CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-473

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type: NDA
Submission Number: 22,473
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Reviewer Name: Maryann Gordon, M.D.
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Established Name: sildenafil citrate
Trade Name: Revatio
Therapeutic Class: phosphodiesterase 5 inhibitor
Applicant: Pfizer

Priority Designation: S
Formulation: intravenous
Dosing Regimen: 10 mg TID administered as an IV bolus
Indication: For the continued treatment of patients who are currently prescribed oral Revatio and who are temporarily unable to take oral medication
Intended Population: patients with pulmonary arterial hypertension

EXECUTIVE SUMMARY

Pfizer, the sponsor of NDA #22473, REVATIO ——— Injection, is seeking approval for the treatment of adult patients with Pulmonary Arterial Hypertension (PAH) who are temporarily unable to take oral medication, and for whom the physician believes continuity of treatment is in the patient's best interest. b(4)

Sildenafil tablet was originally approved in 1998 for the treatment of male erectile dysfunction under the trade name Viagra® (NDA 20-895). The sildenafil tablet was approved in 2005 to improve exercise ability in patients with PAH. Recently, the indication was expanded to include the delay in clinical worsening[1] in the same patient population. Had the sponsor not pursued the additional claim of clinical worsening, there would be no consideration by the Agency for an IV formulation.

The following studies were submitted in support of the IV application:

A148-203, a safety, toleration, PK/PD study with 3 doses of IV sildenafil in healthy volunteers.
A148-208, a PK/PD study comparing oral and IV doses of sildenafil in healthy volunteers.
A148-215, a study measuring the cumulative amount of IV and oral doses of sildenafil in healthy volunteers.
A1481024, a study to assess the effect of IV sildenafil on pulmonary vascular resistance in patients with PAH.
A1481141, a study to investigate the effect of oral sildenafil in delaying clinical worsening in patients with PAH who are also receiving epoprostenol.

The sponsor proposes that intravenous sildenafil is desirable in circumstances where short term interruption of oral sildenafil is necessary and the physician decides that continuation of therapy is in the best interest of the patient. The sponsor is not claiming, nor would the Agency agree, that short term interruption of oral therapy results in immediate and rapid worsening of symptoms of PAH in otherwise stable patients. However, there are instances when a patient with PAH cannot receive oral administration of sildenafil and maintaining therapeutic levels of sildenafil is likely to be important in maintaining the progression effect, even if the effect on exercise cannot be appreciated

The Agency has agreed with the sponsor regarding the following principles:
-Oral sildenafil is effective in reducing the incidence of clinical worsening events.
-Clinical deteriorations are often very difficult to reverse in PAH (Naeje 2007 *Exp Opin Pharmacoth*).
-The data suggest that maintenance of Revatio therapy is important in managing disease progression in PAH.
-The availability of IV formulation would give the physicians the ability to maintain treatment with Revatio in patients temporarily unable to take oral formulation.
-The strategy to select and IV dose based on PK modeling referencing the approved oral dose is acceptable.

[1] Clinical worsening was defined as one or more of the following: death, lung transplantation, hospitalization because of PAH, initiation of bosentan therapy, or clinical deterioration requiring a change in epoprostenol therapy.

-While it is desirable to conduct an efficacy trial in hospitalized PAH patients, it is probably not possible.

The clinical pharmacology package with the current application seeking approval of intravenous (IV) sildenafil included five studies. Two studies (148-203 and 148-301) were single dose studies using IV formulation in 16 patients. Two studies (148-208 and 148-215) compared single doses of the oral and IV formulations in cross-over and parallel manner, respectively, in 18 patients. Study 1481024 investigated safety and efficacy of IV sildenafil in patients with pulmonary hypertension (85 patients) with target plasma concentration of 10-500 ng/mL (given as 20 min infusion).

Additionally, the original Viagra® (NDA #20895) and Revatio® (NDA #21845) applications included several other clinical pharmacology studies. These development programs integrated depiction of single and multiple dose pharmacokinetics, ADME characteristics, bioavailability/bioequivalence studies, potential interactions with other medications, and studies in special populations, including PK evaluation of sildenafil in patients with PAH.

Utilizing the acquired information thus far, the sponsor proposes 10 mg IV injection to match plasma exposure of sildenafil/UK-103,320 for a 20 mg sildenafil citrate dose given orally.

As submitted by the Sponsor, the safety database for sildenafil solution for injection comprises of 93 adult patients (89 with PAH, of whom 70 received IV sildenafil) and 26 healthy volunteers, of whom 23 received sildenafil IV. The following are elements noted from the available information on sildenafil:

1. The oral formulation of sildenafil has been studied to a maximum of 800 mg in healthy volunteers and 80 mg three times a day (TID) in patients with PAH. The single oral doses of up to 800 mg have been tolerated by healthy volunteers where the average maximum concentration (C_{max}) achieved was 5834 ng/mL.

2. The IV formulation as a single dose has been studied up to the 80 mg dose level in healthy volunteers and 40 mg as a single dose in patients with ischemic heart disease with no significant or unexpected adverse events.

3. In patients with PAH, target concentrations ranging from 100 ng/ml to 500 mg/ml have been evaluated for safety and efficacy (the cumulative doses administered correspond to 5.75 mg over 20 minutes to 34 mg over 60 minutes, respectively). During this study the observed mean steady state plasma sildenafil concentrations were 128 (range 57.9-332), and 768 (range 398-2479) ng/mL, respectively.

4. As in the case of the oral formulation, the IV dosage regimens had no unexpected adverse events. The maximum infusion rate administered to these patients was 11mg/5min. Within the range for the therapeutic dose, the disposition of IV sildenafil is linear.

5. The predicted upper 90% prediction interval of C_{max} for the commercial 10 mg IV bolus does not exceed 300 ng/mL. Therefore, the C_{max} after 10 mg IV bolus is much lower than has been observed in healthy volunteers and PAH patients receiving higher doses as an infusion or an oral preparation, which were well tolerated. Administration at the 10 mg IV dose level will provide more than a 20-fold exposure coverage.

6. Absorption of sildenafil citrate after oral administration was approximately 92% whilst the oral bioavailability was ~38% (study 148-215), this difference being due to extensive first pass metabolism. Geometric mean area-under-the-curve (AUCt) values indicated that sildenafil accounted for approximately 60% of the total circulating radioactivity in the plasma after IV dosing and 32% after oral dosing.

7. The amount of circulating metabolite was significantly lower following IV administration versus oral. For the main metabolite of sildenafil (UK-103,320), the geometric mean Cmax value following IV dosing was 7.3% of the equivalent parameter for sildenafil. The geometric mean AUCt value was 14.4% of the equivalent parameter for the parent drug. Following oral dosing, the geometric mean Cmax value for UK-103,320 was 49% of that of the parent drug. The geometric mean AUCt value was 54% of that for sildenafil.

In conclusion,

- The information supplied from NDA #22473 provides enough evidence that an IV bolus dose of 10mg TID will be safe and effective.

- There is sufficient safety experience for sildenafil at exposures significantly higher than that being currently proposed of the approval of IV formulation. Because of the short half life of both sildenafil and the active metabolite UK-103,320 (~4 hours for both) no accumulation of either sildenafil or its metabolites is expected during TID intravenous dosing.

- The adverse event profile for IV sildenafil in adults with PAH was consistent with the adverse event profile for marketed oral Revatio® in adults with PAH. The expected exposures after 10 mg IV bolus is much lower than that observed in both healthy volunteers and PAH patients receiving higher doses as an infusion or oral preparation, which were well tolerated. Therefore, there are no expected safety concerns.

- Based on previous experience for Revatio® in patients with PAH, the efficacy is expected to be similar between 20 mg PO and the proposed 10 mg IV administration.

- The inherent pharmacokinetic differences between oral and IV sildenafil have been evaluated in two separate studies with healthy patients. The estimated bioavailability of the oral formulation has been assessed at the 50 mg oral dose. The estimated bioavailability at this dose level is estimated to be 41% which is similar to that found in the Muirhead reference (~38%). It is also noted that the extent of formation of the active metabolite (UK-103,320) differs between IV and oral formulations. The dose of 10

mg TID given as a bolus injection has been selected to yield similar PDE5 inhibition from total plasma concentration of sildenafil *plus* the major active metabolite UK-103,320 to that observed with a 20 mg TID oral dose. Specifically, the IV dose calculated to yield similar total plasma concentrations of [sildenafil + UK-103,320] for an oral 20 mg dose is ~~~~ mg, rounded to 10 mg for use in clinical practice. This comparison includes adjustment for the bioavailability, and both relative potency and protein binding of both sildenafil and the active metabolite UK-103,320. According to the Clinical Pharmacology reviewer, this approach is deemed appropriate for dose selection. b(4)

- The sponsors are not requesting the IV formulation to be used for long term use.

- The sponsor has demonstrated a clinically and statistically significant effect on the delay in clinical worsening of PAH using the oral formulation. Intravenous Revatio® provides an alternative treatment formulation for the PAH population that is unable to take medications orally as it provides similar exposure to the active moieties.

