.

The study design is shown in the figure below.



Source: Appendix A1

a Subjects in placebo group in A1481131 were randomized to 1 of 3 doses of sildenafil in A1481156 in a blinded manner.
b Placebo subjects randomized into medium or high dosage groups started on 10 mg (as in A1481131) and were force-titrated to final dose after 1 week. Other subjects underwent a dummy up titration to maintain the blind.
c Cardiopulmonary exercise test in subjects developmentally able to perform test.
d Repeat visits every 12 weeks until registration of sildenafil in study indication, oral sildenafil was proven ineffective or unsafe in pulmonary arterial hypertension (PAH), or the sponsor decided to discontinue development for PAH.

Dose adjustments

It was possible for subjects to receive different doses to those initially assigned, based on their randomized group and weight, on the basis of weight change, up titration or down titration. Subjects experiencing weight change could have had their dose adjusted according to the 3 weight groups used to assign doses within each treatment group.

If in the investigator's opinion, the subject would have benefited from an increase in drug dose due to loss of efficacy or a worsening of their disease, the dose could have been adjusted after Week 36 of A1481156 (Week 52). However, if the subject's status deteriorated because of disease progression or evidence of clinical worsening at any time prior to Week 36 in A1481156 (Week 52 from the start of A1481131), but after Day 7, and in the investigator's opinion the subject would benefit from an increase in study drug dose, this was possible following consultation with a sponsor representative.

If in the investigator's opinion, the subject had been experiencing drug-related intolerance, and they were not down-titrated in A1481131, the subject's dose could have been reduced by 50% after at least 1 week of treatment. This dose reduction could

only have occurred once. If, after a subject was down-titrated, the subject continued to appear intolerant, he/she should have been discontinued from study treatment.

Results

Dose adjustments

As of April 4, 2011, a total of 52/234 subjects (22.2%) had at least 1 up-titration in the extension study A1481156, most commonly from the low dose groups or placebo groups (22/42 (52.4%) in the Low/Low and 6/13 (46.2%) in the Placebo/Low dose treatment sequence groups).

The tables below show the number and percent of subjects with increased dose before (first table) and after the unblinding (second table) of the base study when the investigators found out the dose group to which subjects had been randomized.

Table 3.6 Page 1 of 2
Sildenafil Protocol A1481131 and A1481156
Proportion of Subjects Requiring Up/Down Dose-Titrations by Treatment Phase (Blinded/Unblinded) and A1481131/1156 Treatment Sequence
All Subjects Randomized and Treated in A1481131/1156
Treatment Phase: BLINDED

	Sildenafil Low/Low Dose (N=42) n (%)	Sildenafil Medium/Medium Dose (N=55) n (%)	Sildenafil High/High Dose (N=77) n (%)	Placebo/Low Dose (N=13) n (%)	Placebo/Medium Dose (N=19) n (%)	Placebo/High Dose (N=23) n (%)	Placebo/ Non-Randomized (N=5) n (%)
Down Titrations (A1481131)		1 (1.8)					2 (40.0)
Up Titrations (A1481156)							
At least one up titration	7 (16.7)	2 (3.6)	8 (10.4)	1 (7.7)	2 (10.5)	2 (8.7)	
1 up titration	3 (7.1)		6 (7.8)	1 (7.7)	1 (5.3)		
2 up titrations	4 (9.5)	2 (3.6)	2 (2.6)		1 (5.3)	2 (8.7)	
Weight Changes (A1481156)							
At least one weight change	10 (23.8)	14 (25.5)	16 (20.8)	3 (23.1)	5 (26.3)	5 (21.7)	
Weight change - dose increase	10 (23.8)	14 (25.5)	16 (20.8)	3 (23.1)	5 (26.3)	5 (21.7)	
Weight change - dose decrease	2 (4.8)	1 (1.8)	2 (2.6)				

Subject must have a weight decrease >=10% to move into a lower weight stratum.
Date of data cut-off: 04APR2011
PFIZER CONFIDENTIAL Source Data: Table 3.8 Date of Reporting Dataset Creation: 21JUN2011 Date of Table Generation: 22JUN2011 (23:32)

There were 22 (9%, 22/234) subjects who had at least one up titration while the investigators were blinded to dose.

Table 3.6 Page 2 of 2
Sildenafil Protocol A1481131 and A1481156
Proportion of Subjects Requiring Up/Down Dose-Titrations by Treatment Phase (Blinded/Unblinded) and A1481131/1156 Treatment Sequence
All Subjects Randomized and Treated in A1481131/1156
Treatment Phase: UNBLINDED

	Sildenafil Low/Low Dose (N=30) n (%)	Sildenafil Medium/Medium Dose (N=44) n (%)	Sildenafil High/High Dose (N=56) n (%)	Placebo/Low Dose (N=11) n (%)	Placebo/Medium Dose (N=15) n (%)	Placebo/High Dose (N=18) n (%)
Down Titrations (A1481156)			3 (5.4)		1 (6.7)	1 (5.6)
Up Titrations (A1481156)						
At least one up titration	15 (50.0)	7 (15.9)	3 (5.4)	5 (45.5)		
1 up titration	12 (40.0)	7 (15.9)	2 (3.6)	4 (36.4)		
2 up titrations	3 (10.0)		1 (1.8)	1 (9.1)		
Weight Changes (A1481156)						
At least one weight change	4 (13.3)	14 (31.8)	16 (28.6)	1 (9.1)	4 (26.7)	3 (16.7)
Weight change - dose increase	4 (13.3)	13 (29.5)	16 (28.6)	1 (9.1)	4 (26.7)	3 (16.7)
Weight change - dose decrease		2 (4.5)				

Subject must have a weight decrease >=10% to move into a lower weight stratum.
Date of data cut-off: 04APR2011
PFIZER CONFIDENTIAL Source Data: Table 3.8 Date of Reporting Dataset Creation: 21JUN2011 Date of Table Generation: 22JUN2011 (23:32)

There were 30 (17%, 30/174) subjects who had at least one up titration after the investigators were unblinded to dose.

Subject Disposition

Of the 234 subjects treated in A1481131, 220 subjects entered A1481156. There were 6 subjects who had discontinued treatment during A1481131 and 8 subjects who did not consent to continue. Overall, 199 subjects were aged ≥5 years, 115 subjects were

developmentally able, and 165 subjects completed the CHQ-PF28 assessment (were ≥5 years and had questionnaire available in native language).

Demographics

Overall, 38% of subjects were male and 62% were female. The majority was white. Mean ages were around 10 years and mean weight was around 30 kg. The demographics are summarized in the table below.

