CLINICAL PROTOCOL

A MULTINATIONAL, MULTICENTER STUDY TO ASSESS THE EFFECTS OF ORAL SILDENAFIL ON MORTALITY IN ADULTS WITH PULMONARY ARTERIAL HYPERTENSION (PAH)

Compound:	UK 092480
Compound Name:	Sildenafil citrate
US IND Number:	IND CCI
European Clinical Trial Database (EudraCT) Number:	2013-004362-34
Protocol Number:	A1481324
Phase:	3B/4

Document History

Document	Version Date	Summary of Changes
Original protocol	25-Sep-2013	N/A
Amendment 1	18-Nov-2014	Incorporate revisions previously implemented as Administrative Letters. Clarification of secondary endpoint assessment for progression of disease. Clarification of inclusion/exclusion criteria. Permit short term PDE5I use prior to enrollment. Allow temporary discontinuation (up to 14 days) of study treatment to permit temporary treatment with prohibited medications for comorbidities. Addition of riociguat as a prohibited medication. Implementation of multiple country regulatory agency requests. Incorporated updated company template adverse event and publication language. Correction of inconsistencies and typographical errors.
Amendment 2	28 August 2020	Added Appendix 6: To ensure continuity of treatment with sildenafil for subjects in Ukraine, Russia, Czech Republic, Bosnia and Herzegovina, and Mexico, until they can transition to a program that will provide access to prescription sildenafil at the time of the End of Treatment study visit; To increase, in a blinded manner, the dose for subjects receiving 5 mg (TID) to 20 mg (TID), the approved dose in these 5 countries.

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

PROTOCOL SUMMARY

BACKGROUND

In the US, sildenafil was approved for the treatment of adult PAH to improve exercise capacity in June 2005. Subsequently, it was approved in the US to delay clinical worsening in adult patients with PAH (WHO Group 1). In Europe, it was approved in 2005 (EU/1/05/318/001) for the treatment of adult patients with PAH, classified as World Health Organization (WHO) Functional Class (FC) II and III, to improve exercise capacity. The indication in Europe also states that efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease. To date, Revatio® tablets have been approved for use in more than 50 countries and are currently marketed in 49 countries.

Like other PAH-targeted drugs, sildenafil was approved for use in adults based on short-term studies with improvement in exercise capacity as the primary endpoint. In these studies, no greater efficacy was achieved in the primary endpoint with the use of higher doses. Therefore, treatment with doses higher than 20 mg TID is not recommended in current US labeling. Although there are considerable data in adults at doses up to 80 mg TID from long-term, open-label extension studies, there are no long-term controlled data and the effect of sildenafil on the risk of death is unknown.

Sildenafil was approved in the European Union (EU) in May 2011 for the treatment of PAH in pediatric patients (aged 1-17 years). The data to support this application were submitted in variation number EMEA/H/C/638/II/028. Subsequently, Pfizer updated the Summary of Product Characteristics (SmPC) in the EU in September 2011 to include pediatric mortality data to reinforce the dosing recommendations for this population, and to introduce a warning that higher than recommended doses should not be used in pediatric patients with PAH.

Pfizer submitted the Revatio Oral Suspension New Drug Application (NDA) to the Food and Drug Administration (FDA) for the pediatric indication in November 2011.
On 30 August 2012, the FDA approved the NDA for the oral suspension, but did not approve the pediatric PAH indication for Revatio. The FDA has introduced the following warning in the United States Package Insert (USPI): “In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing Revatio dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of Revatio, particularly chronic use, is not recommended in children.” FDA also issued a Drug Safety Communication (DSC) which includes a description of this information from the revised Revatio USPI. A DSC is a specific tool used by the FDA to communicate important information to the public about safety issues, including emerging safety information, about marketed drugs. As a consequence of the finding of a dose-related increase in mortality in pediatric patients with PAH, FDA has asked Pfizer to evaluate the effect of sildenafil on the risk of death in adults with PAH at three dose levels, namely 5 mg, 20 mg and 80 mg TID.

Dose regimens for this trial will be 5 mg, 20 mg and 80 mg TID. The rationale for inclusion of the 5 mg dose in this trial is that the minimum effective dose of sildenafil in adults with PAH is not known. Therefore, it is important to evaluate whether doses lower than 20 mg TID might be similarly effective and relatively safer than the current recommended dose of 20 mg TID when used for the long-term treatment of adult PAH. The rationale for inclusion of the 80 mg TID dose is that, while the current US label does not recommend sildenafil at doses above 20 mg TID, it is known from prescribing practices that some adult patients with PAH are prescribed doses up to 80 mg TID. Therefore, it is important to determine whether the use of doses higher than the approved dose might be less safe than the current recommended dose.

This study will evaluate the relative effects of sildenafil on mortality when administered at the three doses indicated above in adults with PAH. In addition, the relative effects on clinical worsening and 6-minute walking distance (6MWD) will also be assessed.

This is a randomized, double-blind, parallel-group study. Adult subjects with PAH will be randomly assigned 1:1:1 to one of three dosage groups (5 mg, 20 mg and 80 mg TID) and stratified according to PAH treatment at entry (PAH-treatment naïve vs. on PAH-treatment) and etiology of PAH (idiopathic vs. secondary to CTD/surgical repair).

PRIMARY OBJECTIVE

Test for the non-inferiority of sildenafil 80 mg TID vs. 5 mg TID for mortality; mortality rate with the 80 mg TID dose is no worse than doubling the mortality rate for the 5 mg TID dose.

ENDPOINTS

Primary Efficacy Endpoint:

- Time to death (Mortality).

Secondary Efficacy Endpoints:

- Time to first event (Clinical Worsening); and
- 6MWD at Months 6 and 12.

Clinical worsening for the purpose of this study is defined as:

- All-cause mortality;
- Hospital stay for worsening PAH (including but not limited to right heart failure [RHF], initiation of prostanoids, lung transplantation, or septostomy); or

- Disease progression (defined as a reduction from baseline in the 6MWD test by at least 15% and worsening functional class from baseline, both confirmed by a 2nd test/evaluation within 2 weeks (cannot be performed on same day). Patients with functional class IV at baseline only need to meet the 6MWD criteria as they cannot have deterioration in functional class. The date of the event will be the first date of the two 6MWTs.

STUDY DESIGN

This is a randomized, double-blind, parallel-group study in adult patients with PAH that is designed to assess mortality during long-term treatment with sildenafil at three doses. Four hundred and twenty-nine (429) subjects will be enrolled to allow approximately 143 subjects to be randomly assigned to each arm. Approximately 80-120 sites with experience conducting PAH trials will participate in the study.

STUDY TREATMENTS

Subjects will be randomly assigned on a 1:1:1 basis to either blinded sildenafil 5 mg (TID), 20 mg (TID) or 80 mg (TID) at the Baseline visit (Day 1) after successfully fulfilling all inclusion and exclusion criteria. Randomization will be stratified according to PAH treatment at entry (PAH-treatment naïve vs. on PAH-treatment) and etiology of PAH (idiopathic vs. secondary to CTD/surgical repair). Blinded sildenafil treatment is to continue for the duration of the subject's participation in the study. Subjects who discontinue from the trial will continue to be followed for the primary endpoint.

No long term treatment with PDE-5 inhibitors or *treatment with* bosentan or riociquat will be permitted at study entry. Background treatment with endothelin receptor antagonists (ETRAs) other than bosentan (ie, ambrisentan and any other ETRA that becomes available during the conduct of the study provided that the new agent is not a potent CYP3A inducer or inhibitor (Appendix 1) and does not have any clinically evident drug-drug interaction with sildenafil) and/or prostanoids will be allowed and is to be continued during the study. Add-on treatment specific for PAH with drug classes other than PDE-5 inhibitors (ie, ETRAs as described above, oral, inhaled or subcutaneous (SC) prostanoids, or IV epoprostenol) will be permitted as needed for clinical worsening during the trial. Any other novel agents that are approved for use in adult PAH and become available during the course of the study will be permitted as long as they don't have any clinically evident drug-drug interactions and are in the opinion of the investigator are safe when co-administered with sildenafil. Subjects who receive treatment with bosentan or riociguat will be discontinued from study treatment, but followed for survival through the end of the study. While add-on treatment in accordance with subject need is allowed, it will be discouraged until after the assessment of 6MWD at Month 12 provided that this is consistent with the best interest of the subject. Supportive non-PAH-specific treatment (eg, oxygen, digoxin, diuretics and inotropes) will be permitted at any time during the study.

Sample Size Determination

A total of 429 subjects will be randomly assigned to the sildenafil 5 mg TID, 20 mg TID and 80 mg TID treatment groups with approximately143 subjects in each treatment group.

This non-inferiority study is powered at 90% to test the following hypotheses at an overall significance level of 0.025 (1-sided):

- H_0: hazard ratio (80 mg TID /5 mg TID) >=2;
- H_1: hazard ratio (80 mg TID /5 mg TID) <2.

The sample size of the study is calculated based on the following assumptions:

- Equal mortality rate of 15% at 2-years for each arm;
- Accrual rate of 100 subjects/year;
- Two interim analyses with O'Brien-Fleming approach possibly rejecting H_0 or H_1;
- Estimated 20% drop-out rate (including lost to follow-up).

With the estimated recruitment rate, the study is expected to complete enrollment in about 4.3 years with a total duration of about 7.7 years to reach the required number of events (143 deaths).

Statistical Analysis for Primary Endpoint

The primary efficacy analysis will be conducted using the intent-to-treat (ITT) population. All events occurring up until the end of the trial, including events observed from discontinued patients, will be included in the primary efficacy analysis. The efficacy analyses will also be conducted using the per-protocol (PP) population as sensitivity analyses.

Treatment comparison will be conducted using Cox proportional hazard regression model stratified by PAH treatment at entry of the study (PAH-treatment naïve vs. on PAH treatment) and etiology of PAH (idiopathic vs. secondary to CTD/surgical repair). If the 1-sided upper confidence limit of the hazard ratio (80 mg TID/5 mg TID) is less than 2, then the null hypothesis that the mortality rate in the 80 mg is worse than double the rate in 5 mg will be rejected. In the event that the hazard ratio is statistically significantly less than 1, then superiority of 80 mg TID over 5 mg TID will be claimed.

Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Methods

Not applicable for this study.

SCHEDULE OF ACTIVITIES

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

Protocol Activity	**Screen**	**Day 1**	**Wk 2**	**Mo 3, 9**	**Mo 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96 followed by every 6 months until the end of study treatment**	**Mo 15, 21, 27, 33, 39, 45, 51, 57, 63, 69, 75, 81, 87, 93, 99 followed by every 6 months until end of study treatment[h]**	**End of Treat-ment**	**Follow-Up Check (28 days)**
Visit Window	Day -21 to Day -1		± 3 days	±10 days	±10 days	±10 days	± 7 days	± 7 days
Informed consent	X							
Inclusion/Exclusion Criteria	X	X						
Randomization		X						
Demography (including ethnicity, race, weight, height, smoking & alcohol classification)	X							
Primary Diagnosis	X							
Medical History (including drug allergies)	X							
Physical Examination[a]	X	X	X	X	X		X	
WHO Functional Classification[b]	X			X	X		X	
Lung Function Test[c]	X							
Vital Signs (blood pressure and pulse after sitting for 5 minutes)	X	X	X	X	X		X	
12-Lead Electrocardiogram (ECG)[d]	X							
Chest X-Ray (CXR) [f]	X							
Safety Laboratory Tests	X			X	X		X	

Protocol Activity	Screen	Day 1	Wk 2	Mo 3, 9	Mo 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90, 96 followed by every 6 months until the end of study treatment	Mo 15, 21, 27, 33, 39, 45, 51, 57, 63, 69, 75, 81, 87, 93, 99 followed by every 6 months until end of study treatment[h]	End of Treat-ment	Follow-Up Check (28 days)
Pregnancy Test[f]	X	X					X	
Documentation of Method of Contraception	X	X	X	X	X		X	
6-Minute Walk Test (6MWT)	X	X			X		X	
BORG Dyspnea Score	X	X			X		X	
Assessment of Survival and Clinical Worsening		X	X	X	X		X	
Adverse Events		X	X	X	X	X	X	X
Concomitant Treatments	X	X	X	X	X		X	
Dispense Study Drug[g]		X	X	X	X	X		
Dispense Diary		X	X	X	X	X		
Collect & Review Study Drug/Containers			X	X	X	X	X	
Collect & Review Diary			X	X	X	X	X	
Complete Dosing Log and Calculate Compliance			X	X	X	X	X	

a. Complete physical examinations will be performed at Screening, annually and End of Treatment. Brief physical examinations will be performed at other visits as specified in table above
b. WHO Functional Classification- Appendix 3.
c. Performed on subjects with a history of scleroderma, COPD or other chronic or restrictive lung disease to evaluate exclusion criteria.
d. ECG will be performed within the Screening window up to Day 1(for the purposes of scheduling).
e. CXR (PA) will be obtained at Screening or prior to Day 1 unless performed (and results available) within previous 12 months.
f. At Screening, a serum sample will be obtained for quantitative pregnancy test and assayed in the central laboratory. On Day 1, a qualitative urine pregnancy test (must have sensitivity of at least 25 mIU/mL) will be performed at the study site. If indeterminate or positive, a serum sample must be obtained for quantitative pregnancy test and assayed in the central laboratory. Negative results from the Screening and Day 1 tests must be confirmed prior to randomization and dispensation of study medication. Method of contraception must be documented in source documents during screening visit and confirmed prior to randomization. Qualitative urine pregnancy test is to be performed at end of treatment visit. Pregnancy tests are to be performed for missed menses or when pregnancy is suspected. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations.
g. First dose of the day on Day 1 is to be taken in the clinic. Drug will be dispensed every 3 months until the end of study treatment. Adverse event collection and drug accountability will be performed at those visits.
h. If it is impossible for subjects to come to the study site for visits on **these months ONLY**, alternate arrangements can be made. Information can be collected by telephone and drug can be shipped from the site to the subject by courier (with required signature) or dispensed to a subject designated person according to local regulations. This process must be documented in the source documentation and Sponsor must be notified.