- Based on the understanding of the metabolic pathway of sildenafil, any drug interactions with other drugs after IV administration of sildenafil should be less than that after oral administration. Data suggest that sildenafil is metabolized by CYP3A4 in the gut as well as the liver. Predictions based on a pharmacokinetic model suggest that drug-drug interactions with CYP3A4 inhibitors should be less than those observed after oral sildenafil administration. The magnitude of the interaction is expected to be reduced for IV sildenafil, as interactions for oral sildenafil are due, at least in part, to effects on oral first pass metabolism.

- Founded on the wide safety margin for sildenafil and the fact that exposures of sildenafil between the 10 mg IV and 20 mg oral formulations are expected to be similar, switching between formulations should not result in safety issues or lack of efficacy. This is the expectation upon switching formulations in either direction (i.e., oral to IV or IV to oral) during patient hospitalization.

Recommendation on Regulatory Action

Approval

Recommendation on Postmarketing Actions

None

Summary of Clinical Findings

2.7.4.1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies
The safety and efficacy of sildenafil citrate has been extensively investigated in the original male erectile dysfunction (MED) development program, including 31 Phase 2/3 clinical trials and 35 clinical pharmacology studies, and over 4,500 subjects that received sildenafil (NDA 20-895). Since approval of sildenafil for MED, over 35 million patients have received sildenafil for the treatment of MED.

The safety profile of REVATIO oral tablets has been previously established in adults with PAH. The database has previously been submitted (NDA 21-845) to support the safety of the oral formulation for PAH, and an overview of this data is given below.

The remainder of this document presents safety data from seven studies involving intravenous sildenafil. All of the seven studies utilizing IV sildenafil citrate were conducted as part of the original sildenafil citrate submission for the treatment of MED (VIAGRA) [NDA 20-895] with the exception of studies A1481024, A1481134 and A1481157, which were included in the original REVATIO submission (NDA 21-845).

SAFETY REVIEW

REVATIO [redacted] injection is a [redacted] single use vial containing [redacted] sildenafil citrate; the proposed dose is 10 mg (12.5 ml) three times a day (TID) given as a bolus injection. The IV dose was selected because it yielded similar PDE5 inhibition to that obtained with the approved oral dose (20 mg TID) for PAH patients. b(4)

This summary document supports the safety of REVATIO [redacted] injection 10 mg TID in patients with PAH.

Based on a evaluation by the sponsor of available safety data with a worldwide data cutoff date of 31 July 31, 2008[2], the results support the following conclusions:

- The adverse event profile for intravenous sildenafil in adults with PAH is consistent with the adverse event profile for marketed oral REVATIO in adults with PAH.
- Intravenous sildenafil is safe and generally well tolerated at all doses studied in patients with PAH.
- As expected with inhibition of PDE5 and in line with the accumulated knowledge of sildenafil, the most common adverse events reported were headache, hypotension, vasodilatation, and dizziness.

Overall Safety Evaluation Plan and Narratives of Safety Studies
This document discusses safety data from seven studies involving intravenous sildenafil. All of the seven studies utilizing IV sildenafil citrate were conducted as part of the original sildenafil citrate submission for the treatment of male erectile dysfunction (NDA 20-895) with the

[2] all of the studies were completed prior to 2008

exception of studies A1481024, A1481134 and A1481157 which were included in the original submission for pulmonary hypertension (NDA 21-845).

Overview of REVATIO Tablets Safety Data
The most common adverse events were headache, dyspepsia, and flushing.

Overview of REVATIO [redacted] Injection Safety Data b(4)
The safety database for REVATIO [redacted] injection comprises seven completed studies, of which four were conducted in patients (three studies involved patients with pulmonary hypertesnion (PH) and three in healthy volunteers. A summary of these seven studies is shown below.

Table 1. Summary of Studies Included in Intravenous Safety Database

Study	Patient Population/ Number of Patients	Study Design	Dose
Adult Patient Studies			
A1481024	Pulmonary Hypertension Patients/ N=85 (45 PAH patients [35 received sildenafil IV; 10 received placebo]; 34 PVH due to CHF patients [25 received sildenafil IV; 9 received placebo]; 6 hypoxic PH due to COPD patients [all 6 received sildenafil IV])	Phase 2 pilot Double blind Parallel group Single day Placebo-controlled	Series of step-wise IV infusions targeting concentrations of 100, 300, and 500 ng/ml in original study and 10, 50, and 100 ng/ml in extension phase (consisted of initial infusion followed by maintenance infusions to maintain plasma concentration)
148-301	Ischemic Heart Disease Patients/N=8 (all received sildenafil IV) (4 met criteria for definition of PH)	Phase 1 Open label Single day	Four 15 minute infusions to supply step-wise cumulative doses of 5, 10, 20, and 40 mg over 60 minutes
Pediatric Patient Studies			
A1481134	PH after corrective cardiac surgery patients/ N=17 (12 sildenafil IV; 5 placebo)	Phase 2/3 Double blind Parallel group Multiple days Multi-center Placebo-controlled	Bolus loading dose infused over 5 minutes followed by infusion of 1 mg/ml solution to achieve target sildenafil plasma concentrations of approximately 40, 120, and 360 ng/ml
A1481157	PPHN or hypoxic respiratory failure and at risk for PPHN patients/ N=36 (36 sildenafil IV)	Phase 2 Open-label Multiple days Multi-center	Loading dose followed by infusion for up to 7 days to target plasma concentration up to 150 ng/ml
Healthy Volunteer Studies			
148-203	Healthy Volunteers/ N=8 (8 sildenafil IV)	Phase 1 Single blind 4 way cross-over Single escalating doses Placebo controlled	Four single infusions (20, 40, 80 mg sildenafil, and placebo) given as 40 minute infusions
148-208	Healthy Volunteers/ N=12 (12 sildenafil IV)	Phase 1 Open-label 2 way cross-over Single dose	Two single doses of sildenafil 50 mg (50 minute IV infusion and two 25 mg capsules)
148-215	Healthy Volunteers/ N=6 (3 sildenafil IV)	Phase 1 Open-label Parallel group Single dose	Single dose of 25 mg infusion (25 ml of 1 mg/ml solution) or 50 mg powder for oral solution

CHF: Congestive Heart Failure; COPD: Chronic Obstructive Pulmonary Disease; PH: Pulmonary Hypertension; PPHN: Persistent Pulmonary Hypertension of the Newborn; PVH: Pulmonary Venous Hypertension.

Therefore, the safety data base include:
-93 adult patients, most with PAH (96%) and most (80%) having received sildenafil IV;
-53 pediatric patients, most (91%) having received sildenafil IV; and
-26 healthy volunteers, most (88%) having received sildenafil IV.

Data from these seven studies were not pooled because the study populations were varied (PAH patients, neonates and children, males with ischemic heart disease, and healthy volunteers), the studies had different designs, and different doses and dosing regimens were used.

Overall Extent of Exposure
The overall exposure to sildenafil IV is summarized in the table below.

Table 2. Clinical Trial Exposure by Age, Dose, and Duration—IV Sildenafil

Clinical Trial Sildenafil Exposure			
	Number of Subjects Exposed		Total Sildenafil Exposure (days)
	1 day	2-8 days	
Age			
0 to 27 days (n=36) Actual range: 11-71 hours	2	34	145
28 days to 11 years (n=12) Actual range: 3-77 months	--	12	34
18-64 (n=80)	72	8*	96
65-74 (n=14)	14	--	14
≥75 (n=3)	3	--	3
Total Daily Dose of Exposure (Adult Studies: A1481024, 148-301, 148-203, 148-208, 148-215)			
1-10 mg	41	--	41
11-20 mg	15	--	15
21-30 mg	4	--	4
31-40 mg	33	--	33
41-50 mg	12	--	12
80 mg	8	--	8
Dose of Exposure (Paediatric Studies)			
A1481157 Loading Dose Range: 0-1.44 mg; Maintenance Dose Range: 0.2-5.2 mg/day	2	34	145
A1481134 Loading Dose Range: 0.17-0.62 mg; Maintenance Dose Range: 4.4-11.8 mg/day	--	4	10†
Loading Dose Range: 0.55-1.36 mg; Maintenance Dose Range: 14.4-27.8 mg/day	--	4	11†
Loading Dose Range: 1.38-2.32 mg; Maintenance Dose Range: 36.0-52.8 mg/day	--	4	13†

*Subjects received 3 separate sildenafil infusions on 3 different days
†Total Exposure is equal to the sum of calendar dosing days, not the sum of infusion durations
Source: Section 13, Tables 6 and 15 (CSR, A1481024); Appendix V, Tables 3 and 10 (CSR, 148-301); Appendix V, Tables 3 and 5 (CSR, 148-203); Appendix V, Tables 3 and 9 (CSR, 148-208); Appendix V, Tables 3 and 10 (CSR, 148-215); SCS Table 5.1 (A1481157); SCS Table 5.2 (A1481134)

Most of the adults received sildenafil IV for one day, with the most common total daily doses being between 1-10 mg and 31-40 mg.

Demographic and Other Characteristics of Study Population

Adult Patient Studies (A1481024 and 148-301).

Study A1481024 synopsis
This was a pilot, multi-centre study to assess the safety, efficacy and toleration of IVsildenafil in subjects with pulmonary hypertension. Subjects were stratified into one of three groups prior to randomization according to type of pulmonary hypertension [pulmonary arterial hypertension (primary and secondary) (Group 1a), pulmonary venous hypertension due to congestive heart failure (Group 1b), and hypoxic pulmonary hypertension (Group 2).