Table T9. Demographic Characteristics by A1481131/A1481156 Treatment Sequence

	Sildenafil Low/ Low Dose (N=42)	Sildenafil Medium/ Medium Dose (N=55)	Sildenafil High/ High Dose (N=77)	Placebo/ Low Dose (N=13)	Placebo/ Medium Dose (N=19)	Placebo/ High Dose (N=23)	Placebo Non-Randomized (N=5)
Sex, number of subjects							
Male	17	24	26	4	8	8	2
Female	25	31	51	9	11	15	3
Age, years							
Mean (SD)	11.6 (3.1)	9.9 (4.6)	8.5 (4.7)	9.7 (2.9)	9.3 (4.5)	9.3 (3.9)	10.0 (5.2)
Range	5-17	2-17	1-17	4-16	2-16	2-15	3-16
Race, number (%) of subjects							
White	19 (45.2)	26 (47.3)	28 (36.4)	4 (30.8)	7 (36.8)	12 (52.2)	1 (20.0)
Black	1 (2.4)	1 (1.8)	1 (1.3)	0	2 (10.5)	0	0
Asian	6 (14.3)	13 (23.6)	15 (19.5)	0	1 (5.3)	5 (21.7)	1 (20.0)
Other	16 (38.1)	15 (27.3)	33 (42.9)	9 (69.2)	9 (47.4)	6 (26.1)	3 (60.0)
Weight, kg							
Mean (SD)	38.2 (17.4)	32.1 (17.4)	25.8 (14.3)	32.8 (13.8)	29.7 (13.2)	27.9 (13.9)	25.3 (13.6)
Range	20.0-105.0	8.6-106.0	8.2-61.0	19.5-60.0	10.6-54.0	9.1-58.5	12.0-42.0
Height, cm							
Mean (SD)	141.6 (15.6)	130.5 (24.7)	120.8 (26.1)	133.1 (15.3)	127.1 (22.4)	128.4 (26.6)	120.5 (29.1)
Range	111.0-172.0	77.0-192.5	72.0-180.0	110.0-162.0	86.0-155.0	78.0-173.0	89.0-158.5
Body mass index, kg/m^2							
Mean (SD)	18.2 (4.8)	17.6 (3.9)	16.3 (3.4)	17.8 (4.1)	17.7 (4.4)	15.8 (2.5)	16.4 (3.3)
Range	11.7-36.8	11.8-28.6	10.6-30.0	13.1-27.5	13.3-29.5	11.1-19.7	12.5-21.1
Region, number (%) of subjects							
America	10 (23.8)	11 (20.0)	16 (20.8)	6 (46.2)	5 (26.3)	4 (17.4)	2 (40.0)
Asia	6 (14.3)	13 (23.6)	15 (19.5)	0	1 (5.3)	5 (21.7)	1 (20.0)
Europe	16 (38.1)	18 (32.7)	22 (28.6)	4 (30.8)	5 (26.3)	7 (30.4)	0
South America	10 (23.8)	13 (23.6)	24 (31.2)	3 (23.1)	8 (42.1)	7 (30.4)	2 (40.0)

Source: Table 2.1.1
N = number of subjects; SD = standard deviation
Note: America includes Canada, America and Mexico

Concomitant medication

The most common medications used other than study drug included midazolam, paracetamol and fentanyl. Most of the concomitant medications were used as non-specific background therapy for PAH and for the

Dose changes

The number of subjects who experienced an increase or decrease in dose are shown in the table below by dose group. Subjects with weight changes and dose changes are also included.

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Table T13. Summary of Changes in Treatment Group due to Titrations

Number of Subjects in Treatment Group Following Titrations	Sildenafil Low/ Low Dose (N=42)	Sildenafil Medium/ Medium Dose (N=55)	Sildenafil High/ High Dose (N=77)	Placebo/ Low Dose (N=13)	Placebo/ Medium Dose (N=19)	Placebo/ High Dose (N=23)	Placebo Non-Randomized (N=5)	Overall (N=234)
Low	29	1[a]	0	9	0	0	0	39
Medium	8	52	1	4	17	1	0	83
High	5	2	76	0	2	22	0	107
Placebo	0	0	0	0	0	0	5	5

Source: Table 5.2.10.3 and Section 13, Table 15
[a] Subject 11603 (high weight group) received 20 mg following down titration from 40 mg. This is not strictly equivalent to low dose high weight dosage (10 mg).

Efficacy

Peak VO2

Most subjects showed no change from baseline for peak VO2 at year one.

Table T14. Summary of Peak VO2 (mL/kg/min) at Year 1 by A1481156 Treatment Group - ITT Population

	Sildenafil Low Dose (N=33)	Sildenafil Medium Dose (N=32)	Sildenafil High Dose (N=35)
Baseline			
Mean (SD)	18.30 (4.54)	18.11 (4.44)	17.78 (3.65)
Year 1			
Mean (SD)	19.97 (5.17)	18.69 (5.92)	17.93 (4.02)
Mean (SD) Change from Baseline	1.67 (3.64)	0.58 (5.22)	0.15 (3.44)
Mean (SD) % Change from Baseline	11.19 (22.98)	5.37 (31.62)	2.56 (21.46)
Comparison with Low Dose:			
Mean Difference (SE)		-7.02 (6.10)	-9.84 (5.92)
95% Confidence Interval		-19.13, 5.09	-21.60, 1.93
p-value		0.253	0.100
Comparison with Medium Dose:			
Mean Difference (SE)			-2.82 (6.01)
95% Confidence Interval			-14.75, 9.11
p-value			0.640

Source: Tables 5.2.1.3 and 5.2.1.13
VO_2 = volume of oxygen consumed; ITT = intent-to-treat; N = number of subjects in analysis; SD = standard deviation; SE = standard error
ITT population for this table refers only to the subset of the ITT population who were developmentally able.
Baseline was the average of all assessments on or before the first day of study treatment.
Analyses were performed using analysis of covariance with etiology, weight, day of assessment and baseline peak VO_2 as the covariates

WHO functional class

WHO functional class was I or II for most subjects at A1481131 baseline and remained unchanged for the majority of subjects at each visit.

Table T17. Summary of Changes from Baseline in WHO Pulmonary Hypertension Functional Class by A1481156 Treatment Group - ITT Population

	Sildenafil Low Dose	Sildenafil Medium Dose	Sildenafil High Dose
Year 1			
Number of subjects	55	74	100
Improved by 2 Classes, number (%) subjects	1 (1.8)	0	0
Improved by 1 Class, number (%) subjects	3 (5.5)	9 (12.2)	6 (6.0)
No change, number (%) subjects	33 (60.0)	47 (63.5)	65 (65.0)
Worsened by 1 Class, number (%) subjects	12 (21.8)	12 (16.2)	15 (15.0)
Worsened by 2 Classes, number (%) subjects	0	1 (1.4)	1 (1.0)
Discontinued	5	4	10
Died	0	0	1
Missing	1	1	2
Year 2			
Number of subjects	43	54	73
Improved by 2 Classes, number (%) subjects	0	0	1 (1.4)
Improved by 1 Class, number (%) subjects	3 (7.0)	3 (5.6)	5 (6.8)
No change, number (%) subjects	22 (51.2)	30 (55.6)	41 (56.2)
Worsened by 1 Class, number (%) subjects	5 (11.6)	10 (18.5)	10 (13.7)
Discontinued	10	10	12
Died	1	1	4
Missing	2	0	0
Year 3			
Number of subjects	31	41	58
Improved by 2 Classes, number (%) subjects	0	0	0
Improved by 1 Class, number (%) subjects	5 (16.1)	1 (2.4)	5 (8.6)
No change, number (%) subjects	10 (32.3)	18 (43.9)	24 (41.4)
Worsened by 1 Class, number (%) subjects	5 (16.1)	9 (22.0)	9 (15.5)
Discontinued	10	8	13
Died	1	4	5
Missing	0	1	2

Source: Tables 5.2.5.8
WHO = World Health Organization; ITT = intent-to-treat

Mean CHQ-PF28 physical and psychosocial scale scores were similar for all A1481131/A1481156 treatment sequences at Year 1.