SCHEDULE OF ACTIVITIES- For Subjects who discontinue STUDY TREATMENT

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

Protocol Activity	**End of Treatment**	**Follow- Up Check (28 days)**	**Every 3 Months Until the End of Study**
Visit Window	± 7 days	± 7 days	±10 days
Physical Examination[a]	X		
WHO Functional Classification[b]	X		
Vital Signs (blood pressure and pulse after sitting for 5 minutes)	X		
Safety Laboratory Tests	X		
Pregnancy Test[c]	X		
Documentation of method of contraception	X		
6-Minute Walk Test (6MWT)	X		
BORG Dyspnea Score	X		
Assessment of Clinical Worsening	X		
Survival	X		X
Adverse Events	X	X	
Concomitant Treatments	X		
Collect & Review Study Drug/Containers	X		
Collect & Review Diary	X		
Complete Dosing Log and Calculate Compliance	X		

[a] Complete physical examinations will be performed at Screening, annually and End of Treatment. Brief physical examinations will be performed at all other visits

[b] WHO Functional Classification- Appendix 3.

[c] Qualitative urine pregnancy test is to be performed at end of treatment visit.

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

1. INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, disabling, progressive and life-threatening disease, which is characterized by an elevation of pulmonary artery pressure (PAP) defined as >25 mmHg at rest, due to a structural and functional impairment of blood flow across the pulmonary arteries, as reflected by a marked increase in pulmonary vascular resistance (PVR).[1] In many patients, the course of PAH is one of steady deterioration and reduced life expectancy. The prognosis of patients with PAH is generally poor with a clinical course typically characterized by progressive increases in PVR and pressure, ultimately leading to right heart failure and death.

In the lungs, endothelial nitric oxide dilates pulmonary blood vessels by stimulating intracellular guanylate cyclase, thereby elevating intracellular cyclic guanine monophosphate (cGMP) in pulmonary arterial vascular smooth muscle cells.[2] Elevated cGMP reduces levels of intracellular calcium and thereby causes relaxation of smooth muscle cells and ultimately reductions in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR). Sildenafil acts by inhibiting the breakdown of cGMP through PDE-5, an enzyme which metabolizes intracellular cGMP to inactive 5'-GMP, found in human arteries. In the pulmonary vasculature, this action leads to reductions in pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR), providing clinical benefit in adults with PAH.

1.1. Background and Rationale

Sildenafil citrate (Revatio®) has been approved by the FDA and EMEA for use in patients with pulmonary arterial hypertension (PAH). In the US, sildenafil was approved for the treatment of adult PAH to improve exercise capacity in June 2005. Subsequently, it was approved in the US to delay clinical worsening in adult patients with PAH (WHO Group 1). In Europe, it was approved in 2005 (EU/1/05/318/001) for the treatment of adult patients with PAH, classified as World Health Organization (WHO) Functional Class (FC) II and III, to improve exercise capacity. The indication in Europe also states that efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease. To date, Revatio tablets have been approved for use in more than 50 countries and are currently marketed in 49 countries. Like other PAH-targeted drugs, sildenafil was approved for use in adults based on short-term studies with improvement in exercise capacity as the primary endpoint. In these studies, no greater efficacy was achieved in the primary endpoint with the use of higher doses. Therefore, treatment with doses higher than 20 mg TID is not recommended in current US labeling. Although there are considerable data in adults with PAH with doses up to 80 mg TID from long-term, open-label extension studies, there are no controlled data and the effect of sildenafil on the risk of death is unknown.

The efficacy of sildenafil for PAH has been demonstrated in 2 placebo-controlled trials. The A1481140 study was a placebo-controlled 12-week randomized study of sildenafil 20 mg, 40 mg, and 80 mg three times daily (TID).[3] The demographics of the study are representative of the general PAH population.

The second study, A1481141, was a multinational, multi-center, randomized, double-blind, placebo-controlled, parallel group, fixed-dose titration study to assess the safety and efficacy of sildenafil (starting with a dose of 20 mg TID and increased to 40 mg TID and then 80 mg TID as tolerated) when used in combination with intravenous epoprostenol in the treatment of PAH.[4]

With regard to the primary endpoint, in study A1481140, changes in 6 Minute Walk Distance (6MWD) after 12 weeks, a statistically significant increase in 6MWD was observed in all 3 sildenafil dose groups compared to placebo at Week 12. Mean placebo-corrected treatment effects of 45.3 meters (99% CI: 20.5, 70), 46.1 meters (99% CI: 19.9, 72.4) and 49.7 meters (99% CI: 22.9, 76.5), were seen in favor of sildenafil 20 mg (*P <0.0001*), sildenafil 40 mg (*P <0.0001*), and sildenafil 80 mg (*P<0.0001*), respectively. These improvements were evident starting from Week 4. There was little evidence of a dose-response for the primary endpoint. The treatment effect of the primary endpoint in each sildenafil dose group compared with placebo was descriptively summarized in subpopulations of patients defined by baseline walking distance, etiology, disease severity, gender, age, race, geographical location, baseline mPAP, and baseline PVRI. Mean treatment effects consistently showed improvement in 6 MWD in all sildenafil groups compared to placebo. Of particular note is the improvement in 6 MWD seen in patients of WHO Functional Class II and PAH associated with Connective Tissue Diseases (CTDs such as scleroderma, CREST (Calcinosis, Raynaud's syndrome, Esophageal dysmotility, Sclerodactyly, and Telangiectasia), mixed connective tissue disease, and systemic lupus erythematosus). At the recommended doses of 20 mg TID, the increases in walk distance were comparable between the different disease groups, being 40 (95% CI [14, 66]) and 55 (95% CI [24, 85]) meters in the PPH and CTD groups, respectively. Review of the data also shows that the efficacy profile seen with sildenafil was the same across WHO Functional Class II and III patients. Improvements were also seen in other relevant hemodynamic parameters – namely pulmonary vascular resistance (PVR), cardiac output (CO), and right atrial pressure (RAP). Functional classification is widely used as a marker of disease severity in cardiovascular disease. A greater percentage of patients on each of the sildenafil doses (28%, 36% and 42% of patients in 20, 40 and 80 mg, respectively) showed an improvement of at least 1 functional class over the 12-week period compared to placebo (7%).

In Study A1481141, the primary endpoint analysis of mean change from baseline at Week 16 in 6MWD revealed a significantly greater improvement in the sildenafil treated group compared to placebo, (30.1 vs. 4.1 meters, respectively, 95% confidence intervals (CIs): 10.8, 41.2 m; p=0.0009). There was also a statistically significant reduction in the secondary endpoint of mPAP for the sildenafil group compared with the placebo group at Week 16.

Time to clinical worsening was a key secondary endpoint of study A1481141. Clinical worsening was defined as death, lung transplantation, hospitalization due to PAH, initiation of bosentan therapy, or change in epoprostenol dose due to clinical deterioration. Analysis of time to the first event of clinical worsening demonstrated that subjects in the placebo group were three times more likely to experience a clinical worsening event compared to the sildenafil treated patients. Kaplan-Meier estimates at Week 16 of the proportion of patients

experiencing a worsening event were 0.062 in the sildenafil group and 0.187 in the placebo group. Importantly, there was a statistically significant (p=0.0074) delay in time to clinical worsening observed in subjects on background epoprostenol who were treated with sildenafil compared to placebo. Overall Study A1481141 contributes important information to the overall understanding of the efficacy of sildenafil in PAH. These data confirmed the previous observations from the pivotal Study A1481140 by demonstrating improvements in walk distance and hemodynamics when sildenafil is used in combination with epoprostenol. Importantly, this study extends the efficacy profile of sildenafil by demonstrating an important impact on the clinical course of the PAH, by significantly delaying the occurrence of a clinical worsening event during the treatment period. Hence, this study extends the understanding of the clinical benefits of sildenafil, while confirming our understanding of the underlying safety profile. These data support a favorable benefit risk assessment of sildenafil in PAH.

Study A1481244, a 12-week dose-response study investigated the use of 1 mg, 5 mg and 20 mg TID sildenafil in treating subjects with PAH that was less severe, but where chronic therapy was needed (primary objective).[5] This study was conducted as a post-marketing commitment for the FDA. At the end of the dose-response phase, subjects had the option to switch to a 12-week open-label phase during which they received sildenafil 20 mg TID. The 6MWD was chosen as the primary endpoint. Following approval of a "clinical worsening" indication in the United States in mid 2009 based on the results of study A1481141, the DMC recommended terminating the study and the FDA released Pfizer from this commitment in September 2009, stating that this more important claim changed the expectations regarding characterization of the dose-response. Study A1481244 demonstrated an increase in total distance walked in each treatment group during the 6MWD at Week 12 (LOCF, ITT population). The increase was clinically significant in the 5 mg and 20 mg groups (mean changes of 41 meters [95% CI: 25.16, 56.34] and 38 meters [95% CI: 23.77, 52.94], respectively), but smaller and not clinically significant in the 1 mg group (mean change of 14 meters [95% CI: 0.41, 28.00]). There was a decrease in mean PAP score from baseline in each of the treatment groups. A larger decrease was observed in the sildenafil 5 mg and 20 mg groups (mean changes from baseline of -3.4 and -3.3) compared with the sildenafil 1 mg group (mean change of -1.7). None of the decreases were statistically significant. Changes were also observed in other secondary and tertiary endpoints, but the changes were generally similar among the treatment groups. The secondary and tertiary endpoints included mean PAP, PAH functional class, time to clinical worsening, BNP and pro BNP levels, TAPSE index, and BORG score.

In addition, Study A1481243, a multinational, multicenter, randomized, double-blind study to evaluate the efficacy and safety of oral sildenafil 20 mg TID or placebo when added to bosentan for the treatment of subjects, aged 18 years and above, with PAH, was conducted to fulfill commitments to the FDA and EMA.[6] Study A1481243 consists of two phases. The initial phase of the study (Part A) was a 12-week randomized, double-blind, placebo-controlled study in which subjects aged 18 years and above received either placebo or sildenafil 20 mg TID has been completed. Part B of the study is a 12-month, open-label extension phase and is ongoing. All subjects had a diagnosis of PAH as confirmed by increased PAP measured by RHC within the previous 12 months and had been receiving

treatment with bosentan at a stable dose for at least 3 months. The primary objective of the double-blind phase was to assess the effect on exercise capacity after 12 weeks of treatment with sildenafil (20 mg TID) or placebo when administered to subjects with PAH who were stabilized on bosentan therapy. The primary endpoint for Part A was the change in 6MWD at Week 12 compared to baseline. The 6MWT was performed as close to trough levels of sildenafil and as close to peak levels of bosentan as possible.