The study drug infusion consisted of either placebo or sildenafil. The drug infusion was administered at a controlled rate to maintain target plasma concentrations of 100, 300 and 500 ng/ml in the original part of the protocol (all subjects in the original study also received 40 ppm nitric oxide [NO] by inhalation for five minutes). This consisted of:

-an initial infusion of 5.25 mg for 5 minutes followed by
-a maintenance infusion of 0.5 mg for 15 minutes to maintain plasma concentrations of 100 ng/ml, followed by
-a step infusion of 11 mg for 5 minutes, followed by
-a maintenance infusion of 2.25 mg for 15 minutes to maintain target plasma concentrations of 300 ng/ml.
-a final step infusion of 11 mg for 5 minutes, followed by a maintenance infusion of 4 mg for 15 minutes, was administered to maintain target plasma concentrations of 500 ng/ml.

Hemodynamic measurements at each plasma level were performed after 10 minutes of every maintenance step of the infusion. Blood samples were withdrawn from the pulmonary artery to measure plasma levels of study drug at times coinciding with the hemodynamic measurements during the maintenance steps of the infusion.

A total of 88 subjects were randomized to treatment and 85 received treatment.

Demographic Data
Demographic data for subjects in Study A1481024 are shown below. Reasons for excluding subjects from either study are displayed in the appendices.

Table 5. Demographic Characteristics of Subjects in Study A1481024

Characteristic	Sildenafil IV (n=66)	Placebo (n=19)
Gender, n (%)		
Male	31 (47)	12 (63.2)
Female	35 (53)	7 (36.8)
Age, Years		
Mean (SD)	53.5 (12.6)	50.2 (13.6)
Min, Max	22-80	24-73
Race, n (%)		
White	60 (90.9)	16 (84.2)
Black	2 (3.0)	2 (10.5)
Asian	2 (3.0)	1 (5.3)
Other	2 (3.0)	--
Weight (kg)		
Mean (SD)	73.0 (15.6)	76.6 (17.0)
Min, Max	44-129.8	47-110.8
Primary Diagnosis, n (%)		
Primary pulmonary hypertension	66 (100)	19 (100)

Source: SCS Tables 2.1.3 and 2.2.2

This study had more males than females, mean age was about 52 years, most were white, and all had primary PH.

The primary diagnosis of all 85 subjects was pulmonary hypertension, 45 with PAH (35 treated with sildenafil, 10 placebo), 34 with pulmonary venous hypertension because of CHF (25 treated with sildenafil, 9 placebo), and six with hypoxic pulmonary hypertension (6 treated with sildenafil).

Medical History

The most common conditions reported were primary pulmonary hypertension (28 of the 85 subjects), unspecified essential hypertension (14 of the 85 subjects), dyspnea and respiratory abnormalities (11 of the 85 subjects), other chronic pulmonary heart diseases (11 of the 85 subjects), other primary cardiomyopathies (11 of the 85 subjects), atrial fibrillation and flutter (10 of the 85 subjects), chronic ischemic heart disease, unspecified (9 of the 85 subjects), and pure hypercholesterolemia (9 of the 85 subjects).

Concomitant Drug and Non-Drug Treatments

The most common drug treatments were diuretics (68 of the 85 subjects), anticoagulants (67 of the 85 subjects), antihypertensive drugs (60 of the 85 subjects), positive inotropic drugs (35 of the 85 subjects), and drugs used in rheumatic diseases and gout (33 of the 85 subjects).

Study 148-301 synopsis

This was an open-label, single IV dose pilot study of the hemodynamic effects of sildenafil in subjects with stable ischemic heart disease (IHD). In this study, sildenafil was

administered by infusion of a 1 mg/ml solution using a mechanical infusion pump via a catheter in a forearm vein over four 15 minute periods at 20, 20, 40 and 80 ml/hour to supply cumulative doses of 5, 10, 20 and 40 mg sildenafil in 60 minutes. Acute hemodynamic responses were recorded at rest and on exercise. Prior to drug administration (baseline) hemodynamic parameters were to be recorded at one minute intervals during a 4 minute exercise test, and then after 20 minutes of rest, the same parameters were to be assessed at rest at 5 minute intervals over 15 minutes or until there was a less than 10% variation in cardiac output, mean arterial pressure and heart rate. Hemodynamic data were to be collected between the 12th and 15th minute of each infusion, and at one minute intervals during a four minute exercise test immediately after completion of the final infusion. Pulmonary arterial pressure, right atrial pressure, systemic arterial pressure, and heart rate were to be continuously monitored throughout the study. Progression through the infusions depended on satisfactory safety and toleration of the preceding dose.

Demographic Data
All eight subjects were male, with a mean age of 60 years (range 52 to 70 years). Seven subjects were white, and race was unknown for one subject. The mean weight of these eight subjects was 77 kg, with a range of 69 to 88 kg. The primary diagnosis of all eight subjects was angina pectoris, with duration since first diagnosis ranging from 0.5 to 3.0 years (mean 1.7 years).

Medical History
The most common conditions present were chronic airway obstruction not elsewhere classified (2 of the 8 subjects), diabetes mellitus type II w/o mention of complication (2 of the 8 subjects), peripheral vascular disease, unspecified (1 of the 8 subjects), and other and unspecified hyperlipidemia (1 of the 8 subjects).

Concomitant Drug and Non-Drug Treatments
The most common drug treatments were drugs used in rheumatic diseases and gout (4 of the 8 subjects), vasodilators (4 of the 8 subjects), antihypertensive drugs (2 of the 8 subjects), and beta blockers (2 of the 8 subjects).

Pediatric Studies
There were two pediatric studies: A1481134 and A1481157

Study A1481134 synopsis
This was a randomized, multi-center, double blind, placebo-controlled, dose-ranging, parallel group study to be conducted in approximately 252 subjects (63 per treatment group), 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 to assess the efficacy of IV sildenafil on pulmonary hypertension during the post-operative period in children with congenital heart disease who had undergone corrective cardiac surgery. Subjects were randomized to one of four groups: sildenafil low dose, medium dose, high dose, or placebo. Three intravenous sildenafil dosage regimens were selected to achieve target sildenafil plasma concentrations of approximately 40, 120, and 360 ng/ml, respectively, for the three dosage regimens. Each intravenous sildenafil dosage regimen consisted of a bolus loading dose infused over five minutes, followed immediately by a maintenance infusion for 24 to 72 hours. After 30 minutes of

study drug infusion, additional therapy for pulmonary hypertension was to be initiated if clinically indicated based on protocol-defined rules. If the subject was judged clinically stable at 24 or more hours after randomization, the infusion was discontinued. The infusion of study drug continued for a minimum of 24 and maximum of 72 hours.

Study A1481157 synopsis

This was a seven day, open-label, multi-center study in 36 neonatal subjects with PPHN or hypoxic respiratory failure and at risk of developing PPHN. The primary objective for Part 1 of the study was to evaluate the pharmacokinetics of IV sildenafil in near term and term newborns with PPHN or with hypoxic respiratory failure and at risk for PPHN. Study drug infusion started with an IV loading dose of study medication for five minutes. Loading dose duration was changed [for Groups 2 to 6 (30 minute loading dose), Group 7 (no loading dose) and Group 8 (3 hour loading dose]. Subjects received a loading IV dose of study medication to bring the plasma concentration of sildenafil to a targeted level, followed by a maintenance infusion for the remainder of the study. The dose of study drug administered in the first two treatment groups was based on pharmacokinetic parameters of IV sildenafil in adults scaled for various neonatal body weights using allometric methods. As a conservative approach, these two groups were administered a fraction of the dose that was derived on the basis of scaling adult pharmacokinetic parameters by neonatal body weight, and targeting a plasma concentration of 40 ng/ml. Dose escalation for the subsequent treatment groups was based upon the pharmacokinetic data from the previous treatment group(s) and based on toleration by the previous group. Doses were not to be escalated if the average steady-state plasma sildenafil concentration for a treatment group was similar to the highest targeted concentration of 360 ng/ml

Demographics

Demographic data for subjects in Studies A1481134 and A1481157 are shown below.

Table 8. Demographic Characteristics of Subjects in Pediatric Studies

Characteristic	Sildenafil IV (n=48)	Placebo (n=5)
Gender, n (%)		
Male	22 (45.8)	4 (80)
Female	26 (54.2)	1 (20)
Age, Months		
Mean (SD)	3.4 (11.8)	38.8 (77.8)
Min, Max	0-77	3-178
Race, n (%)		
White	17 (35.4)	3 (60)
Black	12 (25)	--
Asian	4 (8.3)	--
Hispanic	8 (16.7)	--
Other	7 (14.6)	2 (40)
Weight (kg)		
Mean (SD)	4.3 (2.2)	15.5 (24.9)
Min, Max	2.5-15.3	3.9-60.0
Primary Diagnosis		
Primary pulmonary hypertension	44 (91.7)	5 (100)
Respiratory failure	4 (8.3)	--

Source: SCS Tables 2.1.2 and 2.2.1

There were more males than females, the ages were 3.4 months for the sildenafil group and nearly 39 months for the placebo group. There were 12 black subjects and most subjects had primary pulmonary hypertension.