Safety

This section contains combined A1481131 and A1481156 safety data using the cut-off date of April 4, 2011 for adverse events and 20 June 20, 2011 for Serious Adverse Events and survival data.

Deaths

There were 35 reported deaths. Of these, 26 occurred when the subject was either on treatment or within 7 days of the last dose and 9 occurred for subjects who had been discontinued from study treatment for more than 7 days.

Sildenafil low/low dose

ID/ country	Sex/ age a	Weight (kg) b	Doses received (mg, tid)	Cause of death	Study day from start of drug	comments
10849/ India	m/11	21-23	10, 20, 40	Cardiac failure	651	4 days before death reported progressive dyspnea and syncope. Concomitant drugs include digoxin, acenocoumarol, spironolactone, furosemide
11611/ Hungary	m/18	58-53	10-40	Cardiac failure Respiratory failure	861	11 days before death was hospitalized for hypotension and loss of consciousness; concomitant drugs before hospitalization include captopril, enalapril, furosemide, digoxin
10814/Poland	f/17	37-49	10-40	Cardiac arrest	2002	No narrative. Subject reported chest pain one day prior to death. Cause of death was reported as worsening PAH
Sildenafil medium/medium dose						
10805/Poland	m/13	43-50	20-10-40	Pulmonary hemorrhage	430	Hospitalized one day before death for severe cyanosis, dyspnea, pulmonary hemorrhage. Concomitant meds include acenocourmarol, oxygen, magnesium hydrogen aspartate.
10829/India	m/18	32-38	20	PAH	861	Prior to death subject called physician complaining of fever and mild dry cough. Next morning subject was found dead. Concomitant meds include acenocourmarol, digitalis,

						amiloride/furosemide, paracetamol
11612/Mexico	f/19	45-47	40-20-40	Pulmonary hypertension. Sudden death	1407	Complained of dyspnea, diaphoresis, palpitations about one week before death. Died suddenly at home. Concomitant meds include omeprazole
10828/India	f/14	23-39	20-40	Cardiogenic shock	1693	No narrative. Suffered worsening PAH and cardiac shock. Concomitnat meds included amifru, digoxin, diltiazem
10841/India	f/18	42-31	20-40	PAH	1308	No narrative. Reported fever, vomiting, chest pain, gastroenteritis, abdominal pain, anorexia, and worsening of PAH. Concomitant meds include spironolactone, torsemide , acenocoumarol , pantoprazole ,shelcal ondansetrone, digoxin doxycycline, ofloxacin
Sildenafil high/high dose						
10411/Malaysia	f/7	16-17	20	PAH	324	Died during sleep. No adverse events reported. Concomitant meds include salbutamol, glucocorticoid steroid, folic acid, vitamins
10423/India	f/7	16-20	20-40	Sudden death	1101	Died suddenly after complaining of chest pain. Concomitant meds include digoxin, amiloride/furosemide and acenocoumarol
10437/Mexico	f/9	16-14	20	Cardiogenic shock	1112	Previous hospitalizations for worsening PAH. Had experienced

						cardiogenic shock, was intubated, developed severe bradycardia, was eventually unresponsive to CPR. Concomitant meds prior to last hospitalization include spironolactone, furosemide, digoxin
10462/Columbia	f/3	9-11	20	Pulmonary hypertension	370	Had been hospitalized for worsening pulmonary hypertension. Concomitant meds prior to last hospitalization include captopril, nifedipine, spironolactone, furosemide
10819/India	f/12	27-31	40	Cardiac failure	471	Had reported worsening dyspnea. One week before death reported gastroenteritis with worsening dyspnea and vomiting. Concomitant meds include amiloride/ furosemide, digoxin, acetylsalicyclic acid, antibiotics
10823/Russia	f/14	27-34	40	Ventricular fibrillation	604	Prior to death, subject reported gastroenteritis with vomiting and diarrhea. The next morning, she was reported to have experienced tachycardia, chest pain followed by syncope and sudden death. Concomitant meds include amiodarone, digoxin, acetylsalicylic acid, furosemide, spironolactone, aspartate potassium

						/magnesium aspartate, pentoxifylline, enalapril, amoxicillin trihydrate/clavulanate potassium, acetylcysteine, paracetamol, bacillus subtilis
10831/Poland	m/16	35-64	40-80	Pulmonary hypertension	1191	Previous hospitalization for serious hypoxemia, dyspnea, weakness. Re hospitalized one day before death with dyspnea, tachypnea. Died at home. Concomitant meds include magnesium, metildigoxin, acetylsalicylic acid, tianeptine, spironolactone, inhaled oxygen
11237/Poland	m/14	29-35	40	Cardiac failure	469	Hospitalized 3 days before death for cyanosis and dyspnea. Suffered a cardiac arrest after draining fluid from the pericardial sac. The subject did not recover and died 2 days later. No concomitant meds reported
11622/India	f/19	50-48	80	Cardiac failure	1093	Subject reported worsening symptoms of shortness of breath and nausea for about 10 days. She was hypotensive and died while being transported to the hospital.
11613/India	f/20	49-58	80	Pulmonary hypertension	1933	No narrative. Reported adverse events include vomiting, toothache, amenorrhoea, dental caries, ruptured Baker's cyst,

						filariasis, worsening pulmonary arterial hypertension, respiratory tract infection, cellulitis, hypokalemia, lower respiratory tract infection
10867/Columbia	f/16	28-37	40	Cardiac failure	995	No narrative. Reported adverse events include leg edema, acute right heart failure
11234/Hungary	f/16	44-57	40-80	Pulmonary embolism	1470	No death narrative. Subject had developed secondary polycythemia. Concomitant meds include captopril, acetylsalicylic acid, potassium, butamirate, cefprozil.
10838/Mexico	f/15	26-43	40	Cardiogenic shock	1602	No death narrative. Serious adverse events included syncope pneumonia, cardiogenic shock
11212/Hungary	f/11	23-49	40-80	Pulmonary hypertension	2351	No death narrative. Serious adverse events included worsening pulmonary hypertension about 2 weeks prior to death
11217	m/11	21-45	40	Pneumonia	2178	No narrative. Serious adverse events reported included worsening of PAH, pneumonia
Placebo/medium dose						
10832/Mexico	f/13	22-26	0-20-40	Right ventricular failure	1921	No narrative. Serious adverse events reported prior to death included right heart failure, electrolyte imbalance
Placebo/high dose						
10856/Columbia	f/12	32-45	0-40	Respiratory arrest (probable allergic reaction to penicillin)	815	Subject had a history of rheumatic fever since 2006 and received benzathine benzylpenicillin every 21 days.. On Study Day 703 the

						subject experienced respiratory arrest and died at another institution after the administration of benzathine benzylpenicillin
11214/Russia	m/14	25-46	0-40-80	Ventricular fibrillation	1874	No death narrative. Reported adverse events include various viral diseases including bronchitis as well as "vegetative dystonia" and deterioration of visual acuity and ventricular fibrillation

a age at time of death,
b weight at baseline/last recorded weight

There is no indication that these deaths are not related to expected deaths in this patient population (the worsening of underlying disease, pneumonia, pulmonary hemorrhage or, in one case, an allergic reaction to penicillin).