Study A1481243 indicated that sildenafil had no benefit over placebo when added to stable treatment with bosentan, for change in 6MWD from baseline during the 12 weeks of the study. Both treatment groups demonstrated mean increases from baseline 6MWD at all visits up to Week 12. The mean (SD) changes from baseline in 6MWD at Week 12 (last observation carried forward [LOCF]) for the intention-to-treat (ITT) population were 13.62 (60.950) m in the sildenafil group and 14.08 (57.557) m in the placebo group. For change from baseline to Week 12 (LOCF) in 6MWD, the least squares (LS) mean difference between the treatment groups (sildenafil minus placebo) was -2.38 m with a 90% CI of (-21.843-17.087) m. The difference between the two treatment groups was not statistically significant (1-sided p-value = 0.5802). Evidence of effect modification by etiology was observed in the subgroup analysis. For subjects with primary PAH (65% of the ITT population), a numerically greater mean increase was observed in the sildenafil group compared with the placebo group; at Week 12 (LOCF), the mean (median) changes from baseline were 26.39 (18.50) and 11.84 (13.50) m for the sildenafil and placebo groups, respectively. However, for subjects with pulmonary hypertension associated with connective tissue disease (35% of the ITT population), a numerically greater mean increase was observed in placebo group; at Week 12 (LOCF); the mean (median) changes from baseline were −18.32 (−1.00) and 17.50 (20.00) m for the sildenafil and placebo groups, respectively.

Overall, 98.0% of subjects in the sildenafil group in study A1481243 and 100% of subjects in the placebo group belonged to functional class (FC) II or III PAH at baseline. During the course of the 12-week double-blind phase, the majority of subjects in each treatment group had no change in FC, indicating no deterioration or improvement over the 12-week treatment period. There were few clinical worsening events during the 12-week double-blind phase. Two (2) subjects in the sildenafil group and 2 subjects in the placebo group were hospitalised due to PAH, and 1 subject in the sildenafil group died. The safety results from Part A demonstrated acceptable safety and tolerability of sildenafil when added to bosentan, with a safety profile similar to sildenafil when used as monotherapy.

As a consequence of the results from Study A1481243, bosentan will not be permitted as background or add-on treatment in this trial. However, other ETRAs and prostanoids will be permitted provided that the agent is not a potent CYP3A inducer or inhibitor (Appendix 1) that has a clinically evident drug-drug interaction with sildenafil.

Sildenafil was approved in the European Union (EU) in May 2011 for the treatment of PAH in pediatric patients (aged 1-17 years). The data to support this application were submitted in variation number EMEA/H/C/638/II/028. Subsequently, Pfizer updated the Summary of Product Characteristics (SmPC) in the EU in September 2011 to include pediatric mortality data from the long-term extension Study A1481156,[7] to reinforce the dosing recommendations for this population, and to introduce a warning that higher than recommended doses should not be used in pediatric patients with PAH.

Pfizer submitted the Revatio Oral Suspension New Drug Application (NDA) to the Food and Drug Administration (FDA) for the pediatric indication in November 2011. On 30 August 2012, the FDA approved the NDA for the oral suspension, but did not approve the pediatric PAH indication for Revatio. The FDA has introduced the following warning in the United States Prescribing Information (USPI): "In a long-term trial in pediatric patients with PAH, an increase in mortality with increasing Revatio dose was observed. Deaths were first observed after about 1 year and causes of death were typical of patients with PAH. Use of Revatio, particularly chronic use, is not recommended in children." FDA has also issued a Drug Safety Communication (DSC) which includes a description of this information from the revised Revatio USPI. A DSC is a specific tool used by the FDA to communicate important information to the public about safety issues, including emerging safety information, about marketed drugs. As a consequence of the finding of a dose-related increase in mortality in pediatrics, FDA has asked Pfizer to evaluate the effect of sildenafil on the risk of death in adults with PAH at three dose levels, namely 5 mg, 20 mg and 80 mg TID.

The rationale for including the 5 mg TID dose in this trial is that the minimum effective dose of sildenafil is not known. The results of A1481244 in adults with PAH as described above indicated that the change from baseline in 6MWD was clinically significant in the 5 and 20 mg groups (mean changes of 41 m and 38 m, respectively), but smaller and not clinically significant in the 1 mg group (mean change of 14 m). Thus, in this study, a dose of 5 mg TID demonstrated a similar effect on exercise capacity as 20 mg TID. Therefore, it is important to evaluate whether doses lower than 20 mg TID might be similarly effective and relatively safer than the current recommended dose of 20 mg when used for the long-term treatment of adult PAH. The rationale for inclusion of the 80 mg TID dose is that, while the current US label does not recommend sildenafil at doses above 20 mg TID, it is known from prescribing practices that some adult patients with PAH are prescribed doses up to 80mg. Therefore, it is important to determine the adverse event profile of doses higher than the approved dose.

The relative effects of sildenafil on mortality when administered at the three doses indicated above in adults with PAH will be evaluated in this clinical study. In addition, the relative effects on clinical worsening and 6-minute walking distance (6MWD) will also be assessed.

Complete information for this compound may be found in the Single Reference Safety Document (SRSD), which for this study is the Investigator's Drug Brochure.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary objective: Test for the non-inferiority of sildenafil 80 mg vs. 5 mg for mortality; mortality rate with the 80 mg dose is no worse than double the mortality rate for the 5 mg dose.

2.2. Endpoints

This study will use an independent endpoint adjudication committee to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using pre-defined endpoint criteria.

For those serious adverse events (SAEs) that are handled as disease related efficacy endpoints (which may include death), a data monitoring committee (DMC) will conduct unblinded reviews on a regular basis throughout the trial (see Data Monitoring Committee Section).

Any SAE that is adjudicated by the endpoint adjudication committee NOT to meet endpoint criteria is reported back to the investigator site of incidence; the investigator at the study site must evaluate and report that SAE to Pfizer, in accordance with the time frames described in the Serious Adverse Event Reporting Requirements section of this protocol. The investigator's SAE awareness date in this instance is identified as the date on which the investigator site of incidence receives the nonendpoint SAE back from the endpoint adjudication committee. Handling these SAEs in this manner will allow Pfizer to meet its sponsor reporting obligations to regulatory authorities upon receipt of such SAEs.

However, when the investigator has judged the SAE to have a causal relationship with the investigational product, the investigator must additionally report the event to the sponsor as described in the Serious Adverse Event Reporting Requirements section, even if that event is a component of the endpoint.

Any events that remain unadjudicated at the annual safety report cutoff date will not be included in the safety tables of the report.

Primary Efficacy Endpoint:

- Time to death (Mortality).

Secondary Efficacy Endpoints:

- Time to first event (Clinical Worsening); and
- 6MWD at Months 6 and 12.

Clinical worsening[8] for the purpose of this study is defined as:

- All-cause mortality;
- Hospital stay for worsening PAH (including but not limited to right heart failure [RHF], initiation of prostanoids, lung transplantation, or septostomy); or

- Disease progression (defined as a reduction from baseline in the 6MWD test by at least 15% and worsening functional class from baseline, both confirmed by a 2nd test/evaluation within 2 weeks (cannot be performed on same day). Patients with functional class IV at baseline only need to meet the 6MWD criteria as they cannot have deterioration in functional class. The date of the event will be the first date of the two 6MWTs.

3. STUDY DESIGN

This is a randomized, double-blind, parallel-group study in adult subjects with PAH that is designed to assess mortality during long-term treatment with sildenafil at three doses. Four hundred and twenty-nine (429) subjects will be enrolled to allow approximately 143 subjects to be randomly assigned to each arm. Approximately 80-120 sites with experience conducting PAH trials will participate in the study. The study is expected to complete enrollment in approximately 4.3 years with total duration of about 7.7 years to reach required number of events (143 deaths).

Subjects will be randomly assigned on a 1:1:1 basis to either blinded sildenafil 5 mg (TID), 20 mg (TID) or 80 mg (TID) at the Baseline visit (Day 1) after successfully fulfilling all inclusion and exclusion criteria. Randomization will be stratified according to PAH treatment at entry (PAH-treatment naïve vs. on PAH-treatment) and etiology of PAH (idiopathic vs. secondary to CTD/surgical repair). Blinded sildenafil treatment is to continue for the duration of the subject's participation in the study. Subjects who discontinue from the trial will continue to be followed for the primary endpoint.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject. These criteria must be met before a subject is randomly assigned into the study. Subject eligibility should be reviewed and documented by an appropriately qualified member of the investigator's study team before subjects are included in the study. Current country label or Investigator's Brochure should be consulted to determine other conditions that would exclude subjects from treatment with sildenafil citrate.

4.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Subjects ≥18 and <75 years of age with any of the following conditions:

    a. Idiopathic Pulmonary Arterial Hypertension (IPAH); or

    b. PAH secondary to connective tissue disease (CTD); or

c. PAH with surgical repair (at least 5 years previously) of atrial septal defect (ASD), ventricular septal defect (VSD), patent ductus arteriosus (PDA) and aorto-pulmonary window.

2. PAH must have been newly diagnosed (confirmed by right heart catheterization) within 12 months prior to randomization (mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest, pulmonary capillary wedge pressure (PCWP) or left ventricular end diastolic pressure (LVEDP) ≤15 mmHg, and pulmonary vascular resistance (PVR) >4 mmHg/L/min or 320 dynes*sec/cm^5);

3. No prior long term PDE-5 inhibitor treatment (Prior episodic use of PDE-5 inhibitors for erectile dysfunction or prior limited trial use (maximum of 4 weeks) provided that PDE-5 was not discontinued for lack of efficacy or adverse event does not disqualify a subject from the study);

4. PAH WHO Functional Class II-IV;

5. Baseline 6MWD ≥50 m.

6. Male or female subjects not of childbearing potential or female subjects of childbearing potential who agree to use a highly effective method of contraception throughout the study **and for at least 28 days after the last dose of assigned treatment**. Female subjects who are not of childbearing potential include those who meet at least one of the following criteria:

   a. Have undergone a documented hysterectomy and/or bilateral oophorectomy;

   b. Have medically confirmed ovarian failure or;

   c. Achieved post-menopausal status, defined as the cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and a serum FSH level within the laboratory's reference range for postmenopausal females.

7. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures; and

8. Evidence of a personally signed and dated informed consent document indicating that the subject (or a legal representative) has been informed of all pertinent aspects of the study.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. PAH secondary to any etiology other than those specified in the inclusion criteria;

2. Significant (ie, >2+) valvular disease other than tricuspid regurgitation or pulmonary regurgitation;

3. Congenital heart disease (unless they meet inclusion criteria in Section 4.1) or pulmonary hypertension due to thromboembolism;
4. Atrial septostomy within 6 months prior to randomization (subjects who are required to undergo this procedure during the study should be withdrawn);
5. Myocardial infarction, unstable angina, cerebrovascular accident (CVA), or transient ischemic attack (TIA) within 6 months prior to randomization;
6. Acutely decompensated heart failure within 3 months prior to randomization;
7. History of cardiac arrest, respiratory arrest, hemodynamic collapse, CPR, ventricular tachycardia, ventricular fibrillation, or uncontrolled atrial fibrillation;
8. History of pulmonary embolism verified by ventilation/perfusion scan, angiogram or spiral chest computerized tomography scan;
9. Hypotension defined as systolic arterial pressure <90 mmHg or diastolic arterial pressure <50 mmHg after sitting for 5 minutes at either Screening or Day 1;
10. Previous long term treatment with PDE-5 inhibitors (Prior episodic use of PDE-5 for erectile dysfunction or prior limited trial use (maximum of 4 weeks) provided that PDE-5 was not discontinued for lack of efficacy or adverse event does not disqualify a subject.);
11. Treatment with bosentan or riociguat within 3 months of randomization;
12. Current treatment with nitrates or nitric oxide;
13. Initiation of new therapy for PAH <3 months prior to randomization or change in background treatment specific for PAH within 30 days prior to randomization (ie, ambrisentan and any other ETRA or novel agent that becomes available during the conduct of the study provided that the new agent is not a potent CYP3A inducer or inhibitor (Appendix 1) that has a clinically evident drug-drug interaction with sildenafil and/or prostanoids);
14. Change in class of supportive therapy used for adjunctive treatment of PAH within 30 days prior to randomization (eg, oxygen, calcium channel blockers, digoxin, diuretics);
15. Current treatment with potent CYP3A4 inhibitors or inducers (Appendix 1);
16. History of chronic obstructive or restrictive lung disease (eg, chronic obstructive pulmonary disease (COPD) or scleroderma) with impairment of lung function demonstrated by total lung capacity (TLC) <70% predicted, or forced expiratory volume (FEV_1) <60% predicted. (Subjects with these pulmonary disorders must have Pulmonary Function Tests performed prior to study entry if they have not been performed in the previous 12 months). If either TLC or FEV_1 do not meet criteria above but in the Investigator's judgment the patient does not have chronic or restrictive lung disease, the Investigator is to contact the sponsor to determine if patient can be enrolled;