Medical History

Studies A1481134 and A1481157. The most common conditions present were hypotension NOS (14 of the 53 subjects), sepsis NOS (8 of the 53 subjects), cardiac failure congestive (5 of the 53 subjects), and trisomy 21 (5 of the 53 subjects). Of the commonly reported medical conditions, sepsis was only reported in the sildenafil group.

Concomitant Drug and Non-Drug Treatments

Studies A1481134 and A1481157. The most common drug treatments were antibacterial drugs (52 of the 53 subjects), drugs used for general anesthesia (50 of the 53 subjects), sympathomimetics (49 of the 53 subjects), hypnotics, sedatives, and anxiolytics (48 of the 53 subjects), electrolyte and water replacement (43 of the 53 subjects), anticoagulants (41 of the 53 subjects), antihypertensive drugs (40 of the 53 subjects), diuretics (40 of the 53 subjects), oxygen treatment (39 of the 53 subjects), analgesics (35 of the 53 subjects), corticosteroids (32 of the 53 subjects), minerals and trace elements (28 of the 53 subjects), intravenous nutrition (26 of the 53 subjects), positive inotropic drugs (26 of the 53 subjects), ulcer-healing drugs, gastrointestinal (26 of the 53 subjects), blood preparations (23 of the 53 subjects), respiratory stimulants and surfactants (18 of the 53 subjects), and bronchodilators (17 of the 53 subjects).

Healthy Volunteer Studies

There were three healthy volunteer studies: 148-203, 148-208, and 148-215

Demographic Data

Demographic data for subjects in Studies 148-203, 148-208, and 148-215 are shown below.

Table 10. Demographic Characteristics of Healthy Volunteers in Phase 1 Studies

Characteristic	Sildenafil IV (n=26)
Gender, n (%)	
Male	26 (100)
Age, Years	
Mean	31.4
Min, Max	18-58
Race, n (%)	
White	25 (96.2)
Black	1 (3.8)
Weight (kg)	
Mean	72.6
Min, Max	59-87.4

Source: SCS Tables 2.1.1.1 and 2.1.1.2

Adverse Events

Assessment of Adverse Events

All patients who received at least one dose of study drug following randomization were included in the evaluation of adverse events. All-causality treatment emergent adverse events (those first reported during study drug treatment or reported with a greater severity compared with baseline during study drug treatment) occurring during and/or within seven days after the period of treatment specified in the applicable protocols were included in the overall assessment. Adverse events included abnormalities observed by the investigator and/or study personnel, as well as events volunteered by the patient or elicited by the investigator.

For all studies, the denominator for the incidence of an adverse event within a treatment group is the total number of patients within that treatment group evaluable for safety (i.e. received at least one dose of study drug). If a patient experienced the same 'dictionary coded' adverse event more than once (even if at different doses), the patient was counted only once in the numerator for that adverse event.
All treatment emergent adverse events were coded using the dictionary version in use at the time of each study, including the Coding Symbol Thesaurus of Adverse Reaction Terms (COSTART) and Medical Dictionary for Drug Regulatory Activities (MedDRA). Studies A1481134 (MedDRA version 8.1) and A1481157 (MedDRA version 8.0) utilized MedDRA to code treatment-emergent adverse events, while the remaining studies utilized COSTART. Differences in dictionaries may result in differences in event terms coded between the studies.

Data were not pooled for adverse events summarization due to the heterogeneous nature of the seven studies. Three of the studies were conducted in healthy volunteers, two in pediatric patients, and two in adult patients. Of the two studies in adult patients, one study included only four patients that met the criteria for the definition of PH and eight patients overall. The studies also utilized various doses and dosing regimens across the seven studies, as well as differed in terms of blinding and endpoints.

Common Adverse Events
Of the 29 adverse events that were reported by more than one subject[3], 11 were reported in the pediatric studies. Of the remaining 18 events, the most commonly reported events included:
-headache (14),
-hypotension (10),
-vasodilatation (10), and
-dizziness (6).

Dizziness was only reported in Study 148-203, after the administration of the higher doses (40 mg and 80 mg infusions).

The other events were reported in more than one IV study as follows:
-headache (3 (4.5%) subjects in A1481024, 7 (87.5%) subjects in 148-203, and 4 (33.3%) subjects in 148-208);
-hypotension (3 (4.5%) subjects in A1481024, 1 (8.3%) subject in A1481134, 6 (16.7%) subjects in A1481157);
-vasodilatation (4 (6.1%) subjects in A1481024, 5 (62.5%) subjects in 148-203, 1 (8.3%) subject in 148-208;

Other notable events reported by more than one subject receiving sildenafil IV were as follows:
-abnormal vision (1 (1.5%) subject in A1481024, 1 (12.5%) subject in 148-203;
-penile erection (1 (1.5%) subject in A1481024, 1 (33.3%) subject in 148-215;
-hemorrhage (1 (8.3%) subject in A1481134, 1 (8.3%) subject in 148-208.

The table below shows all adverse events reported by PAH patients in Study A1481024 and by patients in the oral efficacy trial 1481140.

[3] In one of the seven IV studies

Table 14. All Causality Adverse Events: A1481024 PAH Patients and Pivotal REVATIO Oral Submission Study A1481140

Body System/ Adverse Event	A1481140 (REVATIO PO Submission Study) (n=207)	A1481024 (n=35)
Eye		
Abnormal vision	--	1 (2.9%)
Chromatopsia	5 (2.4%)	1 (2.9%)
Gastrointestinal		
Diarrhea*	21 (10.1%)	1 (2.9%)
Nausea	19 (9.2%)	2 (5.7%)
Infections		
Mastitis	--	1 (2.9%)
Sepsis	--	1 (2.9%)
Musculoskeletal		
Arthralgia	11 (5.3%)	1 (2.9%)
Nervous system		
Headache	95 (45.9%)	1 (2.9%)
Psychiatric		
Abnormal dreams	--	1 (2.9%)
Reproductive		
Penile erection	--	1 (2.9%)
Vaginal hemorrhage	1 (0.5%)	1 (2.9%)
Vascular		
Hot flushes*	3 (1.4%)	1 (2.9%)
Hypotension*	7 (3.4%)	1 (2.9%)
Vasodilatation	--	2 (5.7%)

*Adverse event terms that include NOS data due to some dictionaries listing just the AE term and others listing the AE term plus NOS

Source: CSR Table 6.1.3 (A1481024; Group 1a are PAH patients); Table 6.1.3.2 (A1481140)

Of the 14 adverse events reported by PAH subject in Study A1481024, nausea and vasodilatation were each reported by two PAH patients.

Table 13, located in the attached appendices, shows adverse events reported by patients receiving sildenafil IV and by those patients in the oral efficacy trial A1481140.

Deaths

There were reports of seven subjects who died during any of the seven IV studies. This included two placebo patients and two patients that died prior to randomisation. Two of the deaths occurred in two adult patient studies and the other five deaths were in the two pediatric studies (four of those subjects were from Study A1481134, none of whom received sildenafil). All seven patients are listed below.

Table 17. Listing of Patients Who Died in Any of the 7 IV Studies

Patient Number /Study	Sex/Age/Race	Group/Dose	Day of Death	Cause of Death
00090004/ 148-301	M/70 years/W	Sildenafil/40 mg	Day 14	Postoperative death
0313-10/ A1481024	F/66 years/W	Sildenafil/34 mg	Day 40	Pneumonia
10110031/ A1481157	F/1 day/B	Sildenafil/ Unknown	Day 1	Meconium aspiration Pulmonary hypertension Birth asphyxia
10210006/ A1481134	F/11 months/UNK	Pre-Randomization	N/A	Pulmonary hypertension
10330002/ A1481134	F/15 months/UNK	Pre-Randomization	N/A	Death
10070001/ A1481134	F/6 months/W	Placebo	20	Pulmonary hypertension
10090010/ A1481134	M/14 years/W	Placebo	65	Fungal sepsis

Source: SCS Table 6.5; CSR Tables 6.5 and 6.6 (A1481134); CSR Tables 6.5 and 6.6 (A1481157)

Patient 0090004 in Study 148-301 was hospitalized 12 days after receiving study drug for an emergency coronary artery bypass operation after his disease under study worsened. He died post-operatively the next day.

Patient 0313-10 in Study A1481024 was a 66-year-old female subject who died from pneumonia 40 days post dose.

Patient 10110031 in Study A1481157 was a 25 hour old female subject who died approximately two hours after the start of study drug infusion. Approximately 30 minutes before the study drug infusion had started, she had a medical device complication (blocked endotracheal tube) caused by pulmonary secretions and a right tension pneumothorax.

Pulmonary hypertension was reported as the cause of death in three of the seven subjects (one received sildenafil, one received placebo, and one was in the prerandomization phase at the time of death).

Other Serious Adverse Events

There were 27 subjects (17 sildenafil, 4 placebo, 6 prerandomization) who reported a total of 45 serious adverse events. Most of these subjects were in the pediatric studies (12 in study A1481134 and 6 in study A1481157). There were seven subjects reporting events in study A1481024, one subject each were in study 148-215 and 148-301. Seven of the 27 subjects died during the study period.

Of the 45 serious adverse events reported, six individual adverse events were reported by more than one subject: pulmonary hypertension (4), cardiac failure (3 subjects), cardiac arrest, death, pneumothorax, and thoracic hemorrhage (2 each).