The nine subjects who died after being off study drug for more than 7 days are shown below.

Table 23. Studies A1481131 and A1481156 Combined: Deaths Reported More Than 7 Days After Last Study Treatment

Subject #	AER#	Sex/ Age (years)[a]	Weight (kg)[b]	Treatment in A1481131/ A1481156[c]	Duration of treatment relative to start of A1481131 prior to discontinuation	Reason for discontinuing treatment	Day of Death Relative to last day of dosing	Cause of death/causality
Sildenafil Low/Low Dose								
11604	2009264931	F/17	62-52	10-40 mg TID	1976 days	AE – Cardiac failure	28	Pulmonary haemorrhage/Other - unknown
10836	N/A	F/13	32-30	10 mg TID	128 days	Other – did not enter Study A1481156	406	Not available
Sildenafil Med/Med Dose								
11248	2008161373	M/15	39-40	20 mg TID	462 days	Subject died	9	Right ventricular failure/Disease under study
10432	N/A	F/6	15-17	10 mg TID	363 days	AE - Convulsion	129	Not available
11617	N/A	M/20	106-87	40 mg TID	1253 days	Protocol violation	287	Not available
11605	N/A	F/13	60-59	40 mg TID	531 days	AE- Syncope	289	Not available
Sildenafil High/High Dose								
10826	N/A	F/16	41-46	40-80 mg TID	1254 days	Due to poor condition of subject it was decided to start treatment with bosentan and stop study treatment to avoid protocol violation	60	Not available
11232	N/A	F/9	26-22	40 mg TID	794 days	Progress of disease	147	Not available
Placebo/High Dose								
10834	N/A	F/15	35-36	0-40 mg TID	449 days	Insufficient clinical response	397	Not available

Source: Tables 4.2, 4.5, 4.27, and 4.28 A1481156 Supplemental Safety Report, Module 5.3.5.3
M = male; F = female; N/A = not applicable
a: At time of death
b: Baseline weight and last recorded weight.
c: Sildenafil doses received excluding the 1 week titration dosing (10 mg) that subjects on medium and high doses received at the start of therapy.

Subject 11248 (center 1058) had been discontinued because of the adverse event congestive heart failure. He then was given approved sildenafil at a dose of 80 mg TID and died 9 days later.

Survival analysis

The safety population included 234 subjects who received at least 1 dose of sildenafil in A1481131. The analysis included post-treatment data from subjects who discontinued study treatment.

At the time of the cut-off for survival data[12], 35 deaths had been reported. Of these 35 deaths, 26 had been reported as being on treatment or within 7 days of the last dose. The additional 9 deaths were reported more than 7 days after their last study treatment.

The table below shows the deaths by randomized dose and weight groups.

Table 5. Summary of Deaths by Weight Group and Sildenafil Dose Group

Body Weight (kg)[1]	Low Dose Group	Medium Dose Group	High Dose Group	Total
≥8-20	NA	N=20 n=1 (5%)	N=44 n=4 (9%)	N=64 n=5 (8%)
>20-45	N=40 n=3 (8%)	N=40 n=6 (15%)	N=41 n=14 (34%)	N=121 n=23 (19%)
>45	N=15 n=2 (13%)	N=14[1] n=3 (21%)	N=15 n=2 (13%)	N=44 n=7 (16%)

[1] Subject 11612 had a baseline weight of 44.6kg, but was incorrectly assigned to the >45kg weight group.
NA: not applicable
Source: Table 9.7.660N, A1481156 Supplemental Safety Report, Module 5.3.5.3.

As of May 15, 2009 the percentages of subjects ongoing in the A1481156 treatment groups was comparable (69.1%, 71.6%, and 68.0% for low, medium, and high dose groups respectively). The number of subjects who died either on-treatment (or within 7 days of the last dose) or post-treatment (greater in the high dose group (12/100 subjects, 12.0%) compared to the low (2/55 subjects, 3.6%) and medium (6/74 subjects, 8.1%) dose groups.

Kaplan-Meier survival estimates by A1481156 randomized treatment group are summarized in the table below.

[12] June 20, 2011

Table T22. Summary of Kaplan-Meier Survival Estimates by A1481156 Treatment Group (Time of Death Relative to Day 1 of Active Therapy) – ITT Population

Survival Period	Summary	Sildenafil Low Dose (N=55)	Sildenafil Medium Dose (N=74)	Sildenafil High Dose (N=100)
1 Year	Deaths, number (%) subjects	0	0	1 (1.0)
	Life Table Estimates of Deaths			
	Proportion died[a]	0	0	0.010
	95% confidence interval[a]	0, 0	0, 0	0, 0.031
	Survived, number (%) subjects	55 (100)	74 (100)	99 (99.0)
	Survived 1 year of study	49 (89.1)	69 (93.2)	86 (86.9)
	Discontinued before 1 year of study	6 (10.9)	5 (6.8)	12 (12.1)
	Ongoing for <1 year of study	0	0	1 (1.0)
2 Years	Deaths, number (%) subjects	1 (1.8)	2 (2.7)	7 (7.0)
	Life Table Estimates of Deaths			
	Proportion died[a]	0.023	0.028	0.087
	95% confidence interval[a]	0, 0.067	0, 0.067	0.024, 0.149
	Survived, number (%) subjects	54 (98.2)	72 (97.3)	93 (93.0)
	Survived 2 years of study	31 (57.4)	41 (56.9)	54 (58.1)
	Discontinued before 2 years of study	10 (18.5)	10 (13.9)	16 (17.2)
	Ongoing for <2 years of study	13 (24.1)	21 (29.2)	23 (24.7)
3 Years	Deaths, number (%) subjects	2 (3.6)	5 (6.8)	9 (9.0)
	Life Table Estimates of Deaths			
	Proportion died[a]	0.052	0.093	0.126
	95% confidence interval[a]	0, 0.124	0.014, 0.173	0.046, 0.206
	Survived, number (%) subjects	53 (96.4)	69 (93.2)	91 (91.0)
	Survived 3 years of study	20 (37.7)	28 (40.6)	38 (41.8)
	Discontinued before 3 years of study	14 (26.4)	11 (15.9)	18 (19.8)
	Ongoing for <3 years of study	19 (35.8)	30 (43.5)	35 (38.5)