17. Within 5 years of Screening, history of malignancy (except for adequately treated basal cell or squamous cell carcinoma of the skin), human immunodeficiency virus (HIV) or any other disease likely to limit life expectancy;

18. Known allergy or adverse reaction to sildenafil or any other ingredient in Revatio®;

19. Known hereditary degenerative retinal disorders, such as retinitis pigmentosa, history of visual loss, untreated proliferative diabetic retinopathy, or history of non-arteritic ischemic optic neuropathy (NAION);

20. Known priapism, hearing loss, vision changes, or epistaxis due to any episodic use of PDE-5 inhibitor;

21. History of alcoholism or drug abuse, or prior symptoms of drug- or alcohol-related withdrawal;

22. Participation in any other experimental studies involving other drug or non-drug therapies within 30 days before the current study begins and during study participation;

23. Pregnant females; breastfeeding females; females of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after last dose of investigational product;

24. Any severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial; or

25. Subjects who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the trial.

4.3. Life Style Guidelines

All female subjects who, in the opinion of the investigator, are biologically capable of having children and are sexually active, must agree to use a highly effective method of contraception consistently and correctly for the duration of the active treatment period and for at least 28 days after the last dose of investigational product. The investigator, in consultation with the subject, will select the most appropriate method of contraception for the individual subject from the permitted list of contraception methods, and instruct the subject in its consistent and correct use. The investigator, at each study visit, will confirm and document consistent and correct use. In addition, the investigator will instruct the subject to call immediately if the selected birth control method is discontinued or if pregnancy is known or suspected.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include:

1. Established use of oral, inserted, injected or implanted hormonal methods of contraception are allowed provided the subject remains on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper containing intrauterine device (IUD);

3. Male condom or female condom used WITH a spermicide (ie, foam, gel, film, cream, suppository);

4. Male sterilization with appropriately confirmed absence of sperm in the post-vasectomy ejaculate; and

5. Bilateral tubal ligation or bilateral salpingectomy.

   Alternate language for Sweden (or any other country preference).

   To qualify as a highly-effective method for birth control the method must offer a documented protection from pregnancy with a pearl index of <1 (according to the ICH M3 definition). Male condom or female condom used with a spermicide as well as oral low-dose gestagens does not qualify as highly-effective methods for birth control. The following methods for birth control (with typical use) offers a protection from pregnancy with a pearl index of < 1 and can be accepted by MPA as highly effective;

1. Oral (except low-dose gestagen (lynestrenol and norestisteron), injectable, or implanted hormonal contraceptives;

2. Intrauterine device;

3. Intrauterine system (for example, progestin-releasing coil);

4. Vasectomized male (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate);

5. Bilateral tubal occlusion;

6. Abstinence from penile-vaginal intercourse, when this is the female's preferred and usual lifestyle.

4.4. Sponsor Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list located in the coordinator's manual/team SharePoint site/study portal.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study number, contact information for the investigational site, and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subjects participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subject directly and if a subject calls that number they will be directed back to the investigational site.

5. STUDY TREATMENTS

Study treatment groups will be oral sildenafil 5 mg TID, sildenafil 20 mg TID, and sildenafil 80 mg TID; study treatment assignments will be blinded. Blinded sildenafil treatment is to continue for the duration of the subject's participation in the study. Subjects who discontinue from the assigned study treatment will continue to be followed for the primary endpoint of mortality.

No prior long term treatment with PDE-5 inhibitors or treatment with bosentan or riociquat will be permitted at study entry. Background treatment with endothelin receptor antagonists (ETRAs) other than bosentan (ie, ambrisentan and any other ETRA that becomes available during the conduct of the study provided that the new agent is not a potent CYP3A inducer or inhibitor (Appendix 1) and does not have any clinically evident drug-drug interaction with sildenafil) and/or prostanoids will be allowed and is to be continued during the study. Add-on treatment specific for PAH with drug classes other than PDE-5 inhibitors (ie, ETRAs as described above, oral, inhaled or subcutaneous (SC) prostanoids, or IV epoprostenol) will be permitted as needed for clinical worsening during the trial. Any other novel agents that are approved for use in adult PAH that become available during the course of the study will be permitted as long as they don't have any clinically evident drug-drug interactions and are in the opinion of the investigator safe when co-administered with sildenafil. Subjects who receive treatment with bosentan or riociguat will be discontinued from study treatment, but followed for survival through the end of the study. While add-on treatment in accord with subject need is allowed, it will be discouraged until after the assessment of 6MWD at Month 12 provided that this is consistent with the best interest of the subject. Supportive non-PAH-specific treatment (eg, oxygen, digoxin, diuretics and inotropes) will be permitted at any time during the study.

5.1. Allocation to Treatment Randomization

Subjects will be randomly assigned on a 1:1:1 basis to either blinded sildenafil 5 mg (TID), 20 mg (TID) or 80 mg (TID) at the Baseline visit (Day 1) after successfully fulfilling all inclusion and exclusion criteria.

Table 1. Allocation to Treatment

Treatment Group	Number of Subjects Randomly Assigned
Sildenafil 5 mg TID	143
Sildenafil 20 mg TID	143
Sildenafil 80 mg TID	143

Treatment with blinded study treatment will begin with the 1st dose being administered at the clinic on Day 1.

A central randomization scheme using an automated interactive voice response system (IVRS/IWRS) incorporating a central randomization and drug supply scheme will be used. Instructions on IVRS/IWRS will be provided under separate cover.

5.2. Breaking the Blind

The study will be sponsor, subject and investigator blinded. At the initiation of the study, the study site will be instructed on the method for breaking the blind. The method will be either a manual or electronic process. Blinding codes should only be broken in emergency situations for reasons of subject safety. Whenever possible, the investigator or sub-investigator consults with a member of the study team prior to breaking the blind. When the blinding code is broken, the reason must be fully documented and entered on the case report form. The subject will be discontinued from study treatment, but will continue to be followed for survival at the timepoints specified in the schedule of activities for the duration of the study.

5.3. Drug Supplies

5.3.1. Formulation and Packaging

The study medication will be provided as blinded tablets of 5 mg, 20 mg, and 80 mg sildenafil and corresponding matching placebo. All study medication will be dispensed in double-blind, triple-dummy blisters in cartons.

Formulation and Packaging			
Treatment Group	**Active Treatment**	**Placebo Tablet**	**Placebo Tablet**
Sildenafil 5 mg TID	5 mg tablets	20 mg matching placebo	80 mg matching placebo
Sildenafil 20 mg TID	20 mg tablets	5 mg matching placebo	80 mg matching placebo
Sildenafil 80 mg* TID	80 mg tablets	5 mg matching placebo	20 mg matching placebo

*** Subjects randomly assigned to 80 mg dose will receive 20 mg TID starting on Day 1 for 2 weeks and then be titrated up to their randomized dose. Subjects randomly assigned to the 5 and 20 mg doses will start on their randomized dose on Day 1**.

The investigator or designee (eg, pharmacist), will ensure that all study drug is stored in a secured area, under recommended storage conditions and in accordance with applicable regulatory requirements. Study staff (study coordinator, research nurse or pharmacist, as designated in site study delegation log) will dispense test article to the subject.

5.3.2. Preparation and Dispensing

Subjects will be provided with tablets of the strength 5 mg or 20 mg or 80 mg and corresponding matching placebo for the other 2 strengths. Three tablets (1 active plus 2 placebos) will be taken orally three times per day. The medication will be provided in blisters in cartons. Each 3 tablet dose will be identified by time (morning, afternoon, evening) and segregated by day. Subjects randomly assigned to 80 mg TID must start on 20 mg TID and be titrated up to 80 mg TID at Week 2. These subjects will be dispensed blinded 20 mg tablets and placebo (for 5 mg and 80 mg doses) for 2 weeks. At the Week 2 visit, the randomized dose of 80 mg TID will be dispensed to these subjects (with 5 mg and 20 mg placebo). Subjects randomly assigned to the 5 mg and 20 mg TID dose groups will be dispensed their assigned treatment on Day 1. To maintain the blind, all subjects will be provided with a 2- week supply of study medication on Day 1 and then will return to the clinic for a Week 2 visit. The first dose of study medication will be administered at the study site. Blinded study drug will be provided in blister packs. At all visits subjects will be provided with sufficient number of blister packs to ensure supplies last to their next visit.

5.3.3. Administration

On Day 1, subjects will be randomly assigned to one of the three blinded groups: 5 mg sildenafil, 20 mg sildenafil or 80 mg sildenafil (TID) in a 1:1:1 ratio. Subjects randomly assigned to 80 mg dose will receive 20 mg TID on Day 1 and for 2 additional weeks, and then titrated up to their randomized dose of 80 mg TID at Week 2. Subjects randomly assigned to the 5 and 20 mg doses will start their randomized dose on Day 1.

At Baseline (Day 1), the subject will be given their morning dose in the clinic. The subject will be instructed to take three tablets three times a day at least 4-6 hours apart with or without food. Instruction on storage requirements will be provided to the subject at this time.

If a subject misses a dose, he/she should take it as soon as it is remembered, but no later than 4 hours before the next dose.

For study visits in which the 6MWT will be performed (Months 6, 12, 18, 24, 30,36, 42, 48 and every 6 months thereafter as well as end-of-treatment visit) subjects will be instructed to take their morning dose approximately 4 to 6 hours prior to the scheduled 6MWT time.

Subjects who temporarily discontinue study treatment (for up to 14 days) due to required short-term treatment of prohibited medications, such as nitrates, can be restarted on study treatment. Sublingual nitroglycerin can be used in an acute situation but the subject will need to discontinue study treatment if frequent/chronic use is required.

In the event that subject is unable to tolerate the study medication, they will be withdrawn from the study treatment, but will continue to be followed for survival at the timepoints specified in the schedule of activities for the duration of the study. All reasons for study drug withdrawal will be documented in the CRF.

Subject will be asked to return cartons (containing used and unused blister packs) at each visit and will be issued enough supplies for treatment until the next visit.

5.3.4. Compliance

Subject compliance (defined as having taken 80% to 120% of study medication) will be assessed at each clinic visit (except Day 1) by counting the tablets remaining since last dispensing. Subjects who are non-compliant will be counseled on the importance of complying with study requirements.

Subsequently, if by investigator assessment the subject is not at least 80% compliant with study medication or other protocol specified requirements, the subject will not be considered as having completed all protocol requirements. Investigators should indicate on the appropriate CRF page non-compliance with study treatment.

Inventory control of all study medications must be rigorously maintained throughout the duration of the study until all medication has been accounted for and/or returned to the sponsor. Any discrepancies noted between Drug Dispensing Records and the drug inventory must be reported to Pfizer.

5.4. Drug Storage and Drug Accountability

Drug should be stored in accordance with the drug label. It is to be stored at controlled room temperature 15°C-30°C (59°F-86°F). (For Malaysia room temperature is defined as 15°C-25°C (59°F-77°F).

Storage conditions stated in the Single Reference Safety Document (SRSD) *(Investigator Brochure (IB)*, will be superseded by the label storage.

The investigator, or designee (eg, pharmacist), will ensure that all study drugs are stored in a secured area, under recommended storage condition and in accordance with applicable regulatory requirements. Investigators and site staff are reminded to check temperatures (ie, manually or by using alarm systems to alert of any excursions) and ensure that thermometers are working correctly as required for proper storage of the investigational products. Temperature monitoring procedures and equipment should include the monitoring of minimum and maximum temperatures for awareness of potential temperature excursions at times when site staff are not actively monitoring/recording temperatures. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

The investigator must ensure that authorized personnel correctly receive deliveries of investigational product from the sponsor and that all receipts are recorded in writing. Drug shipments must be recorded as "received" in the automated tele-randomization system. All drug shipment confirmation notices from the automated tele-randomization system must be retained in the site study files.

To ensure adequate records, all study drugs dispensed to subjects will be accounted for on drug accountability inventory forms completed as instructed by Pfizer. Documentation will include date of receipt and amounts dispensed to and returned by study subjects. All blisters (including empty blisters packs) must be returned to the investigator by the subject.