Table 18. Summary of Number of Subjects Reporting Serious Adverse Events in Sildenafil IV Studies by Treatment Group

System Organ Class	Preferred Event Term	Sildenafil	Placebo	Pre-Randomization
Cardiac disorders	Cardiac failure	2	1	--
Respiratory, thoracic and mediastinal disorders	Pneumothorax	2	--	--
Respiratory, thoracic and mediastinal disorders	Pulmonary hypertension[§]	2	1	1
Cardiac disorders	Hypertrophic cardiomyopathy	1	--	--
Cardiac disorders	Right ventricular failure	1	--	--
Congenital, familial and genetic disorders	Anomalous pulmonary venous connection	1	--	--
General disorders and administration site conditions	Death[†]	1	--	1
Infections and infestations	Bronchiolitis	1	--	--
Infections and infestations	Lower respiratory tract infection	1	--	--
Infections and infestations	Mediastinitis	1	--	--
Infections and infestations	Pneumonia[†]	1	--	--
Infections and infestations	Sepsis	1	--	--
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Bladder transitional cell carcinoma[*]	1	--	--
Respiratory, thoracic and mediastinal disorders	Apnoeic attack	1	--	--
Respiratory, thoracic and mediastinal disorders	Dyspnoea	1	--	--
Respiratory, thoracic and mediastinal disorders	Neonatal Asphyxia[†]	1	--	--
Respiratory, thoracic and mediastinal disorders	Neonatal Aspiration[†]	1	--	--
Respiratory, thoracic and mediastinal disorders	Pneumothorax spontaneous tension	1	--	--

Table 18 continued

System Organ Class	Preferred Event Term	Sildenafil	Placebo	Pre-Randomization
Respiratory, thoracic and mediastinal disorders	Pulmonary fistula	1	--	--
Surgical and medical procedures	Coronary artery bypass	1	--	--
Vascular disorders	Hypotension	1	--	--
Cardiac disorders	Cardiac arrest	--	2	--
Cardiac disorders	Left ventricular failure	--	1	--
Infections and infestations	Fungal sepsis[†]	--	1	--
Infections and infestations	Herpes zoster	--	1	--
Infections and infestations	Staphylococcal infection	--	1	--
Nervous system disorders	Convulsion	--	1	--
Renal and urinary disorders	Renal failure acute	--	1	--
Renal and urinary disorders	Renal tubular necrosis	--	1	--
Respiratory, thoracic and mediastinal disorders	Respiratory arrest	--	1	--
Respiratory, thoracic and mediastinal disorders	Respiratory failure	--	1	--
Surgical and medical procedures	Catheter placement	--	1	--
Vascular disorders	Haematoma	--	1	--
Cardiac disorders	Supraventricular tachycardia	--	--	1
Injury, poisoning and procedural complications	Sternal fracture	--	--	1
Respiratory, thoracic and mediastinal disorders	Thoracic haemorrhage	--	--	2

[*]Subject reporting this SAE was randomized to sildenafil oral, and not sildenafil IV
[†]SAEs that were reported as cause of death, and discussed in Section 2.7.4.2.1.2
[§]Three of these 4 SAEs were reported as cause of death, and are listed in Section 2.7.4.2.1.2
Source: SCS Table 6.3

Discontinuations

Overall, there were 19 subjects in the sildenafil IV groups who were discontinued from one of the seven IV trials. Of these 19, 7 subjects (37%) discontinued because of an adverse event.

Hypotension and labile blood pressure were the only events reported more than one subject (two subjects for each event).

The 19 subjects who discontinued are shown in the table below.

Table 19. Listing of Discontinuations for Subjects Receiving REVATIO IV

Study Number/Patient Number	Reason for Discontinuation
A1481024/273	AE: Nausea—considered related to treatment; occurred on Day 1, as soon as dosing started (subjects dose at AE onset was 0.163 mg) with duration of 0.83 hours
A1481024/274	AE: Hypotension—considered related to treatment; occurred on Day 1, 0.05 hours post dose (subjects dose at AE onset was 0.15 mg)
A1481024/295	SAE: Sepsis—considered not related to treatment (investigator attributed to acute bacteremia upon Swan-Ganz insertion; occurred on Day 1, 0.12 hours post dose with duration of nine days
A1481024/5	Drop in systemic blood pressure of 10% or more (defined as requiring withdrawal in the protocol); not reported as AE
A1481024/11	Due to discomfort of lying down
A1481024/15	Drop in systemic blood pressure of 10% or more (defined as requiring withdrawal in the protocol); not reported as AE
A1481024/18	Drop in systemic blood pressure of 10% or more (defined as requiring withdrawal in the protocol); not reported as AE
A1481024/29	Drop in systemic blood pressure of 10% or more (defined as requiring withdrawal in the protocol); not reported as AE
A1481024/129	Drop in systemic blood pressure of 10% or more (defined as requiring withdrawal in the protocol); not reported as AE
A1481024/133	IV pump unable to deliver drug at the required rate and the subject being uncomfortable when lying down
A1481024/139	Drop in systemic blood pressure of 10% or more (defined as requiring withdrawal in the protocol); not reported as AE
A1481024/211	Due to starting treatment with Iloprost
148-301/00090004	Death: subject died following an emergency coronary artery bypass graft operation the day before he was due for a follow-up visit
A1481134/10090018	Withdrawn due to lack of efficacy
A1481157/10030002	AE: Hypotension NOS—considered related to treatment; occurred on Day 1, 0.03 hours after the start of study drug infusion and lasted for 0.17 hours
A1481157/10050020	SAE: Anomalous pulmonary venous connection—considered not related to treatment (causality considered to be a congenital anomaly); diagnosed on Day 3 (46 hours after the start of study drug infusion) of study
A1481157/10110017	AE: Labile blood pressure—considered not related to treatment (causality considered to be an illness attributed retrospectively to hypertrophic cardiomyopathy); occurred on Day 1 of study, 0.42 hours after the start of study drug infusion and lasted for 6.08 hours
A1481157/10110021	AE: Labile blood pressure—considered related to treatment; occurred on Days 2 and 3 of study, approximately 16.75 hours after the start of study drug infusion
A1481157/10110031	Death: subject died due to meconium aspiration, pulmonary hypertension, and birth asphyxia two hours after start of study drug infusion; approximately 30 minutes prior to start of study drug infusion, subject had a blocked endotracheal tube caused by pulmonary secretions and a pneumothorax NOS

Source: CSR Section 13, Table 13 (A1481024); Table 4.2 (148-301); Section 13, Table 13 (A1481134); Section 13, Table 13 (A1481157)

Other significant adverse events

Vision

There were 4 subjects who reported vision related adverse events: abnormal vision (one subject in Study A1481024 and one subject in Study 148-203), chromatopsia and lacrimation disorder (one subject each in Study A1481024).

Bleeding Events

There were three subjects who received sildenafil IV and reported a bleeding event: two subjects reported hemorrhage (study A1481134 and study 148-208) and one subject reported vaginal hemorrhage (study A1481024). None of these adverse events was considered to be serious.

Local Tolerance
There were four subjects who received sildenafil IV and reported an infusion related adverse event: one subject reported a hematoma (coded as hemorrhage), one subject reported a hematoma on the venepuncture site, one subject experienced erythema on the infusion and venepuncture site, one subject experienced right femoral thrombosis. None of these four adverse events was assessed as serious.

Clinical Laboratory Evaluations
Adult Patient Studies
In Study A1481024, a total of 41 abnormal laboratory test result was reported by 33% (22/66) of the subjects who received sildenafil IV. The most common laboratory test abnormalities were elevated blood urea nitrogen (9 subjects), elevated total bilirubin (9), elevated monocytes (6), elevated MCV (4), elevated basophils (4), and low MCH (3). Other events were reported by one subject each. No event was considered to be clinically significant.

In Study 148-301, four subjects reported clinically significant laboratory test abnormalities: elevated GGT (2 subjects), elevated eosinophils (2), elevated MCH (1), elevated MCV (1), and elevated basophils (1).

Pediatric Studies
In Study A1481134, laboratory test abnormalities reported as adverse events included bacteria blood identified, bacterial culture positive, blood HCO3 increased, blood chloride decreased, oxygen saturation decreased, acidosis, hyperglycemia, hypoglycemia, and hypokalemia.
Two subjects reported elevated AST; one elevated AST (109 U/L) was thought to be the result of post bypass hemolysis and the other elevated AST (28 U/L) was of unknown etiology.

In Study A1481157, laboratory test abnormalities were not evaluated for abnormalities according to abnormality criteria, since there was not a standard criterion for neonates.

Healthy Volunteer Studies
There were reports of isolated abnormalities, all of which thought not to be clinically significant (I concur).

Vital Signs
Adult patients studies
In Study A1481024, subjects with PAH showed a general trend over the infusion period of a reduction in the mean absolute values of systolic blood pressure, diastolic blood pressure, and mean blood pressure (systemic mean blood pressure values in original group with nitric oxide.

No changes were observed in heart rate across the different sildenafil target plasma concentrations, regardless of whether they received nitric oxide.

In Study 148-301, there were no clinically relevant findings in median changes in vital signs or 12-lead ECGs.