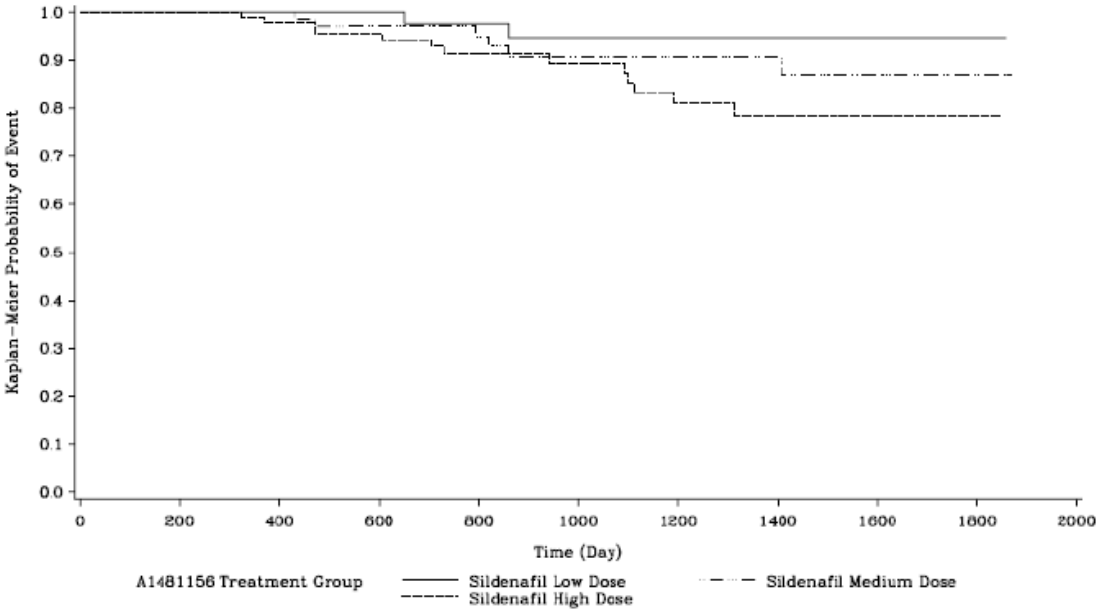
Source: Table 5.2.9.7
N = number of subjects; ITT = intent-to-treat
The number of deaths was too small to estimate median time to death.
[a] Kaplan-Meier estimates

The probability of survival at 3 years was 94.8%, 90.7%, and 87.4% for the low, medium, and high dose groups, respectively. This analysis includes 21 deaths and excludes subject 11604.

The 1, 3 and 5 year survival rates of pediatric PAH patients prior to the availability of therapy approved for adults with PAH have been reported as 37-66%, 29-52%, and 29-35%, respectively[13].

[13] Barst, R, Ertel SI, Beghettii M, et al. Pulmonary arterial hypertension: a comparison between children and adults. Eur Respir J 2011; 37:655-677.

Figure F3. Kaplan-Meier Survival Curve by A1481156 Treatment Group (Time of Death Relative to Day 1 of Active Therapy) – ITT Population



The number of deaths in each of the treatment groups 20/100 (20%) in the high dose treatment group (sildenafil high/high dose and placebo/high dose),10/74 (13.5%) in the medium dose treatment group (sildenafil medium/medium dose and placebo/medium dose) and 5/55 (9%) in the low dose treatment group (sildenafil low/low dose and placebo/low dose), respectively. The table below shows the number and percent of deaths by weight and dose groups.

Table 5. Summary of Deaths by Weight Group and Sildenafil Dose Group

Body Weight (kg)[1]	Low Dose Group	Medium Dose Group	High Dose Group	Total
≥8-20	NA	N=20 n=1 (5%)	N=44 n=4 (9%)	N=64 n=5 (8%)
>20-45	N=40 n=3 (8%)	N=40 n=6 (15%)	N=41 n=14 (34%)	N=121 n=23 (19%)
>45	N=15 n=2 (13%)	N=14[1] n=3 (21%)	N=15 n=2 (13%)	N=44 n=7 (16%)

[1] Subject 11612 had a baseline weight of 44.6kg, but was incorrectly assigned to the >45kg weight group.
NA: not applicable
Source: Table 9.7.660N, A1481156 Supplemental Safety Report, Module 5.3.5.3.

The hazard ratio comparisons for survival from the start of sildenafil by sildenafil dose groups and also from the start of Study A1481131 by Study A1481131 randomized groups are shown below.

Table 10. Treatment Group Comparisons for Survival from the Start of A1481131 and the Start of Sildenafil

Comparison	Stratified HR (95% CI)		
	Low Dose Group	Medium Dose Group	High Dose Group
Start of A1481131			
Comparison with Placebo	1.45 (0.39, 5.42)	2.44 (0.75, 7.93)	4.33 (1.45,12.93)
Comparison with Low dose	-	1.68 (0.56, 5.05)	2.99 (1.08, 8.28)
Comparison with Medium dose	-	-	1.77 (0.78, 4.01)
Start of Sildenafil			
Comparison with Low dose	-	1.85 (0.63 to 5.44)	3.50 (1.29 to 9.51)
Comparison with Medium dose	-	-	1.89 (0.88 to 4.07)

Source: Table 7.5 and Table 7.8, A1481156 Supplemental Safety Report, Module 5.3.5.3

The high dose group exhibits hazard ratios with 95% confidence intervals that exclude 1 (equivalence).

Up and down titrations in dose were permitted during the trial. (N.B. Dose increases resulting from changes in body weight were not considered up-titrations). The table below shows the titrations and dose adjustments with respect to weight changes allowed in the extension study.

Table 11. Summary of Dose Increases by Sildenafil Dose Groups

	Low Dose Group (N=55)	Medium Dose Group (N=74)	High Dose Group† (N=100)
At least one up 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 Increases‡	18 (33%)	36 (49%)	39 (39%)

† Dummy up-titrations would have been used for subjects who were already receiving the highest dose within their weight group.

‡An increase in weight to a new weight category would result in a subject receiving the dose of the new weight category within that treatment group (this not regarded as an up-titration).

The table below shows the proportions of deaths by concentration groups.

Table 12. Proportions of Deaths by Concentration Groups

Predicted Average Steady State Concentration (ng/ml)						
<25	25 - <50	50 - <75	75 - <100	100 - <125	125 < 150	150 +
4/43 (9.3%)	6/53 (11.3%)	2/24 (8.3%)	8/34 (23.5%)	8/33 (24.2%)	4/24 (16.7%)	3/18 (16.7%)

Source: Table 9.7.668N A1481156 Supplemental Safety Report, Module 5.3.5.3.

There is no obvious concentration-effect response.

The table below shows the baseline characteristics for the subjects who died and those who were alive at last contact.

Table 9.1.669N Page 1 of 2
Summary of Baseline Characteristics including BNP and Pro-BNP in the Overall Population and Alive/Dead
Sildenafil Protocol Pediatric_Responses