At the end of the trial, Pfizer will provide instructions as to disposition of any unused investigational product. If Pfizer authorizes destruction at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer. Destruction must be adequately documented. Unless otherwise authorized by Pfizer, at the end of the clinical trial all drug supplies unallocated or unused by the subjects must be returned to Pfizer or its appointed agent (eg, Contract Research Organization (CRO)).

5.5. Concomitant Medication(s)

Concomitant medications should remain stable throughout the treatment phase of the study, where possible. Changes in concomitant medications can and should be made where issues of subject safety are evident. Current country label or Investigator's Brochure should be consulted to determine other medications that cannot be administered with sildenafil citrate.

Prohibited During Study

- Bosentan is not permitted. Subjects who receive bosentan will be discontinued from study treatment and followed for survival for the duration of the study;

- Riociguat is not permitted. Subjects who receive riociguat will be discontinued from study treatment and followed for survival for the duration of the study;

- Any agent that is a potent CYP3A inducer or inhibitor (Appendix 1) that has the potential for any clinically evident drug-drug interaction with sildenafil;

- Concomitant therapy with any PDE-5 inhibitor; and

- Nitrates or nitric oxide. Sildenafil was shown to potentiate the hypotensive effects of nitrates, and its administration to patients who are using organic nitrates, either regularly and/or intermittently, in any form is contraindicated.

Permitted During Study

- Background treatment with endothelin receptor antagonists (ETRAs) other than bosentan (ie, ambrisentan and any other ETRA that becomes available during the conduct of the study provided that the new agent is not a potent CYP3A inducer or inhibitor that has any clinically evident drug-drug interaction with sildenafil) and/or prostanoids will be permitted and is to be continued during the study.

- Add-on treatment specific for PAH with drug classes other than PDE-5 inhibitors (ie, ETRAs as described above, oral, inhaled or SC prostanoids, or IV epoprostenol) will be permitted as needed for clinical worsening during the trial.

- Any other novel agents that are approved for use in adult PAH that become available during the course of the study will be permitted as long as there are no clinically evident drug-drug interactions and are in the opinion of the investigator safe when co-administered with sildenafil.

- Supportive non-PAH-specific treatment (eg, oxygen, digoxin, diuretics and inotropes) will be permitted at any time during the study.

- Warfarin (and other vitamin K antagonists), angiotensin-converting enzyme (ACE) inhibitors, angiotension-2 receptor blockers (ARB), calcium channel blockers will be permitted during the study.

- Medications for other concurrent illnesses necessary for the subject's well-being are permitted at the discretion of the investigator.

All concomitant medications (including changes in doses) should be entered in the appropriate CRF page.

Prior Medications

Prohibited Prior Medications

- Subjects who had prior long term treatment with PDE-5 inhibitors will be not be eligible to participate in the study

- Subjects should not have had a change in dose or class of standard background therapy used for treatment of PAH (eg, oxygen, calcium channel blockers, digoxin, diuretics) within 30 days prior to randomization. Exception is established treatment with anticoagulants where a subject's dose may need to be adjusted based on INR and changes in flow rate of oxygen.

- All prior medications taken for the treatment of PAH should be entered in the appropriate CRF page.

6. STUDY PROCEDURES

6.1. Screening (up to 21 days prior to Day-1)

- The following will be done:

- Inclusion and exclusion criteria;

- Demographic details (including ethnicity, race, weight, height, smoking and alcohol usage);

- Primary diagnosis;

- Medical history including drug allergies;

- Complete physical examination;

- WHO Functional Class;

- Lung function tests to determine total lung capacity (TLC) and forced expiratory volume ($FEV_{1)}$ in subjects with a history of scleroderma, COPD or other chronic or restrictive lung disease (if not performed within the last 12 months);

- Vital signs: blood pressure and pulse rate after sitting for 5 minutes;

- 12-Lead electrocardiogram (any time within the Screening window up to Day 1):

- Chest X-Ray (PA; obtained at Screening or prior to Day 1 unless performed and results available within previous 12 months);

- Blood sample for biochemistry and hematology (safety laboratory tests);

- Quantitative serum pregnancy test for women of childbearing potential;

- In women of childbearing potential, documentation in the source documents of assignment of a highly effective method of contraception that will be used for the length of the study;

- 6MWT;

- BORG dyspnea score;
- Collection of prior and concomitant treatment(s); and
- Informed consent.

6.2. Day 1 (up to 21 days after screening visit)

The following will be done:

- Review inclusion and exclusion criteria to confirm eligibility;
- Brief physical examination;
- Vital signs: blood pressure and pulse rate after sitting for 5 minutes;
- A qualitative urine pregnancy test (sensitivity of at least 25 mIU/mL) for women of childbearing potential will be obtained at the study site (if result is indeterminate or positive, a serum sample should be collected for quantitative pregnancy test and assayed by the central laboratory and study drug should not be dispensed). **Result must be negative prior to dispensation of study medication;**
- For women of childbearing potential, confirm that a highly effective method of contraception is being used;
- 6MWT;
- BORG dyspnea score;
- Assessment of survival and clinical worsening;
- Collection of adverse events;
- Collection of concomitant treatment(s);
- Randomization (IVRS/IWRS);
- Dispense study drug (2-week supply);
- 1st dose of study drug, subject instruction on dosing, storage; and
- Dispense diary.

6.3. Week 2 (±3 days of Day 1 visit)

The following will be done:

- Brief physical examination;

- Vital signs: blood pressure and pulse rate after sitting for 5 minutes;
- For women of childbearing potential, confirm that a highly effective method of contraception is being used;
- Assessment of survival and clinical worsening;
- Collection of adverse event(s);
- Collection of concomitant treatment(s);
- Collect and review returned study medication blister packs;
- Collect and review subject diary for dosing and adverse events;
- Complete dosing log and calculate compliance;
- Dispense new cartons of study medication; and
- Dispense new subject diary.

6.4. Months 3 and 9 (Visit window ± 10 days)

The following will be done:

- Brief physical examination;
- WHO Functional Class;
- Vital signs: blood pressure and pulse rate after sitting for 5 minutes;
- Blood sample for biochemistry and hematology (safety laboratory tests);
- For women of childbearing potential, confirm that a highly effective method of contraception is being used;
- Assessment of clinical worsening and survival;
- Collection of adverse event(s);
- Collection of concomitant treatment(s);
- Collect and review returned study medication blister packs;
- Collect and review subject diary for dosing and adverse events;
- Complete dosing log and calculate compliance;

- Dispense new cartons of study medication;
- Dispense new subject diary.

6.5. Months 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66, 72, 78, 84, 90 and 96 (followed by every 6 months until end of study treatment; Visit window ± 10 days)

The following will be done:

- Physical examination (Complete exam will be performed annually at months 12, 24, 36, 48, 60, 72, 84 and 96 until the end of the study treatment; a brief exam will be performed at the other visits);
- WHO Functional Class;
- Vital signs: sitting blood pressure and pulse rate after sitting for 5 minutes;
- Blood sample for biochemistry and hematology (safety laboratory tests);
- For women of childbearing potential, confirm that a highly effective method of contraception is being used;
- 6MWT performed close to trough levels of sildenafil (ie, at least 4 hours after the last scheduled dose);
- BORG dyspnea score;
- Assessment of survival and clinical worsening;
- Collection of adverse event(s);
- Collection of concomitant treatment(s);
- Collect and review returned study medication cartons;
- Collect and review subject diary for dosing and adverse events;
- Complete dosing log and calculate compliance;
- Dispense new cartons of study medication;
- Dispense new subject diary.

6.6. Months 15, 21, 27, 33, 39, 45, 51, 57, 63, 69, 75, 81, 87, 93, 99 (followed by every 6 months until end of study treatment; Visit window ± 10 days)

The following will be done:

- Collection of adverse event(s);
- Collect and review returned study medication cartons;
- Collect and review subject diary for dosing and adverse events;
- Complete dosing log and calculate compliance;
- Dispense new cartons of study medication;
- Dispense new subject diary.

If it is impossible for subjects to come to the study site for visits on these months ONLY, alternate arrangements can be made. Information can be collected by telephone and drug can be shipped from the site to the subject by courier (with required signature) or dispensed to a subject designated person according to local regulations. This process must be documented in the source documentation and Sponsor must be notified.

6.7. End of Treatment Visit (Visit window ± 7 days)

The following will be done:

- Complete physical examination;
- WHO Functional Class;
- Vital signs: sitting blood pressure and pulse rate after sitting for 5 minutes;
- Blood sample for biochemistry and hematology (safety laboratory tests);
- A qualitative urine pregnancy test (sensitivity of at least 25 mIU/mL) for women of childbearing potential will be obtained at the study site (if result is indeterminate or positive a serum sample should be collected for quantitative pregnancy test and assayed by the central laboratory and study drug should not be dispensed);
- For women of childbearing potential, confirm that a highly effective method of contraception is being used and will continue for at least 28 days after discontinuation of study treatment;
- 6MWT (performed close to trough levels of sildenafil (ie, at least 4 hours after the last scheduled dose);
- BORG dyspnea score;

- Assessment of survival and clinical worsening;
- Collection of adverse event(s);
- Collection of concomitant treatment(s);
- Collect and review returned study medication cartons;
- Collect and review subject diary for dosing and adverse events;
- Complete dosing log and calculate compliance.

6.8. Follow-up Check (28 days ± 7 days)

Collection of adverse event(s).

6.9. Study Treatment Withdrawal

Subjects who discontinue randomized study treatment for any reason will continue to be followed for survival at the time points specified in the schedule of activities for the duration of the study. All efforts should be made to follow all subjects for these data through standard of care visits or phone contact regardless of their participation in required study assessments (ie, 6MWT).

6.10. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for addition of prohibited medication, safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures at a given study site.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record. In any circumstance, every effort should be made to document subject outcome, if at all possible. The investigator should inquire about the reason for withdrawal, request the subject to return all unused investigational product(s), request the subject to return for a final visit, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

7.1. 6-Minute Walk Test (6MWT)

The distance that a subject can walk in 6 minutes will be measured. Subjects will be asked to perform the test at a pace that is comfortable for them, with as many breaks as they needed. Pulse oximetry will be performed for safety as per the protocol of the clinical site – ie, either continuous or at the start and finish of the test, depending on the usual procedure used by the clinical site. The 6MWT will be conducted at Screening, Day 1, Months 6, 12, 18, 24, 30, 36, 42, 48 and every 6 months thereafter until and including the end of treatment visit. This test should be conducted as close to sildenafil trough levels as possible (ie, least 4 hours after the last scheduled dose). The average of the 6MWT performed at Screening and Day 1 randomization visits will be used for the baseline value. The study personnel that performed the 6MWT will be trained to perform these tests according to a study specific protocol (Appendix 2 of the protocol) in order to ensure standardization across sites. It is encouraged that the same study personnel are to conduct the 6MWT assessments for all subjects at a particular center, throughout the study duration. If this is not possible, this will not be considered a protocol violation.

7.2. WHO Functional Class

The World Health Organization Pulmonary Hypertension Criteria for Functional Capacity and Therapeutic Class (for definitions Appendix 3) is to be assessed at Screening, Months 3, 6, 9, 12, 18, 24, 30, 36, and every 6 months until end of therapy and at the end of treatment visit. The centers should attempt to have the same individual assess each subject throughout the study.

7.3. Clinical Worsening

Time from randomization to clinical worsening will be assessed at Day 1, Week 2, Months 3, 6, 9, 12 and every 6 months thereafter up to and including the end of treatment visit. For the purposes of this study, clinical worsening is defined as: all-cause mortality; hospital stay for worsening PAH (including but not limited to right heart failure [RHF] initiation of prostanoids, lung transplantation, or septostomy); or disease progression (defined as a reduction from baseline in the 6MWD test by at least 15% and worsening functional class from baseline, both confirmed by a 2nd test/evaluation within 2 weeks (cannot be performed on same day). Patients with functional class IV at baseline only need to meet the 6MWD criteria as they cannot have deterioration in functional class. The date of the event will be the first date of the two 6MWTs.

7.4. *B*ORG Dyspnea Score

The BORG dyspnea score is to be assessed at the end of the 6MWT at Screening, Day 1 (baseline), Months 6, 12, 18, 24, 30, 36 and every 6 months thereafter with the final assessment at the end of treatment visit. The subjects will be asked to score their dyspnea on the BORG dyspnea scale (Appendix 4) at the completion of the 6MWT. This score should reflect the maximum degree of dyspnea that the subject experiences at any time during the

6MWT. If possible, the same study personal should conduct the 6MWT and BORG dyspnea assessments for all subjects at a particular center, throughout the study duration. If this is not possible, the same tester will ideally perform all tests for a particular subject. This will not be considered a protocol violation.