Pediatric Studies
There were no observable changes in the physical examination in study A1481134. There were no clinically significant changes in vital signs, supine blood pressure and heart rate, and respiration rate in study A1481157

Healthy Volunteer Studies
In Study 148-203, data summaries showed evidence of small, transient decreases in supine systolic and diastolic blood pressure and small, transient increases in supine pulse rate following sildenafil citrate treatment. At the end of the infusion mean reductions in systolic and diastolic blood pressures were estimated by the sponsor to be between 2.5 mmHg (20mg) – 9.2 mmHg (80mg) and 2.8 mmHg (20mg) – 6.9 mmHg (40mg), respectively. Mean increases in pulse ranged between0.4 bpm (40mg) and 2.9 bpm (20mg). The ECG parameters showed no consistent changes. There were no reports of clinically significant changes in ECG findings.

In Study 148-208, slight decreases in diastolic blood pressure were seen with both IV and oral routes of administration of sildenafil. There was no obvious effect on heart rate or ECG.

Othere safety data
There is nothing suspect in the safety post marketing safety reporting, literature review, and compassionate use reports. These sections are reproduced here in their entirety as supplied by the sponsor.

Post Marketing Safety Data

REVATIO ———— Injection has not been approved for marketing in any country as of the time of this submission; therefore, no post-marketing data for this product is available. Relevant information obtained from previous post-marketing experience with other REVATIO formulations is reflected in the proposed label for the new formulation. b(4)

Although there is no post-marketing data available for REVATIO———— Injection, there is the possibility that IV preparations could be prepared from the oral formulations of sildenafil. The sponsor's database was searched for sildenafil non-clinical study cases reported through 31 July 2008 that reported a route of administration for sildenafil of intravenous or parenteral and either reported the indication as pulmonary hypertension or did not report an indication. Cases that did not report an indication for sildenafil were reviewed and were included if review suggested that sildenafil was being used for pulmonary hypertension or if the information reported was insufficient to determine the indication for sildenafil. The database search identified three non-clinical study sildenafil cases that reported an intravenous route of administration (these are expected to be intravenous formulations prepared by the prescriber/patient starting from the oral finished drug formulation). Two of these three cases specifically reported an indication of pulmonary hypertension, while in the remaining case insufficient information was reported to determine the indication of sildenafil. A summary of these cases is provided below. b(4)

Case 2004005766 was a case report of severe retinopathy of prematurity (ROP) in a preterm infant who was treated with intravenous sildenafil for severe respiratory failure. This case report was from a letter in *Br J Ophthalmol 2004;* 88 (2):306-7 and involved a male patient who was born at 26 weeks gestation, weighing 525 g. He was ventilated from birth for respiratory insufficiency, secondary to respiratory distress syndrome. He required high flow oxygen ventilation and received surfactant at delivery and 16 hours later. His oxygen requirements then stabilized at 30-50%. At 29 weeks his oxygen requirements increased to 100% due to coagulase negative *Staphylococcus aureus* and candida sepsis. He was treated with ambisome and 5-flucytosine. However, he was only able to maintain oxygen saturations of 70-80% while receiving positive pressure ventilation on 80-90% oxygen. At 31 weeks +2 days post-conception he was commenced on inhaled nitric oxide (NO) 5-40 ppm. There was no demonstrable improvement in oxygenation and it was decided to start sildenafil 3 days later in addition to the NO. During the period of treatment with sildenafil, there was an improvement in his clinical condition, with his oxygen requirements falling to 30-40% by 33 weeks. A subphrenic collection was discovered at 33 weeks, and ciprofloxacin and metronidazole were started. At 34 weeks he was found to dilate poorly, to have bilateral iris neovascularisation, hazy media, and dilated and tortuous fundal vessels. He was treated the following day with bilateral peripheral laser photocoagulation to ischaemic retina. The ROP regressed over the ensuing weeks and he remains under review. Sildenafil was discontinued at 34 weeks of life, after 16 days of treatment, because of a rising alanine aminotransferase level. There was no rebound hypoxia observed. Other than intrauterine growth retardation, no further risk factors for ROP such as intraventricular haemorrhage were identified. The patient had been examined by an ophthalmologist weekly from 31 weeks and no ROP was seen up to and including the 33 week check.

Case 2004107759 was spontaneously reported by a pharmacist, who reported that a child (age and gender unspecified) experienced a lack of efficacy while receiving VIAGRA (sildenafil) taken for the treatment of pulmonary hypertension. The medication was administered intravenously (unknown dose). The reporter stated that the drug was not indicated for pediatric pulmonary hypertension or for intravenous administration. No further information was reported.

Case 2003029835 was spontaneously reported by a physician, who reported that he prescribed a male patient (age unknown) VIAGRA tablets. The patient dissolved the tablets (quantity unknown) and injected this solution IV. The patient suffered from necrosis, and no further information was reported.

Two of these cases specifically reported that the indication was pulmonary hypertension, and involved use of sildenafil IV in a premature neonate and a child of unknown age. The case involving the neonate reported events of retinopathy of prematurity, alanine aminotransferase increased, and subphrenic collection, while the case involving the child reported lack of efficacy, although the duration of sildenafil therapy was not reported. In the remaining case, the indication for sildenafil could not be determined upon review and involved the patient dissolving sildenafil tablets and injecting the solution that he prepared. None of these three cases involved a commercial formulation of sildenafil IV prepared by the MAH.

Literature Review

A literature search for studies involving intravenous sildenafil was performed. The studies identified involved a variety of patients with pulmonary hypertension who have been treated with IV sildenafil. Most of the studies were small and uncontrolled, and the majority of studies used short infusions ranging from 0.025 mg/kg over 10 minutes to 0.3 mg/kg/min for 14 days in infants and 300 mcg over 6 minutes to 60 mg over an hour in adults. A study in COPD used two bolus administrations of 12.5 and 37.5 mg 20 minutes apart. There were no clinically important effects on the change in systemic blood pressure or adverse events suggestive of hypotension. There is very little published data on the IV administration of sildenafil in adult patients with PAH; however, the data published thus far in these and other PH populations would support the safety and efficacy of this formulation.

Compassionate Use

Clinicians have requested the supply of compassionate intravenous sildenafil for the management of patients with pulmonary hypertension where, in the physician's opinion, there has been no alternative therapy available to treat these patients. Intravenous sildenafil has been supplied to the following patients listed in Table 20, however, many of these cases would be outside of the indication currently proposed for intravenous REVATIO.

Table 20. Compassionate Supply of Intravenous Sildenafil

Patient	Indication	Country	Date Supplied	
Infant D.O.B	Pulmonary hypertension	United Kingdom		b(6)
Infant D.O.B	Pulmonary hypertension Pulmonary Hypoplasia	United Kingdom		
Infant D.O.B	Pulmonary hypertension	United Kingdom		b(6)
Infant D.O.B	Pulmonary hypertension CHD Post cardiac surgery	Philippines		
41 yr old male	PH post cardiac surgery Malabsorption	United Kingdom		b(6)
77 yr old male	PH post cardiac surgery Malabsorption	United Kingdom		
39 yr old female	PAH Pregnant - planned Caesarian Section	United Kingdom		b(6)

Table 20 continued

Patient	Indication	Country	Date Supplied
24 yr old female	PAH Pregnant - planned Caesarian Section	United Kingdom	
Infant D.O.B	Pulmonary hypertension	United Kingdom	
28 yr old female	PAH Pregnant - planned Caesarian Section	United Kingdom	
Infant D.O.B	PH Diaphragmatic hernia	United Kingdom	
27 yr old female	PAH Termination of preganancy	United Kingdom	
58 yr old male	PH Post heart transplant Malabsorption	United Kingdom	
56 yr old female	PH Post heart transplant Malabsorption	United Kingdom	
75 yr old male	PH Post cardiac surgery Malabsorption	United Kingdom	

b(6)

b(6)

b(6)

b(6)

Financial Disclosure

There are 7 studies submitted in defense of NDA #22473.

Financial disclosure was submitted previously for the original NDA #21845.

Subjects who participated in study A128-208 were employees of Pfizer, and therefore, certification for this study was not required.

For the 3 studies (A148-203, -215, -301) that had an end date plus one year prior to 2-2-1999, equity interests information was not compiled. The sponsor states that these "studies were not funded via variable compensation and none of the investigators in the studies holds any form of propriety interest in Revatio.

For the 2 studies started after 2-2-1999, 21 of the 258 investigators had financial information to disclose: b(6)

"19 investigators have significant payments of other sorts greater than 525K and 2 investigators disclosed equity greater than 550K. One investigator participated in both studies and and had significant payments of other sorts. signed a financial disclosure form for but could not be located to complete a financial disclosure form for even after Pfizer conducted due diligence process. Therefore is listed as due diligence on the 3454 for and also on two 3455's for b(6) b(6)

———— and ———— to reflect payments of other sorts. This information is listed in the 3455 Forms in Module 1, Section 1.3.4. b(6)

The individual investigators listed on the two covered studies identified in group 2 were sent the Financial Disclosure Form directly or via the principal investigator for their center. In addition, if necessary, we contacted the center by telephone and/or sent 2 separate follow-up letters to those individuals who did not return the Financial Disclosure Form. Although Pfizer was unable to obtain financial disclosure information specific to Equity in Pfizer for 22 of the investigators, Pfizer has examined its financial data regarding the other categories of financial arrangements including significant payments of other sorts for all investigators. Additionally, all investigators are contacted at the time of the submission to remind them of the obligation to disclose financial information for Pfizer Inc and affiliated companies, including Warner-Lambert, Agouron, Pharmacia, Pharmacia & Upjohn, Searle/Monsanto and Sugen, which are wholly owned by Pfizer."