	Overall (n=234)	Death on Treatment or After Withdrawal (n=35)	Alive at Last Contact (n=199)
Etiology			
Primary pulmonary hypertension	78 (33.3%)	26 (74.3%)	52 (26.1%)
Secondary PH - congenital shunt	85 (36.3%)	4 (11.4%)	81 (40.7%)
Secondary PH - surgical repair	71 (30.3%)	5 (14.3%)	66 (33.2%)
Gender			
Female	145 (62.0%)	25 (71.4%)	120 (60.3%)
Male	89 (38.0%)	10 (28.6%)	79 (39.7%)
Weight			
<=20kg	66 (28.2%)	5 (14.3%)	61 (30.7%)
>20kg	168 (71.8%)	30 (85.7%)	138 (69.3%)
Down Syndrome			
No	186 (79.5%)	33 (94.3%)	153 (76.9%)
Yes	48 (20.5%)	2 (5.7%)	46 (23.1%)
Region			
America	40 (17.1%)	2 (5.7%)	38 (19.1%)
Asia	41 (17.5%)	11 (31.4%)	30 (15.1%)
Europe	72 (30.8%)	13 (37.1%)	59 (29.6%)
South America	81 (34.6%)	9 (25.7%)	72 (36.2%)
Countries with >2 Deaths			
Colombia	34 (14.5%)	3 (8.6%)	31 (15.6%)
Hungary	21 (9.0%)	3 (8.6%)	18 (9.0%)
India	27 (11.5%)	10 (28.6%)	17 (8.5%)
Mexico	14 (6.0%)	5 (14.3%)	9 (4.5%)
Poland	33 (14.1%)	7 (20.0%)	26 (13.1%)
Russia	13 (5.6%)	3 (8.6%)	10 (5.0%)
Countries with >20 Subjects			
Colombia	34 (14.5%)	3 (8.6%)	31 (15.6%)
Guatemala	25 (10.7%)		25 (12.6%)
Hungary	21 (9.0%)	3 (8.6%)	18 (9.0%)
India	27 (11.5%)	10 (28.6%)	17 (8.5%)
Poland	33 (14.1%)	7 (20.0%)	26 (13.1%)
United States	39 (16.7%)	2 (5.7%)	37 (18.6%)

	Overall (n=234)	Death on Treatment or After Withdrawal (n=35)	Alive at Last Contact (n=199)
WHO Classification of Pulmonary Hypertension			
Class I	75 (32.1%)	6 (17.1%)	69 (34.7%)
Class II	120 (51.3%)	15 (42.9%)	105 (52.8%)
Class III/IV	36 (15.4%)	14 (40.0%)	22 (11.1%)
Missing	3 (1.3%)		3 (1.5%)
Peak VO2			
<median	57 (24.4%)	18 (51.4%)	39 (19.6%)
>=median	58 (24.8%)	5 (14.3%)	53 (26.6%)
Missing	119 (50.9%)	12 (34.3%)	107 (53.8%)
PVRI			
<median	109 (46.6%)	9 (25.7%)	100 (50.3%)
>=median	108 (46.2%)	25 (71.4%)	83 (41.7%)
Missing	17 (7.3%)	1 (2.9%)	16 (8.0%)
mPAP			
<median	113 (48.3%)	11 (31.4%)	102 (51.3%)
>=median	118 (50.4%)	24 (68.6%)	94 (47.2%)
Missing	3 (1.3%)		3 (1.5%)
Cardiac Index			
<median	110 (47.0%)	21 (60.0%)	89 (44.7%)
>=median	110 (47.0%)	13 (37.1%)	97 (48.7%)
Missing	14 (6.0%)	1 (2.9%)	13 (6.5%)
BNP			
<median	80 (34.2%)	10 (28.6%)	70 (35.2%)
>=median	80 (34.2%)	13 (37.1%)	67 (33.7%)
Missing	74 (31.6%)	12 (34.3%)	62 (31.2%)
Pro-BNP			
<median	94 (40.2%)	6 (17.1%)	88 (44.2%)
>=median	93 (39.7%)	24 (68.6%)	69 (34.7%)
Missing	47 (20.1%)	5 (14.3%)	42 (21.1%)
RAP			
<median	93 (39.7%)	10 (28.6%)	83 (41.7%)
>=median	138 (59.0%)	25 (71.4%)	113 (56.8%)
Missing	3 (1.3%)		3 (1.5%)

* Includes subjects reporting D-transposition of the great arteries.
Median Peak VO2 = 18.2 ml/kg/min
Median PVRI = 14.3 wood units*m2
Median mPAP = 62 mmHg
Median Cardiac Index = 3.2 litres/min/m2
Region: Mexico was changed from America to South America.
Median BNP = 13.7 pg/ml Median Pro-BNP = 232.6 pg/m
Median RAP = 7.0 mmHg
Date of data cut-off: 04APR2011

The majority of deaths (74%, 26/35) were associated with primary pulmonary arterial hypertension etiology. The majority of subjects who died (74%, 25/34) had baseline PVRI above the median (14.3 Wood units*m2), 24/35 had mPAP greater than the median (62 mmHg), 71% (25/35) had RAP greater than the median (7mmHg), and 40% (14/35) were in subjects who were classified as WHO functional class III or IV at baseline. Not unexpectedly, sicker subjects (those with worse hemodynamic parameters) are more likely to die.

Other serious adverse events
Cut off date for safety was October 22, 2009.

Discontinuations for serious adverse events
There were 12 subjects who were permanently discontinued from the study because of an adverse event and the event did not become lethal. These subjects are shown in the table below.

Table T27. Summary of Discontinuations due to Adverse Events by A1481131/A1481156 Treatment Sequence

Subject Number	Sex/Age	Weight (kg)	Dose at Onset of AE (mg)	Preferred Term	Start Day/ Stop Day	Severity	Outcome	Causality
Sildenafil Low/Low Dose								
11201	F/7 years	26.5	10	Weight decreased	37/121	Mild	Unknown	Study drug
			Post	Weight decreased	1/>6[a]	Mild	Unknown	Study drug
Sildenafil Medium/Medium Dose								
10432	F/5 years	14.6	10	Convulsion	358/370	Moderate	Resolved	Other
			Post	Convulsion	1/56[a]	Moderate	Resolved	Other
10442*	M/4 years	14	10	Cardiac operation	476/483	Severe	Resolved	Disease under study
			Post	Cardiac operation	1/17[a]	Severe	Resolved	Disease under study
11248*	M/13 years	39	20	Right ventricular failure	230/>463	Severe	Still present	Disease under study
11605	F/10 years	60.3	40	Syncope	531/531	Moderate	Resolved	Other[b]
Sildenafil High/High Dose								
10417	M/20 months	10.5	20	Cardiac failure congestive	201/>202	Severe	Still present	Disease under study
10420	M/20 months	10	10	Stridor	10/10	Severe	Resolved	Study drug
10434	F/5 years	14	20	Cardiac failure	282/293	Severe	Resolved	Disease under study
			20	Dyspnea	284/293	Severe	Resolved	Disease under study
11202	F/9 years	25	40	Dyspnea	495/517	Moderate	Resolved	Study drug
			40	Hypoxia	379/517	Severe	Resolved	Study drug
			Post	Hypoxia	1/37[a]	Severe	Resolved	Study drug
Placebo/Low Dose								
10807	M/12 years	42.9	10/0	Rash macular	113/114	Mild	Resolved	Study drug
Placebo/Medium Dose								
11210	F/16 years	37.5	0	Malaise	1/368	Moderate	Still present	Disease under study
			Post	Malaise	1/>29[a]	Moderate	Still present	Disease under study
Placebo/High Dose								
11203	F/9 years	26	40	Dyspnea exertional	1566/1595	Moderate	Resolved	Disease under study

Source: Table 4.2.1.1 (*Source: Section 13, Table 3 [recorded as discontinuing due to an adverse event on the adverse event log page of the case report form but not on the subject summary page])
Post = post-treatment phase (later than within 7 days of last dose)
Age and weight are at screening.
Start and stop days are relative to Day 1 of A1481131, except [a] Post-treatment phase, relative to 7 days after final dose.
[b] Worsening of pulmonary hypertension

In addition to the 12 subjects discussed above, there were 2 additional discontinuations not originally reported as adverse events. Subject 10862 (sildenafil high/high dose) had worsening underlying disease so the study drug was stopped and bosentan (a drug prohibited by the study) was started. Subject 11232 (sildenafil high/high dose) was discontinued for disease progression).