7.5. Hematology and Biochemistry Analysis

Blood (approximately 10 ml) will be drawn (at visits as specified in the Schedule of Activities), as per details to be provided in the central laboratory manual, to provide sufficient plasma for the below tests. All tests during the dose response treatment phase will be performed by centralized laboratories. Hard copies of all results will be provided to the investigator and transferred electronically to Pfizer. Additional blood samples may be collected the discretion of the investigator in keeping with their normal standards of care. These samples will be analyzed by local labs and data need not be sent to Pfizer.

The following safety laboratory tests will be performed:

Hematology

- Hemoglobin;
- Hematocrit;
- White Blood Cell Count (leucocytes);
- Platelets.

Biochemistry

- Albumin;
- Alkaline Phosphatase;
- Alanine Aminotransferase (ALT (SGPT));
- Aspartate Aminotransferase (AST (SGOT));
- Bilirubin (Total);
- Creatinine;
- Potassium;
- Total Protein;
- Sodium;
- Urea (BUN).

7.6. Change in Chronic Use of Background Therapy

Change in background therapy will be assessed at all visits, defined as 1 or more additions or discontinuations in the doses or class(es) of drugs used as background medication (ie, oxygen, diuretics, calcium channel blockers and digoxin) compared to Day 1 (baseline). Increases and decreases in doses will also be collected for specific background therapies for treatment of PAH.

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However it is anticipated that from time to time there may be circumstances, outside of the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well being of the subject. When a protocol required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.7. Pregnancy Testing

For female subjects of childbearing potential, a quantitative serum pregnancy test must be performed at Screening and sent to the central laboratory. A qualitative urine pregnancy test with sensitivity of at least 25 mIU/mL is to be performed at the study site on the Day 1 visit prior to randomization. Both pregnancy tests must be negative before the subject may receive the investigational product. A qualitative urine pregnancy test with sensitivity of at least 25 mIU/mL is also to be performed at the study site at the end of treatment visit. Pregnancy tests will also be done whenever one menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). If the result is inconclusive, a quantitative serum pregnancy test must be performed. In the case of a positive hCG test, the subject will be withdrawn from study medication, but may remain in the study. Pregnancy tests may also be repeated as per request of IRB/IECs or if required by local regulations. A highly effective method of contraception being used by the subject must be documented in the source documentation prior to randomization and confirmed at every study visit.

Qualitative urine pregnancy tests must be sensitive to at least 25 mIU/mL. Qualitative urine point-of-service pregnancy tests are to be conducted with the test kit provided by the central laboratory in accord with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminant or positive result on the qualitative point-of-service urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

7.8. Electrocardiogram (ECG)

12-lead ECG measurement will be obtained at Screening. For the purposes of scheduling, this test can be performed at anytime between Screening and up to and including Day 1. Clinically significant findings, based on the Investigator's judgment, will be reported as medical history on the Case Report Form (CRF).

All ECGs will be performed and archived at the Investigator's site.

7.9. Chest X-Ray (CXR)

A CXR (PA) will be obtained at Screening or prior to Day 1 unless performed and results available within previous 12 months.

7.10. Physical Examinations

Physical examinations will be performed at visits as specified in the Schedule of Activities throughout the duration of the study until and including the end of treatment visit. Changes in physical examination findings (relative to the screening visit), deemed clinically significant changes in the judgment of the investigator, will be recorded as adverse events. Ethnicity, race, weight (kg) and height (cm), smoking and alcohol usage will also be obtained at Screening.

7.11. Vital Signs

Blood pressure and pulse rate, after sitting for five minutes, will be recorded at visits as specified in the Schedule of Activities. If systolic blood pressure significantly decreases and is accompanied by clinical manifestations considered significant by the investigator, the investigator should record this as an adverse event and consider withdrawal of the subject from the study treatment.

7.12. Subject Diary

A subject diary will be given to subjects to log any missed doses of study medication and document any adverse events which occurred since the previous visit.

8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the Sponsor, any non-serious adverse event that is determined by the Sponsor to be serious will be reported by the Sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least one dose of study treatment through the last subject visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;

- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong drug, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (AE) page and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

  Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error should be captured on the medication error version of the adverse event (AE) page and, if applicable, any associated AE(s) are captured on an AE CRF page.

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.
- Lack of efficacy should be reported as an AE when it is associated with an SAE.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

8.6.1. Protocol-Specified Serious Adverse Events

Unless the investigator believes that there is a causal relationship between study drug and an efficacy endpoint specified below, the events highlighted below should not be reported by the investigator as SAEs as described in the Serious Adverse Event Reporting Requirements section of this protocol. These events are anticipated to occur in a population with PAH.

Efficacy endpoints that will not be reported in an expedited manner:

1. Death;
2. Clinical Worsening.

Should an aggregate analysis indicate that these prespecified events occur more frequently than expected based on the expectation of frequency of the event(s) in question in the population for comparison, eg, based on epi data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analysis of safety data will be performed on a regular basis per internal standard operating procedures.

These events will be reported on a CRF form for Clinical Endpoints for adjudication by the CEC. Any potential clinical endpoint that is adjudicated by the CEC NOT to meet endpoint criteria is reported back to the investigator site of incidence; the investigator at the study site must evaluate and report that SAE to Pfizer, in accordance with the timeframes described in the Serious Adverse Event Reporting Requirements section of this protocol. The investigator's SAE awareness date in this instance is identified as the date that the investigator site of incidence receives the non-endpoint SAE back from the CEC.

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see Section on SAE Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's Law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin value ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 X ULN or not available;
    - For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:
    - For subjects with pre-existing AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 X ULN, or ≥8 X ULN (whichever is smaller).
- Concurrent with
    - For subjects with pre-existing values of total bilirubin above the normal range: Total bilirubin increased from baseline by an amount of at least one time the upper limit of normal **or** if the value reaches ≥3 times the upper limit of normal (whichever is smaller).

The subject should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test LFT abnormalities identified at the time should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment laboratory abnormality);

- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting

purposes, as defined by the Sponsor (see Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy (also referred to as exposure in-utero (EIU) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or if the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product.

2. An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on a Serious Adverse Event (SAE) Report Form and Exposure in Utero (EIU) Supplemental Form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination and notify Pfizer of the outcome as a follow up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Occupational Exposure

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to safety within 24 hours of Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF), however a copy of the completed SAE Report form is maintained in the study master file.

8.12. Withdrawal Due to Adverse Events (See Also Section on Subject Withdrawal)

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.13. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

8.14. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.14.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. If an SAE occurs, Pfizer is to be notified within 24 hours of notification that an SAE has been deemed a non-endpoint and has been sent back to the site. The investigator's SAE awareness date in this instance is identified as the date that the investigator receives the non-endpoint SAE back from the endpoint adjudication committee. As noted in the Endpoints section, when the investigator has judged the SAE to have a causal relationship with the investigational product, the investigator must report the event to the sponsor within 24 hours of investigator awareness, even if that event is a component of the endpoint.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines and/or illnesses must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.14.2. Non-Serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.14.3. Sponsor Reporting Requirements to Regulatory Authorities

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

A detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

9.1. Sample Size Determination

Total of 429 subjects will be randomly assigned into sildenafil 5 mg TID, 20 mg TID and 80 mg TID treatment group with 143 subjects in each treatment group.

This non-inferiority study is powered at 90% to test the following hypotheses at overall significance level of 0.025 (1-sided):

- H_0: hazard ratio (80 mg TID /5 mg TID) >=2;
- H_1: hazard ratio (80 mg TID /5 mg TID) <2.

The sample size of the study is calculated based on the following assumptions:

- Equal mortality rate of 15% at 2-years for each arm;
- Accrual rate of 100 subjects/year;
- Two interim analyses with O'Brien-Fleming approach possibly rejecting H_0 or H_1;
- Estimated 20% drop-out rate (including lost to follow-up).

With the estimated recruitment rate, the study is expected to complete enrollment in about 4.3 years with total duration of about 7.7 years to reach required number of events (deaths) of 143.

9.2. Efficacy Analysis

9.2.1. Analysis of Primary Endpoint

The primary efficacy analysis will be conducted using the intent-to-treat (ITT) population. All events occurring up until the end of the trial, including events observed from discontinued patients, will be included in the primary efficacy analysis. The efficacy analyses will also be conducted using the per-protocol (PP) population as sensitivity analyses.

Treatment comparison will be conducted using Cox proportional hazard regression model stratified by PAH treatment at entry of the study (PAH-treatment naïve vs. on PAH treatment) and etiology of PAH (idiopathic vs. secondary to CTD/surgical repair). If the 1 sided upper confidence limit of the hazard ratio (80 mg TID/5 mg TID) is less than 2, then the null hypothesis that the mortality rate in the 80 mg TID is worse than double the rate in

5 mg TID will be rejected. In case that the hazard ratio is statistically significantly less than 1, then superiority of 80 mg TID over 5 mg TID will be claimed. Treatment comparison will also be evaluated using the exact test as sensitivity analysis.

9.2.2. Analysis of Secondary Endpoints

For continuous endpoints, analysis of covariance (ANCOVA) or analysis of variance (ANOVA) will be used. Estimated mean differences between treatments (80 mg TID vs. 5 mg TID, 80 mg TID vs. 20 mg TID, 20 mg TID vs. 5 mg TID) and their respective 95% CI and p-values will be calculated.

For categorical endpoints, treatment comparison will be conducted using Chi-square test or Fisher's exact test, whichever is appropriated. Differences in rate and its 95% CI and p-value will be calculated for each treatment comparison (80 mg TID vs. 5 mg TID, 80 mg TID vs. 20 mg TID, 20 mg TID vs. 5 mg TID).

For time-to-event endpoints, similar analyses as used for primary endpoint will be used.

9.3. Pharmacokinetic and Pharmacokinetic-Pharmacodynamic Analyses

Not applicable for this study.

9.4. Safety Analysis

Safety analyses will be carried out for the ITT population. All adverse events will be coded and grouped by system organ class. The incidence and rate of each treatment emergent adverse event will be tabulated by treatment. Tabulations by maximum severity and relationship to study treatment will also be included.

Vital signs and safety laboratory data will be explored through the use of standard presentations of descriptive statistics.

9.5. Interim Analysis

Interim analyses with statistical analyses on hypotheses testing will be performed when about 50% and 75% of mortality events have occurred.

O'Brien-Fleming approach will be used for decision making, ie, reject H_0 with 1-sided p-value <0.0015, and <0.0092 for the interim analyses with 50% and 75% of the mortality events, respectively, or reject H_1 with 1-sided p-value >0.3701 and >0.0982 for the interim analyses with 50% and 75% of the mortality events, respectively. The final p-value for rejecting H_0 will be <0.022 (1-sided). The actual stopping boundaries will depend on the exact timing of each interim analysis.

9.6. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be engaged to monitor multiple parameters of study conduct including mortality rate, clinical worsening and other safety data, safeguard the interest of study subjects and provide recommendations on continuing the conduct of the study.

The DMC will be responsible for ongoing monitoring of the safety of subjects in the study according to the DMC Charter. The DMC is to meet at least twice per year to review aggregate safety data throughout the study. In addition, the DMC will meet after each interim analysis with formal hypotheses testing; the recommendations made by the DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

9.7. Clinical Endpoint Adjudication Committee (CEC)

This protocol will use an independent CEC wherein, to maintain scientific integrity, adjudication of all individual potential disease-related efficacy endpoints will be performed. Specified clinical events will be reviewed on an ongoing basis by members of the adjudication committee to determine whether endpoint criteria are met according to the CEC Charter. In contrast, the DMC is responsible for ongoing analysis of aggregate safety data and outcomes.

Any SAE that is adjudicated by the CEC to NOT to meet endpoint criteria is reported back to the investigator site of incidence; the investigator at the study site must evaluate and report that SAE to Pfizer, in accordance with the timeframes described in the Serious Adverse Event Reporting Requirements section of this protocol (See 8.14.1 and 8.14.3).

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's subject chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

11.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996,2008 & 2013).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Subject names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial subject. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study subject, or his/her legal representative, is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legal representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient subjects have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

13.2. End of Trial in all Other Participating Countries

End of Trial in all other participating countries is defined as *Last Subject Last Visit.*

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of sildenafil at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 30 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), www.pfizer.com, and/or the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

www.clinicaltrials.gov.