The sponsor outlined the steps taken to minimize the potential for bias in module 1.3.4.

120-day Safety Update

Because the pivotal and supportive studies for this application were all complete at the time of the NDA submission with no further pertinent data becoming available during the review period, we (FDA and Pfizer) agreed that a 4 month safety update would not provide any new meaningful data relevant to the application, and a waiver to CFR 314.50(d)(5)(vi)b was granted in the correspondence dated Sep 22, 2008.

Appendices

Table 4. Exclusion Criteria for Adult Patient Studies (A1481024 and 148-301)

CRITERIA COMMON TO BOTH STUDIES
Subjects who were hepatitis B surface antigen positive
Intended donation of blood or blood products during the study or for one month prior to and after the study
Treatment with any experimental drug during the three months prior to the study

CRITERIA UNIQUE TO STUDY	
A1481024	**148-301**
Subjects who had any clinically significant abnormalities following the review of the screening physical examination, ECG or safety laboratory test results. Abnormalities of doubtful significance were discussed with a Pfizer clinician prior to inclusion of that subject	Evidence of any clinically significant diseases other than ischaemic heart diseases or hyperlipidaemia; Patients with any clinically significant abnormality following review of pre-study laboratory data and full physical examination other than related to ischaemic heart disease or hyperlipidaemia. All laboratory tests outside the normal range but of dubious clinical significance will be discussed with the Sponsor's Project Manager.
Any form of alcohol abuse (regularly drink more than 28 units of alcohol per week) and/or any other drug abuse	Any form of alcohol abuse (more than 21 units of alcohol per week (males) or 14 units of alcohol per week (females)
Subjects who had bleeding diathesis or a recent clinical bleeding episode	Personal history of bleeding disorder or migraine
Subjects who had haemodynamic instability or low blood pressure (systolic arterial pressure <95 mmHg)	Patients with a supine diastolic blood pressure of greater than 105 mmHg or a supine systolic blood pressure of less than 95 mmHg at screen
Subjects who had a history of stroke, myocardial infarction or life threatening arrhythmia within the last six months	Patients with a history of stroke; Patients who, within the previous 12 weeks, have undergone coronary bypass surgery or had a myocardial infarction, cerebrovascular accident, or unstable angina; Patients with a history of recurrent and significant cardiac dysrhythmia
Subjects who had severe cardiac failure (NYHA IV classification) or unstable angina within the last six months	Patients who would be unable to use a supine bicycle
Subjects who had impairment of renal or hepatic function or hematological abnormalities, which were greater than three times the upper limit of normal	Females of childbearing potential
Subjects who were prescribed and/or taking nitrates or nitric oxide donors in any form (i.e. oral, sublingual, buccal, transdermal, inhalational or aerosols). These subjects could partake if the nitrates/nitric oxide donors were stopped 48 hours prior to receiving study drug treatment except for sublingual short acting GTN that was allowed two hours prior to catheterisation	Patients who, in the opinion of the investigator, cannot be withdrawn from betablockers, ACE inhibitors, long acting nitrates, diuretics or calcium channel blockers for 48 hours
Subjects who had known hereditary degenerative retinal disorders such as retinitis pigmentosa	History of clinically significant asthma or previous hypersensitivity to any drug
Subjects who had previously participated in any other clinical trial with the study drug (i.e. who were randomised to receive active or double blind treatment) or had been administered the commercially available sildenafil (VIAGRA) tablet	--
Subjects who were on alpha blockers, potent cytochrome P450 3A4 inhibitors (e.g. erythromycin, ketoconazole, itraconazole and protease inhibitors)	--

Table 7. Exclusion Criteria for Pediatric Studies (A1481134 and A1481157)

A1481134	A1481157
Current use of post-operative measures intended for prophylaxis or treatment against pulmonary hypertension as specified in the protocol.	Prior or immediate need for cardiopulmonary resuscitation or ECMO
The occurrence of post-operative complications that resulted in hypoxemia (other than pulmonary hypertension) due to lung disease.	Profound hypoxemia: PaO2 < 30 mmHg on any ABG drawn within 30 minutes of starting study drug infusion
Serious post-operative bleeding resulting in hypotension.	Hypotension (mean arterial pressure < 35 mmHg) or shock any time during screening
Receipt of concomitant medication specified in the protocol such as nitrates or nitric oxide donors, open-label sildenafil within 48 hours prior to surgery or anytime post-operatively, supplemental arginine; long acting alpha-blockers, endothelin antagonists (eg, bosentan); potent cytochrome P450 3A4 inhibitors, Ritonavir or Nicorandil. Therapies that were prohibited at the time of entry into the study, when used specifically for prophylaxis or treatment of pulmonary hypertension include: • Agents used at relatively high doses for the purpose of deep/heavy sedation, such as fentanyl • Agents used for continued paralysis, such as pancuronium (except when used to manage clinical situations such as open chest or critical airway) • Alkalinisation by methods such as hyperventilation (pCO2<30 mm Hg) or bicarbonate (HCO3) infusion • Vasodilators; nitric oxide and extracorporeal membrane oxygenation (ECMO)	Receipt of any prohibited concurrent medication/therapy at any time prior to randomisation: Potent cytochrome P450 3A4 inhibitors (eg erythromycin, ketoconazole, itraconazole, and protease inhibitors); Ritonavir or Nicorandil; endothelin antagonists (eg bosentan); nitrates or NO donors in any form, except the prior or concurrent use of iNO. A subject was eligible if nitroprusside was used, only if it was discontinued at least two hours prior to study drug infusion; Vasodilators [eg alpha blocker, magnesium sulfate, calcium channel blockers, other phosphodiesterase inhibitors, prostacyclins, etc] This excluded milrinone, which was allowed during the study as concurrent therapy; Supplemental arginine administered for the purpose of improving NO-dependent vasodilation. Maintenance quantities in total parenteral nutrition were allowed; Open-label sildenafil other than study drug
Impairment of renal function (serum creatinine >2.5 upper limit of normal (ULN)) or hepatic function (alanine transaminase (ALT) or aspartate transaminase (AST) >3.0 ULN), Conjugated bilirubin >2.0 ULN; Total bilirubin >2.0 ULN; Leukopenia (WBC <2500/μL).	Impairment of renal function [serum creatinine > 2.5 x upper limit of normal (ULN)], hepatic function (ALT or AST > 3 x ULN or conjugated bilirubin > 2 x ULN), or haematological abnormalities: Severe anaemia [haemoglobin < 9 g/dl], thrombocytopenia (platelets < 50,000 cells/ul), or leucopenia (white blood cells < 2,500 cells/ul) at the screening examination
Known hereditary degenerative retinal disorders such as retinitis pigmentosa	Known hereditary degenerative retinal disorders such as retinitis pigmentosa
Any form of alcohol abuse and/or any other drug/substance abuse within the past year, or symptoms of drug or alcohol-related withdrawal in the neonate	Symptoms of drug or alcohol related withdrawal
--	Low pulmonary vascular resistance as evidenced by large left to right intracardiac or ductal shunting based on the screening echocardiogram
--	Life threatening or lethal congenital anomaly
--	Congenital heart disease exclusive of interatrial communication or patent ductus arteriosus
--	Lung hypoplasia syndromes diagnosed on the basis of prolonged oligohydramnios or hydrops fetalis
--	Congenital diaphragmatic hernia
--	Active seizures (within 12 hours of study drug infusion)
--	Apgar score of <3 at five minutes after birth
--	Bleeding diathesis

Table 13. All Causality Common Adverse Events (All Adverse Events Reported by Patients Receiving Sildenafil IV) by Body System: IV Studies and Pivotal REVATIO Oral Submission Study

Body System/ Adverse Event	A1481140 (REVATIO PO Submission Study) (n=207)	A1481024 (n=66)	148-301 (n=8)	A1481134 (n=12)	A1481157 (n=36)	148-203[1] (n=8)	148-208 (n=12)	148-215 (n=3)
Blood								
Thrombocytopenia	--	--	--	--	1 (2.8%)	--	--	--
Cardiac								
Bradycardia*	--	--	--	1 (8.3%)	1 (2.8%)	--	--	--
Nodal arrhythmia	--	--	--	1 (8.3%)	--	--	--	--
Congenital								
Anomalous pulmonary venous connection	--	--	--	--	1 (2.8%)	--	--	--
Congenital ventricular septal defect	--	--	--	--	1 (2.8%)	--	--	--
Patent ductus arteriosus	--	--	--	--	1 (2.8%)	--	--	--
Ear								
Tinnitus	1 (0.5%)	--	--	--	--	1 (12.5%)	--	--
Vertigo	6 (2.9%)	1 (1.5%)	--	--	--	--	--	--
Eye								
Abnormal vision	--	1 (1.5%)	--	--	--	1 (12.5%)	--	--
Chromatopsia	5 (2.4%)	1 (1.5%)	--	--	--	--	--	--
Lacrimation disorder	--	1 (1.5%)	--	--	--	--	--	--