Although the reasons for the discontinuations are not unexpected in this subject population, there were more discontinuations in the high dose sildenafil (6) compared to mid dose (4) and low dose (1).

Serious adverse events

Nearly one third of subjects (31%, 71/229)who received sildenafil at some point in the study reported at least 1 serious adverse event.

Table T23. Overall Summary of Incidence of Adverse Events by A1481131/A1481156 Treatment Sequence

Number (%) of Subjects	Sildenafil Low/ Low Dose	Sildenafil Medium/ Medium Dose	Sildenafil High/ High Dose	Placebo/ Low Dose	Placebo/ Medium Dose	Placebo/ High Dose	Placebo Non-Randomized
All Causalities							
Evaluable for AEs	42	55	77	13	19	23	5
Number of AEs	225	347	471	77	101	92	12
With AEs	39 (92.9)	52 (94.5)	66 (85.7)	13 (100)	19 (100)	19 (82.6)	3 (60.0)
With SAEs	9 (21.4)	22 (40.0)	30 (39.0)	1 (7.7)	3 (15.8)	6 (26.1)	0
With Severe AEs	6 (14.3)	18 (32.7)	25 (32.5)	2 (15.4)	1 (5.3)	3 (13.0)	1 (20.0)
Discontinued due to AEs	1 (2.4)	4 (7.3)	4 (5.2)	1 (7.7)	1 (5.3)	1 (4.3)	0
With Dose Reduced or Temporary Discontinuation due to AEs	6 (14.3)	7 (12.7)	13 (16.9)	1 (7.7)	3 (15.8)	0	1 (20.0)

The subjects randomized to medium and high dose sildenafil reported more serious adverse events compared to those who were randomized to low dose sildenafil.

Two subjects reported serious adverse events that were the result of right heart catheterization:

> Subject 02711604, after undergoing cardiac catheterization on study day 2, the subject was discharged from the hospital later he experienced wavering gait “as if she were drunk,” followed by an episode of faintness, cyanosis, dyspnea and blurred vision. The symptoms resolved spontaneously 30 minutes later. The subject was readmitted after being transported back to the hospital by ambulance. At the time of admission, the subject was asymptomatic, with an oxygen saturation of 95% by oxymetry. On the following day the subject was sleepy and had bradycardia and wavering gait. The subject also experienced one episode of enuresis at noon. The subject recovered from the events and was discharged from the hospital on study day 6. In response to the events of faintness, cyanosis, dyspnea, blurred vision, and wavering gait, treatment with sildenafil continued unchanged.
>
> Subject 102910427 from the base study was undergoing a right heart catheterization, was sedated with ketamine and midazolam, after which the subject desaturated with 60% oxygen level. The subject developed bronchospasm, respiratory distress and bradycardia. The subject recovered within 20 minutes and oxygen saturation reached 100%. The right heart catheterization was postponed.

Clinical laboratory abnormalities

Of the 228 subjects participating in the extended study, 167 (73%) had at least one abnormality (baseline values were normal). The most frequent abnormalities are shown in the table below by treatment group.

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Table T31. Summary of Most Frequent Laboratory Abnormalities (Normal Baseline) by A1481131/A1481156 Treatment Sequence

Parameter	Criteria	Sildenafil Low/ Low Dose (N=42) n/N (%)	Sildenafil Medium/ Medium Dose (N=55) n/N (%)	Sildenafil High/ High Dose (N=76) n/N (%)	Placebo/ Low Dose (N=13) n/N (%)	Placebo/ Medium Dose (N=19) n/N (%)	Placebo/ High Dose (N=23) n/N (%)	Placebo Non-Random. n/N (%)
Hemoglobin	<0.8 x baseline	1/20 (5)	3/41 (7)	3/52 (6)	1/9 (11)	0/11 (0)	0/16 (0)	0
Platelets	<75 x 10^3/mm^3	0/32 (0)	2/43 (5)	1/54 (2)	1/8 (13)	0/13 (0)	0/22 (0)	0
Lymphocytes (abs)	<0.8 x LLN	5/34 (15)	6/43 (14)	7/59 (12)	1/9 (11)	1/17 (6)	0/17 (0)	0
	>1.2 x ULN	2/34 (6)	6/43 (14)	5/59 (8)	1/9 (11)	0/17 (0)	2/17 (12)	0
Total neutrophils (abs)	<0.8 x LLN	1/33 (3)	5/49 (10)	3/67 (4)	0/11 (0)	0/17 (0)	0/17 (0)	0
	>1.2 x ULN	5/33 (15)	12/49 (24)	11/67 (16)	3/11 (27)	1/17 (6)	4/17 (24)	0
Basophils (abs)	>1.2 x ULN	15/35 (43)	20/49 (41)	25/60 (42)	3/11 (27)	7/17 (41)	9/18 (50)	0
Eosinophils (abs)	>1.2 x ULN	2/41 (5)	5/51 (10)	5/68 (7)	0/13 (0)	0/18 (0)	0/21 (0)	0
Monocytes (abs)	>1.2 x ULN	7/37 (19)	10/50 (20)	8/70 (11)	3/13 (23)	2/18 (11)	3/20 (15)	0
Blood urea nitrogen	>1.3 x ULN	1/40 (3)	4/50 (8)	7/71 (10)	0/11 (0)	3/17 (18)	1/22 (5)	0
Sodium	>1.05 x ULN	1/39 (3)	6/53 (11)	5/73 (7)	1/13 (8)	2/19 (11)	2/23 (9)	0
Potassium	>1.1 x ULN	3/41 (7)	3/53 (6)	10/71 (14)	1/13 (8)	0/17 (0)	3/22 (14)	1/50 (20)

Source: Table 7.1.1
Abnormalities present in ≥10% of subjects on 1 or more treatment sequence are presented.
abs = absolute; LLN = lower limit of normal; ULN = upper limit of normal
n/N = number of subjects with a laboratory abnormality meeting specified criteria/total number of subjects with normal or missing baseline with at least 1 observation of the given laboratory test while on study treatment or during lag time.

The most common abnormality was basophils (absolute) >1.2 x ULN Overall there is little difference between treatment groups for the percent of subjects reporting any abnormality.

- Alanine aminotransferase (ALT) increased – 2/77 subjects (2.6%; Subjects 10409 and 10416) on the sequence sildenafil high/high dose.)The event was reported on Days 1021-1126 for Subject 10409 and on Days 1039-1221 for Subject 10416. In both cases ALT increase did not exceed 2 x ULN and was not accompanied by elevation in bilirubin levels.
- Bilirubin increased – 1/55 subjects (1.8%, Subject 11628) on the sequence sildenafil medium/medium dose. The event was reported from Day 1 onwards.
- Hemoglobin increased – 1/77 subjects (1.3%, Subject 11234) on the sequence sildenafil high/high dose (the subject had elevated hemoglobin prior to study entry).
- Liver function test abnormal – 1/42 subjects (2.4%, Subject 10801) on the sequence sildenafil low/low dose, considered to be treatment-related. The subject had elevated aspartate aminotransferase (AST) of 130 U/L (ULN 41 U/L) and ALT of 198 U/L (ULN 30 U/L) on Day 1203 with normal bilirubin and alkaline phosphatase levels. ALT and AST had returned to normal by Day 1287.
- Transaminases increased – 1/19 subjects (5.3%, Subject 11219) on the sequenceplacebo/medium dose, ALT and AST were elevated on Day 1, with ALT 40 U/L (ULN 30 U/L) and AST 47 U/L (ULN 41 U/L). Transaminases remained elevated during the study with highest ALT value of 87 U/L reported on Day 1036 and highest AST value of 51 U/L reported on Day 616. Increases were considered to be treatment-related. Bilirubin remained within normal limits throughout the study.