Pfizer posts clinical trial Basic Results on www.clinicaltrials.gov for all Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of a Pfizer product.

The timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

- For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, Food and Drug Administration FDA-approved products, Pfizer posts results within one year of the primary completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV);

- For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval, or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

- For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year of discontinuation of the program (if there are no plans for out-licensing or within two years if out-licensing plans have not completed).

Primary Completion Date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

www.pfizer.com

Pfizer posts clinical trial results on www.pfizer.com for all Pfizer-sponsored interventional studies in patients that assess the safety and/or efficacy of an FDA-approved Pfizer product with a LSLV on or after 27-Sep-2007 for which Basic Results were posted on www.clinicaltrials.gov.

EudraCT

Pfizer posts clinical trial results on EudraCT in accordance with Commission Guideline 2012/C 302/03 *Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006* for studies with centers in the European Economic Area and with LSLV on or after 01-May-2004, regardless of the marketing status of the compound.

15.2. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-center study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

1. Badesch DB, Champion HC, Gomez-Sanchez MA, Hoeper MM, Loyd JE, Manes A, McGoon M, Naeije R, Olschewski H, Oudiz RJ, Torbicki A. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol.2009; 54(1):S55-66.

2. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Kelpetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2009;30: 2493-2537.

3. Galie N, Ghofrani HA, Torbicki A, Barst R, Rubin LJ, Badesch DB, Fleming T, Parpia T, Burgess G, Branzi A, Grimminger F, Kurzyna M, Simonneau G. Sildenafil citrate therapy for pulmonary arterial hypertension. N Engl J Med.2005; 353: 2148-57.

4. Simonneau G, Rubin LJ, Galie N, Barst R, Fleming TR, Frost AE, Engel PJ, Kramer MR, Burgess G, Collings L, Cossons N, Sitbon O, Badesch DB. Addition of sildenafil to long-term intravenous epoprostenol therapy in patients with pulmonary arterial hypertension, a randomized trial. Ann Intern Med.2008; 149:521-530.

5. Data on file (B1741244 CSR 26 Jul 2013), Pfizer.

6. Data on file (B1741243 CSR 17 Mar 2011), Pfizer.

7. Data on file (B1741156 CSR 28 Aug 2013), Pfizer.

8. McLaughlin VV, Badesch DB, Delcroix M, Fleming TR, Gaine SP, Galie N, Gibbs JSR, Kim NH, Oudiz RJ, Peacock A, Provencher S, Sitbon O, Tapson VF, Seeger W. Endpoints and clinical trial design in pulmonary arterial hypertension. J Am Coll Cardiol.2009; 54(1)S97-107.

17. APPENDICES

Appendix 1. CYP3A Inhibitors or Inducers

The FDA classification of CYP enzyme inhibitors and inducers are provided in the tables below. For the purposes of this protocol, both strong and moderate inhibitors of the CYP3A enzyme (≥2-fold increase in AUC or >50% decrease in clearance of a substrate) are considered to be potent inhibitors and are therefore prohibited during the study. Similarly, both strong and moderate inducers of the CYP3A enzyme (>50% decrease in AUC of a substrate) are prohibited during the study.

Please refer to the shaded areas of the tables below for prohibited drugs. These lists are not exhaustive. Other drugs known or expected to result in a similar effect on CYP3A enzymes should also be avoided.

Classification of In Vivo Inhibitors of CYP Enzymes (1)

CYP Enzymes	Strong Inhibitors(2) ≥ 5-fold increase in AUC or > 80% decrease in CL	Moderate inhibitors(3) ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL	Weak inhibitors(4) ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL
CYP1A2	ciprofloxacin, enoxacin, fluvoxamine	methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, vemurafenib, zileuton	acyclovir, allopurinol, caffeine, cimetidine, daidzein,(5), disulfiram, echinacea,(5) famotidine, norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil
CYP2B6			clopidogrel, ticlopidine prasugrel
CYP2C8		gemfibrozil(6)	fluvoxamine, ketoconazole, trimethoprim
CYP2C9		amiodarone, fluconazole, miconazole, oxandrolone	capecitabine, cotrimoxazole, etravirine, fluvastatin, fluvoxamine, metronidazole, sulfinpyrazone, tigecycline, voriconazole, zafirlukast
CYP2C19	fluconazole,(7) fluvoxamine,(8) ticlopidine(9)	esomeprazole, fluoxetine, moclobemide, omeprazole, voriconazole	allicin (garlic derivative), armodafinil, carbamazepine, cimetidine, etravirine, human growth hormone (rhGH), felbamate, ketoconazole, oral contraceptives(10)

CYP Enzymes	Strong Inhibitors(2) ≥ 5-fold increase in AUC or > 80% decrease in CL	Moderate inhibitors(3) ≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL	Weak inhibitors(4) ≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL
CYP3A	boceprevir, clarithromycin, conivaptan, grapefruit juice,(11) indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, (12) nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole	amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice,(11) imatinib, verapamil	alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo,(5) , goldenseal,(5) isoniazid, lapatinib, nilotinib, oral contraceptives, pazopanib, ranitidine, ranolazine, tipranavir/ritonavir, ticagrelor, zileuton
CYP2D6	bupropion, fluoxetine, paroxetine, quinidine	cinacalcet, duloxetine, terbinafine	amiodarone, celecoxib, clobazam, cimetidine, desvenlafaxine, diltiazem, diphenhydramine, Echinacea,(5) escitalopram, febuxostat, gefitinib, hydralazine, hydroxychloroquine, imatinib, methadone, oral contraceptives, pazopanib, propafenone, ranitidine, ritonavir, sertraline, telithromycin, verapamil, vemurafenib

(1) Please note the following: This is not an exhaustive list. For an updated list, see the following link http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.
(2) A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a substrate for equal or more than 5-fold.
(3) A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold.
(4) A weak inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 2-fold but equal to or more than 5-fold.
(5) Herbal product.
(6) Gemfibrozil also inhibits OATP1B1.
(7) Fluconazole is listed as a strong CYP2C19 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor.
(8) Fluvoxamine strongly inhibits CYP1A2 and CYP2C19, but also inhibits CYP2C8/2C9 and CYP3A.
(9) Ticlopidine strongly inhibits CYP2C19, but also inhibits CYP3A, CYP2B6, and CYP1A2.
(10) Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol.
(11) The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain

preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).
(12) Withdrawn from the United States market.

Classification of In Vivo Inducers of CYP Enzymes(1)

CYP Enzymes	**Strong Inducers** ≥ 80% decrease in AUC	**Moderate Inducers** 50-80% decrease in AUC	**Weak Inducers** 20-50% decrease in AUC
CYP1A2		montelukast, phenytoin, smokers versus non-smokers(2)	moricizine, omeprazole, phenobarbital,
CYP2B6		efavirenz, rifampin	nevirapine
CYP2C8		rifampin	
CYP2C9		carbamazepine, rifampin	aprepitant, bosentan, phenobarbital, St. John's wort(3,4)
CYP2C19		rifampin	artemisinin
CYP3A	avasimibe,(5) carbamazepine, phenytoin, rifampin, St. John's wort(3)	bosentan, efavirenz etravirine, modafinil, nafcillin	amprenavir, aprepitant, armodafinil, clobazamechinacea,(4) pioglitazone, prednisone, rufinamide, vemurafenib
CYP2D6	None known	None known	None known

(1) Please note the following: This is not an exhaustive list. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm.
(2) For a drug that is a substrate of CYP1A2, the evaluation of the effect of induction of CYP1A2 can be carried out by comparative PK studies in smokers vs. non-smokers.
(3) The effect of St. John's wort varies widely and is preparation-dependent.
(4) Herbal product.
(5) Not a marketed drug.

Reference: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry. Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations. February 2012; 42-43.

Appendix 2. Six-Minute Walk Test Protocol

The following protocol **MUST** be used to administer the 6-minute walk test. This is in compliance with the ATS statement: Guidelines for the six-minute walk test.

Please note that nitrates (in any form) may not be administered at any time during the course of this study.

A separate checklist/worksheet will be provided by Pfizer prior to study initiation and it is important that this checklist is completed prior to each 6-minute walk test being performed. This will help improve standardization and reduce variability across sites.

In accordance with the ATS Guidelines for the 6-minute walk, all technicians must be trained in performing the 6-minute walk and evidence that this training has been completed needs to be documented (for example in the site initiation visit report) by the Pfizer Study Personnel prior to study initiation. Ideally, the same tester should perform all the tests for all subjects at each site. If this is not possible, the same tester should ideally perform all tests for a particular subject.

The test should ideally be performed at approximately the same time of day for all evaluations and must be performed as close to expected trough levels (ie, at least 4 hours after the previous dose) of study medication as possible. The study staff should be available to provide support for the subject, only if the subject should require medical assistance, but otherwise should not assist the subject in any way. It is especially important that the subject is not actively encouraged to walk further or faster during the actual 6-minute walk test. A chair or wheelchair can be available should the subject indicate that they wish to rest. If drip stands, oxygen cylinders or oximeters are used during the test then these should be on drip stands so they do not interfere with the subject during the procedure. These may also be pushed by the medical staff at the rate that the subject walks. It is vitally important that the medical staff walk at the pace of the subject and do not walk faster or slower than is comfortable for the subject. Resuscitation equipment should be available. Importantly if the baseline walk test is performed on oxygen, then all future tests for the study should be performed on oxygen. Likewise if a dripstand or oximeter is used during the first test, these must also be used during subsequent tests to ensure consistency across tests. Subjects who usually use walking aids, should use these for all tests.

In the event that the subject suffers an adverse event during the 6-minute walk this must be recorded in the CRF. Likewise, if any medication is administered, including oxygen, this must be recorded. **Please note that any medication that might influence exercise capacity (eg, bronchodilators) should be avoided for at least 2 hours prior to the start of the exercise test.** Any medication taken in the 2 hours prior to, during or immediately after the 6-minute walk test must be recorded on the worksheet together with the time taken.

The area for the walk test should be pre-measured over a suitable distance (eg, 25 – 30 meters) with graduations spaced and marked either with a tape measure or wall or floor labels. The calibrated distance must be checked by an independent person and documented at the beginning of the study and each time the markings are changed. This only needs to be

done once if the markings are permanent for the duration of the study but must be repeated should the markings be altered. The direction of the walk should be up and down and not circular. The area where the test is to be performed must be free of objects and distractions.

In preparation for the test, the subject should be advised to have a light meal or snack at least 2 hours prior to the test and to wear comfortable clothing and shoes (trainers or sneakers). It is important to ensure that similar footwear be worn for this test throughout the study. Prior to starting the test, the subject should sit and rest in a chair at the starting position to ensure that they are completely rested prior to the test commencing. A period of 10 - 15 minutes is suggested. The subject should also be informed that the time for the test begins once they have crossed the starting point and continues for 6 minutes regardless of any rest periods taken during the test.

The subject will be instructed to walk as far as they can during the 6 minutes at a pace that is comfortable to them. They may stop and rest if necessary but time will continue (does not stop). Elapsed time will be read to the subject every 2 minutes. No other encouragement or conversation should occur with the subject during the walk test.

After 6 minutes has elapsed the subject will be asked to stop walking at whatever point they have reached. The number of laps completed must be recorded and the distance that the subject covered during the 6 minutes' walking time will be the distance that is to be recorded in the CRF. The exact number of meters walked must be recorded. Distances walked should be rounded off to the nearest meter as follows: Intervals between 0.5 meters and above must be rounded up and intervals less than 0.5 meters must be rounded down to the nearest meter.

Pulse oximetry will be performed for safety as per the protocol of the clinical site – ie, either continuous or at the start and finish of the test, depending on the usual procedure used by the clinical site.

Reference: Guyatt GH, Sullivan MJ, Thompson, PH, et al. The 6-minute walk: A new Measure of Exercise Capacity in Subjects with Chronic Heart Failure. Can Med Assoc J. 1985; 132; 919-923.

Appendix 3. WHO Pulmonary Hypertension Functional Classification

Adapted from New York Heart Association Criteria For Functional Capacity and Therapeutic Class

Definitions:

Class I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain or near syncope.

Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnea or fatigue, chest pain or near syncope.

Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnea or fatigue, chest pain or syncope.

Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Note: Attempts should be made to ensure that the same individual assesses each patient throughout the study.

Reference: Modified after New York Heart Association Functional Classification World Symposium— Primary Pulmonary Hypertension 1998, executive summary, Rich, S., editor.