Body System/ Adverse Event	A1481140 (REVATIO PO Submission Study) (n=207)	A1481024 (n=66)	148-301 (n=8)	A1481134 (n=12)	A1481157 (n=36)	148-203[1] (n=8)	148-208 (n=12)	148-215 (n=3)
Gastrointestinal								
Abdominal pain*	11 (5.3%)	1 (1.5%)	--	--	--	--	--	--
Constipation	4 (1.9%)	--	--	1 (8.3%)	--	--	--	--
Diarrhea*	21 (10.1%)	1 (1.5%)	--	--	--	--	--	--
Dry mouth	1 (0.5%)	1 (1.5%)	--	--	--	--	--	--
Ileus paralytic	--	--	--	--	1 (2.8%)	--	--	--
Nausea	19 (9.2%)	2 (3.0%)	--	--	--	--	--	1 (33.3%)
Rectal disorder	--	--	--	--	--	--	--	1 (33.3%)
General								
Appl./inj./incision/ insertion site reaction	--	--	--	--	--	--	1 (8.3%)	--
Appl./inj./incision/ insertion/device complication	--	--	--	--	--	--	1 (8.3%)	--
Chills	--	--	--	--	--	1 (12.5%)	--	--
Drug withdrawal syndrome	1 (0.5%)	--	--	1 (8.3%)	2 (5.6%)	--	--	--
Feeling jittery	1 (0.5%)	--	--	--	1 (2.8%)	--	--	--
Oedema*	1 (0.5%)	--	--	1 (8.3%)	2 (5.6%)	--	--	--
Peripheral swelling	--	--	--	--	1 (2.8%)	--	--	--
Procedure (Medical/Surgical/ Health Service)	--	1 (1.5%)	--	--	--	--	--	--

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Pyrexia	13 (6.3%)	--	--	3 (25.0%)	--	--	--	--
Hepatobiliary								
Hyperbilirubinaemia	--	--	--	--	3 (8.3%)	--	--	--
Infections								
Bronchial infection	1 (0.5%)	--	--	1 (8.3%)	--	--	--	--
Gastroenteritis[1]	5 (2.4%)	--	--	--	--	--	1 (8.3%)	--
Mastitis	--	1 (1.5%)	--	--	--	--	--	--
Pharyngitis	3 (1.4%)	--	--	--	--	1 (12.5%)	2 (16.7%)	--
Rhinitis[1]	6 (2.9%)	--	--	--	--	3 (37.5%)	1 (8.3%)	--
Sepsis	--	1 (1.5%)	--	--	--	--	--	--
Urinary tract infection[1]	3 (1.4%)	1 (1.5%)	--	--	--	--	--	--
Injury								
Collapse of lung	--	--	--	--	1 (2.8%)	--	--	--
Investigations								
AST increased	2 (1.0%)	--	--	1 (8.3%)	--	--	--	--
Bacteria blood identified	--	--	--	1 (8.3%)	--	--	--	--
Bacterial culture positive	--	--	--	1 (8.3%)	--	--	--	--
Blood bicarbonate increased	--	--	--	1 (8.3%)	--	--	--	--
Blood chloride decreased	--	--	--	1 (8.3%)	--	--	--	--

Body System/ Adverse Event	A1481140 (REVATIO PO Submission Study) (n=207)	A1481024 (n=66)	148-301 (n=8)	A1481134 (n=12)	A1481157 (n=36)	148-203[1] (n=8)	148-208 (n=12)	148-215 (n=3)
Body temperature increased	1 (0.5%)	--	--	--	1 (2.8%)	--	--	--
Cardiac murmur NOS	1 (0.5%)	--	--	--	1 (2.8%)	--	--	--
Oxygen saturation decreased	1 (0.5%)	--	--	1 (8.3%)	1 (2.8%)	--	--	--
Weight gain	--	2 (3.0%)	--	--	--	--	--	--
White blood cell count increased	1 (0.5%)	--	--	--	1 (2.8%)	--	--	--
Metabolism								
Acidosis	--	--	--	1 (8.3%)	--	--	--	--
Hyperglycaemia NOS	--	--	--	--	1 (2.8%)	--	--	--
Hypokalaemia	2 (1.0%)	--	--	1 (8.3%)	1 (2.8%)	--	--	--
Musculoskeletal								
Arthralgia	11 (5.3%)	2 (3.0%)	--	--	--	1 (12.5%)	--	--
Back pain	24 (11.6%)	--	1 (12.5%)	--	--	--	--	1 (33.3%)
Myalgia	19 (9.2%)	2 (3.0%)	--	--	--	--	--	--
Nervous system								
Convulsions NOS	--	--	--	--	1 (2.8%)	--	--	--
Dizziness	26 (12.6%)	--	--	--	--	6 (75.0%)	--	--
Headache	95 (45.9%)	3 (4.5%)	--	--	--	7 (87.5%)	4 (33.3%)	--
Hypoaesthesia	3 (1.4%)	1 (1.5%)	--	--	--	--	--	--

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Body System/ Adverse Event	A1481140 (REVATIO PO Submission Study) (n=207)	A1481024 (n=66)	148-301 (n=8)	A1481134 (n=12)	A1481157 (n=36)	148-203[1] (n=8)	148-208 (n=12)	148-215 (n=3)
Psychiatric								
Abnormal dreams	--	1 (1.5%)	--	--	--	--	--	--
Euphoria	--	--	--	--	--	1 (12.5%)	--	--
Renal								
Anuria	--	--	--	1 (8.3%)	--	--	--	--
Urinary frequency	--	--	--	--	--	1 (12.5%)	--	--
Reproductive								
Penile erection	--	1 (1.5%)	--	--	--	--	--	1 (33.3%)
Vaginal hemorrhage	1 (0.5%)	1 (1.5%)	--	--	--	--	--	--
Respiratory								
Apnoeic attack	--	--	--	1 (8.3%)	--	--	--	--
Atelectasis	--	--	--	1 (8.3%)	1 (2.8%)	--	--	--
Cough increased	--	--	--	--	--	2 (25.0%)	--	--
Dyspnoea*	9 (4.3%)	1 (1.5%)	--	--	--	--	--	--
Laryngeal oedema	--	--	--	--	1 (2.8%)	--	--	--
Lung disorder NOS	--	--	--	--	1 (2.8%)	--	--	--
Lung infiltration NOS	--	--	--	--	1 (2.8%)	--	--	--
Pleural effusion	--	--	--	1 (8.3%)	--	--	--	--
Pneumothorax NOS	--	--	--	--	2 (5.6%)	--	--	--
Pulmonary hypertension	--	--	--	2 (16.7%)	--	--	--	--
Respiratory disorder*	1 (0.5%)	1 (1.5%)	--	--	--	1 (12.5%)	--	--

Body System/ Adverse Event	A1481140 (REVATIO PO Submission Study) (n=207)	A1481024 (n=66)	148-301 (n=8)	A1481134 (n=12)	A1481157 (n=36)	148-203[1] (n=8)	148-208 (n=12)	148-215 (n=3)
Stridor	--	--	--	1 (8.3%)	--	--	--	--
Skin								
Decubitus ulcer	--	--	--	--	1 (2.8%)	--	--	--
Pruritus	9 (4.3%)	1 (1.5%)	--	--	--	--	--	--
Rash*	7 (3.4%)	--	--	1 (8.3%)	--	1 (12.5%)	--	--
Vascular								
Arterial thrombosis limb	--	--	--	1 (8.3%)	--	--	--	--
Haemorrhage	--	--	--	1 (8.3%)	--	--	1 (8.3%)	--
Hot flushes*	3 (1.4%)	1 (1.5%)	--	--	--	--	--	--
Hypertension NOS	--	--	--	--	1 (2.8%)	--	--	--
Hypotension*	7 (3.4%)	3 (4.5%)	--	1 (8.3%)	6 (16.7%)	--	--	--
Hypotension aggravated	--	--	--	--	1 (2.8%)	--	--	--
Labile blood pressure	--	--	--	--	2 (5.6%)	--	--	--
Postural hypotension	--	--	--	--	--	2 (25.0%)	--	--
Thrombophlebitis	1 (0.5%)	--	--	--	1 (2.8%)	--	--	--
Vasodilatation	--	4 (6.1%)	--	--	--	5 (62.5%)	1 (8.3%)	--

*Adverse event terms that include NOS data due to some dictionaries listing just the AE term and others listing the AE term plus NOS
[1]148-203 incidence rates were calculated by reviewing individual subjects and AEs, as each patient received multiple doses, and AEs reported based on dose; n for each AE is unique patients experiencing the AE (if patient experienced same AE at multiple doses it was only counted once)
Source: CSR Table 6.1.3.2 (A1481140); SCS Table 2.1.3 for number of patients that received sildenafil IV and CSR Table 6.1.3 for events (A1481024); CSR Table 6.3 (148-301); 6.1.3 (A1481134); 6.1.3 (A1481157); Appendix V, Table 7 (148-203); 6.3 (148-208); 6.3 (148-215)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22473	ORIG-1	PFIZER INC	REVATIO

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/s/

MARYANN GORDON
10/28/2009

SHARI L TARGUM
10/28/2009