Appendix 4

Study A1481134
Study Title: A randomized, multicenter, double-blind, placebo-controlled, dose-ranging, parallel group study of intravenous sildenafil in the treatment of children, aged 0 to 17 years, with pulmonary hypertension after corrective cardiac surgery.

Primary Objective: to assess the efficacy of intravenous (IV) sildenafil, over 24 hours of treatment, on pulmonary hypertension during the post-operative period in children aged 0 (≥34 weeks gestational age) to 17 years with congenital heart disease who have undergone corrective cardiac surgery.

Secondary Objectives: to assess the safety and tolerability of IV sildenafil in children with corrected congenital heart disease and pulmonary hypertension (as assessed by clinical laboratory parameters, physical examination, vital signs and frequency and severity of adverse events), to establish an effective dose range of IV sildenafil in the treatment of pulmonary hypertension in children following corrective cardiac surgery, to investigate the PK-effect relationship, to determine the population PK parameters, and to evaluate the healthcare resource utilization associated with the use of sildenafil compared to alternate therapies.

Study Design: A randomized, multi-center, double-blind, placebo-controlled, dose-ranging, parallel group study conducted in subjects aged 0 (≥34 weeks gestational age) to 17 years, receiving one of three doses of IV sildenafil or placebo for a minimum of 24 hours. Randomization of subjects was to be stratified by age (neonate or non-neonate) and by study center. No more than 25% of subjects were to be greater than one year old. Three intravenous sildenafil dosage regimens were selected to achieve target sildenafil plasma concentrations of approximately 40, 120, and 360 ng/mL. Each regimen consisted of a bolus loading dose infused over five minutes, followed by a maintenance infusion for 24 to 72 hours, the infusion of study drug continued for a minimum of 24 and maximum of 72 hours.

Results and Conclusions:
Enrollment into Study A1481134 was exceptionally slow resulting in only recruiting 18/252 patients after 18 months. Of the 87 subjects that were screened, 18 were randomized and 17 received treatment. Four
(4) of these 17 treated subjects, two each on sildenafil (17%) and placebo (40%), received additional therapy for treatment of post-operative pulmonary hypertension within 24 hours of start of study drug infusion. Eight (8) of the 17 subjects, 5 on sildenafil (42%) and 3 on placebo (60%), received additional therapy for pulmonary hypertension to Day 28 follow-up. The principal explanation for the slow recruitment was that severe acute postoperative pulmonary hypertension occurs at a lower rate than was originally thought to be the case in pediatric cardiac intensive care. Recruitment was also impaired by the availability of inhaled nitric oxide (NO). In February 2005, the FDA

agreed that due to these challenges, it would not be possible to complete the study and that it was acceptable to terminate this study. The planned population pharmacokinetic analyses were not conducted because of insufficient pharmacokinetic data (only 12 subjects having PK data, each subject with 4 concentrations).

Of the 17 treated subjects, 15 (88.2%) reported adverse events. The most commonly reported adverse event was pulmonary hypertension. Two of the treated subjects discontinued; one subject (placebo) died due to pulmonary hypertension related to the disease under study, and one subject (medium dose) was withdrawn during active treatment due to a lack of efficacy.

2 subjects reported serious treatment-emergent AEs. Ten (10) subjects reported non-treatment-emergent SAEs (events that occurred more than 7 days after the end of treatment). One (1) subject reported temporary discontinuation of study drug due to severe pulmonary hypertension aggravated by the disease under study. Four (4) deaths were reported, 2 occurred pre-randomization and 2 occurred in subjects receiving placebo (causes of death: pulmonary hypertension [as described in discontinuations above] and fungal sepsis [post-treatment]).

Appendix 5

Study A1481157
Study Title: A 7-Day, open-label, multicenter, pharmacokinetic study (part 1) followed by a 7-Day, randomized, multicenter, double-blind, placebo-controlled, dose-ranging, parallel group study (part 2) of IV sildenafil in the treatment of neonates with persistent pulmonary hypertension of the newborn (PPHN) or hypoxic respiratory failure and at risk of developing PPHN.

Primary Objective: for Part 1 of this study was to evaluate the pharmacokinetics of intravenous (IV) sildenafil in near term and term newborns ($\geq$34 weeks gestational age and $\leq$72 hours of age) with PPHN or with hypoxic respiratory failure and at risk for PPHN.
Secondary Objectives: for Part 1 of the study were to assess the safety and tolerability of IV sildenafil as measured by clinical laboratory parameters, physical examination, vital signs [blood pressure, heart rate, respiratory rate and oxygen (O_2) saturation], oxygenation index (OI), and the frequency and severity of adverse events.

Study Design: The study was planned as a two part study. The first part (Part 1) was a PK study conducted at only a few sites. The PK results of Part 1 were to be used to determine doses and infusion rates for the second part (Part 2) of the study. However, Part 2 of the study was not performed due to recruitment difficulties resulting from the widespread use of inhaled NO to treat PPHN.

Results and Conclusions:
During the conduct of part 1 of Study A1481157 it became apparent that the objectives of the second part (which required 256 patients) could not be met, since there was a reluctance amongst investigators to treat subjects with placebo or a new chemical entity. This reluctance occurred because the use of inhaled NO had become a standard of immediate care in the majority of major neonatal intensive care units. Following discussion with FDA in February 2005, it was agreed that this study in PPHN was not feasible and the study was terminated.

A total of 36 subjects were recruited in eight treatment groups, where ‘step up’ was dependent on the tolerability in successive groups. The target plasma concentrations ranged from 18.5 to 150 ng/mL.

One subject died during the study. This child died two hours after the start of the study drug infusion from a combination of her underlying illnesses of meconium aspiration, birth asphyxia and pulmonary hypertension, which was further complicated by tension pneumothorax. Four subjects reported treatment-emergent SAEs; one had hypotension, one had anomalous pulmonary venous connection, and two had a pneumothorax. In addition, 2 other SAEs were reported: cardiomyopathy was reported for 1 subject more than 7 days after the end of sildenafil treatment, and 1 subject had pneumothorax

present at the start of treatment. Four subjects discontinued study treatment due to treatment-emergent AEs; 1 due to hypotension, 2 due to labile blood pressure, and 1 due to anomalous pulmonary venous connection, also reported as a SAE. One (1) case of labile blood pressure and the hypotension were considered to be caused by the study drug. No subjects had dose reductions or temporary discontinuations due to treatment-emergent AEs. One (1) subject had her loading dose rate of administration reduced but still received the scheduled total loading dose by increasing the duration.

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