Appendix 4. BORG Dyspnea Scale

SCALE	SEVERITY	
0	Nothing at all	
0.3		
0.5	Extremely weak	Just noticeable
0.7		
1	Very weak	
1.5		
2	Weak	Light
2.5		
3	Moderate	
4		
5	Strong	Heavy
6		
7	Very strong	
8		
9		
10	Extremely strong	“Maximal”
11		
●	Absolute maximum	Highest possible

Instruction. Use this rating scale to report how strong your perception is. It can be exertion, pain or something else. First look at the verbal expressions. Start with them and then the numbers. Of these ten (10) or ”Extremely strong”, “Maximal” is a very important intensity level. This is the most intense perception or feeling you have ever had.

If your experience or feeling is “Very weak”, you should say “1”, if it is “Moderate”, say “3”. Note that “Moderate” is “3” and thus weaker than “Medium”, “Mean” or “Middle”. If the experience is “Strong” or “Heavy” (it feels “Difficult”) say “5”. Note that “Strong” is about half of “Maximal”. If your feeling is “Very strong”, choose a number from 6 to 8. If your perception or feeling is stronger than ”10”, - “Extremely strong”, “Maximal” – you can use a larger number, e.g. 12 or still higher (that’s why “Absolute maximum” is marked with a dot “●”).

It's very important that you report what you actually experience or feel, not what you think you should report. Be as spontaneous and honest as possible and try to avoid under- or overestimating. Look at the verbal descriptors and then choose a number.

When rating exertion give a number that corresponds to how hard and strenuous you perceive the work to be. The perception of exertion is mainly felt as strain and fatigue in your muscles and as breathlessness or any aches.

0 “Nothing at all”, means that you don’t feel any exertion whatsoever, no muscle fatigue, no breathlessness or difficulties breathing.

1 “Very weak” means a very light exertion. As taking a shorter walk at your own pace.

3 “Moderate” is somewhat but not especially hard. It feels good and not difficult to go on.

5 “Strong”. The work is hard and tiring, but continuing isn't terribly difficult. The effort and exertion is about half as intense as “Maximal”.

7 “Very strong” is quite strenuous. You can still go on, but you really have to push yourself and you are very tired.

10 “Extremely strong – Maximal” is an extremely strenuous level. For most people this is the most strenuous exertion they have ever experienced previously in their lives.

● Is “Absolute maximum” for example ”12” or even more.

Any questions?

Borg CR10 scale®

English

Appendix 5. Overall Risk Benefit Assessment for Study

OVERALL RISK-BENEFIT ASSESSMENT FOR STUDY

1. STUDY DESIGN AND OBJECTIVES

Study A1481324 is a randomized, double-blind, parallel-group study in adult patients with Pulmonary Arterial Hypertension (PAH) that is designed to assess mortality during long-term treatment with sildenafil at three doses. Four hundred and twenty-nine (429) subjects will be enrolled, to allow approximately 143 subjects to be randomly assigned to each treatment group, in a 1:1:1 basis to either blinded 5 mg (TID), 20 mg (TID) or 80 mg (TID) sildenafil citrate. Subjects will receive corresponding blinded matching placebo for the other 2 strengths. Approximately 80-120 sites with experience conducting PAH trials will participate in the study. The primary objective of the study is to test for the non-inferiority of sildenafil 80 mg TID vs. 5 mg TID for mortality (ie, to determine if the mortality rate with 80 mg TID dose is no worse than double the mortality rate for the 5 mg TID dose). The study is expected to complete enrollment in about 4.3 years with a total duration of about 7.7 years to reach the required number of events (143 deaths). Interim analyses with statistical analyses on hypotheses testing will be performed when about 50% and 75% of mortality events have occurred. Subjects who discontinue study treatment will continue to be followed for mortality until the completion of the study.

Primary Efficacy Endpoint:

- Time to death (Mortality).

Secondary Efficacy Endpoints:

- Time to first event (Clinical Worsening); and
- 6MWD at Months 6 and 12.

Clinical worsening for the purpose of this study is defined as:

- All-cause mortality;
- Hospital stay for worsening PAH (including but not limited to right heart failure [RHF], initiation of prostanoids, lung transplantation, or septostomy); or
- Disease progression (defined as a reduction from baseline in the 6MWD test by at least 15% and worsening functional class from baseline, both confirmed by a 2nd test/evaluation within 2 weeks (cannot be performed on same day). Patients with functional class IV at baseline only need to meet the 6MWD criteria as they cannot have deterioration in functional class. The date of the event will be the first date of the two 6MWTs.
- Potential Benefits.

The rationale for including the 5 mg TID dose in this trial is that the minimum effective dose of sildenafil is not known. The results of study A1481244 (A Multinational, Multicentre, Randomized, Parallel Group, Double-Blind Study to Assess the Efficacy and Safety of 1 mg, 5 mg and 20 mg TID of Oral Sildenafil in the Treatment of Subjects Aged 18 Years and Over With Pulmonary Arterial Hypertension (PAH)) indicated that the change from baseline in 6MWD was clinically significant in the 5 and 20 mg groups (mean changes of 41 m and 38 m, respectively), but smaller and not clinically significant in the 1 mg group (mean change of 14 m). Thus, in this study (A1481244), a dose of 5 mg TID demonstrated a similar effect on exercise capacity as 20 mg TID. Therefore, it is important to evaluate whether doses lower than 20 mg TID might be similarly effective and relatively safer than the current recommended dose of 20 mg TID when used for the long-term treatment of adult PAH.

The rationale for inclusion of the 80 mg TID dose is that, while the current US label does not recommend sildenafil at doses above 20 mg TID, it is known from prescribing practices that some adult patients with PAH are prescribed doses up to 80 mg. Of note, Study A1481140 (A Multinational, Multi-Centre, Randomised, Double-Blind, Double-Dummy Placebo-Controlled Study to Assess the Efficacy and Safety of 20, 40, and 80 mg TID Sildenafil in the Treatment of Pulmonary Arterial Hypertension in Subjects Aged 18 Years and Over) demonstrated that at the recommended dose of 20 mg TID, a placebo-corrected increase in walk distance of 45 m was observed ($p<0.0001$). Placebo-corrected increases of 46 m ($p<0.0001$) and 50 m ($p<0.0001$) were also observed in subjects on sildenafil 40 mg and 80 mg sildenafil TID, respectively, indicating no significant difference in effect between sildenafil doses. Out of 277 subjects who were treated in A1481140, 259 subjects were treated in a separate long-term extension study (A1481142). In general, increases in the 6MWD were consistent at all time-points and sustained throughout the period of observation (over 4 years). The changes in the BORG dyspnoea test score from the A1481140 baseline by visit up to Month 54 showed no worsening of breathlessness with increased distance walked. The improvements from A1481140 baseline in the SF-36 Quality of Life (QoL) domain scores for all subjects were similar at all follow-up time-points indicating long-term maintenance of the effect. Therefore, it is important to determine the long-term adverse event profile of doses higher than the approved dose. Mean treatment effects consistently showed improvement in 6MWD in all sildenafil groups compared to placebo in all adult subpopulations studied to date. Of particular note is this improvement in patients in WHO Functional Class II and PAH associated with connective tissue disease (CTD; scleroderma, CREST, mixed CTD and systemic lupus erythematosus). At the recommended doses of 20 mg TID, the increases in walk distance were comparable between the different disease groups, being 40 (95% CI 14, 66) and 55 (95% CI 24, 85) meters in the PPH and CTD groups, respectively. The sildenafil population contained 107 (39%) subjects in WHO Functional Class II, and treatment with sildenafil resulted in an improvement in 6-minute walk test distances at all doses and in particular, an improvement of 50 (95% CI 25,74) meters was seen with the recommended dose of 20 mg TID. Therefore, it is important to determine the long-term adverse event profile of doses higher than the approved dose.

The relative effects of sildenafil on mortality when administered at the three doses (5 mg, 20 mg and 80 mg TID) in adults with PAH will be evaluated in this clinical study. In addition, the relative effects on clinical worsening and 6-minute walking distance (6MWD) will also be assessed.

Use of Sildenafil citrate

The potential risks associated with sildenafil identified are based on the totality of nonclinical and clinical data across the entire development program.

Vasodilatory action

Sildenafil has vasodilator properties, resulting in mild and transient decreases in blood pressure. Subjects with certain underlying conditions could be adversely affected by such vasodilatory effects, for example, patients with resting hypotension (blood pressure <90/50 mmHg), patients with fluid depletion, severe left ventricular outflow obstruction or autonomic dysfunction. Subjects with hypotension or acutely decompensated heart failure are excluded from participation in the study.

Cardiovascular risk factors

Serious cardiovascular events, including myocardial infarction, sudden cardiac death, ventricular arrhythmia, cerebrovascular hemorrhage and transient ischemic attack have been reported postmarketing in temporal association with the use of sildenafil for erectile dysfunction. Most, but not all, of these patients had pre-existing cardiovascular risk factors. Many of these events were reported to occur during or shortly after sexual activity, and a few were reported to occur shortly after the use of sildenafil without sexual activity. Others were reported to have occurred hours to days after the use of sildenafil and sexual activity. It is not possible to determine whether these events are related directly to sildenafil, to sexual activity, to the patient's underlying cardiovascular disease, to a combination of these factors, or to other factors. Subjects with a history of these conditions are excluded from participation in the study.

Visual events

Non-arteritic anterior ischemic optic neuropathy (NAION), a rare condition and a cause of decreased vision or loss of vision, has been reported rarely post-marketing with the use of all phosphodiesterase type 5 (PDE5) inhibitors, including sildenafil. Most of these patients had risk factors such as low cup to disc ratio ("crowded disc"), age over 50, diabetes, hypertension, coronary artery disease, hyperlipidemia and smoking. An observational study evaluated whether recent, episodic use of PDE5 inhibitors (as a class), typical of erectile dysfunction treatment, was associated with acute onset of NAION. The results suggest an approximately 2-fold increase in the risk of NAION within 5 half-lives of PDE5 inhibitor use. Based on published literature, the annual incidence of NAION is 2.5-11.8 cases per 100,000 males aged ≥ 50 per year in the general population. In case of sudden visual loss, patients should be advised to stop taking sildenafil and consult a physician immediately.

Individuals who have already experienced NAION are at increased risk of NAION recurrence. Subjects with a history of NAION are excluded from participation in the study.

Alpha-blockers

Concomitant administration of sildenafil to patients taking alpha-blocker therapy may lead to symptomatic hypotension in a few susceptible individuals. In order to minimize the potential for developing postural hypotension, patients should be hemodynamically stable on alpha-blocker therapy prior to initiating sildenafil treatment. Subjects enrolled in the study must be stable on treatment for 30 days prior to randomization.

Veno-occlusive disease

Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno occlusive disease. Subjects with a history of pulmonary embolism are excluded from participation in the study.

Retintis pigmentosa

The safety of sildenafil has not been studied in patients with known hereditary degenerative retinal disorders such as retinitis pigmentosa (a minority of these patients have genetic disorders of retinal phosphodiesterases). Subjects with a history of degenerative retinal disorders are excluded from participation in the study.

Bleeding disorders

Studies with human platelets indicate that sildenafil potentiates the antiaggregatory effect of sodium nitroprusside *in vitro*. There is no safety information on the administration of sildenafil to patients with bleeding disorders or active peptic ulceration. Subjects with any severe acute or chronic medical condition or laboratory abnormality will be excluded from participation in the study.

Priapism

Sildenafil should be used with caution in patients with anatomical deformation of the penis (such as angulation, cavernosal fibrosis or Peyronie's disease), or in patients who have conditions which may predispose them to priapism (such as sickle cell anemia, multiple myeloma or leukemia). Subjects with known priapism are excluded from participation in the study.

Hearing impairment

Sudden decrease or loss of hearing has been reported in a small number of postmarketing and clinical trials cases with the use of all PDE5 inhibitors, including sildenafil. Most of these patients had risk factors for sudden decrease or loss of hearing. No causal relationship has been made between the use of PDE5 inhibitors and sudden decrease or loss of hearing. Subjects with known hearing loss are excluded from participation in the study.

Pregnancy Related Risks / Use of Birth Control

The effects of sildenafil on a pregnancy, or a nursing child are not known. Pregnant or breastfeeding females are excluded from participation in the study. Women of childbearing potential (physically able to have children) who are sexually active are required to use birth control consistently and correctly during the study and for at least 28 days after their last dose of study drug.

Vitamin K antagonists

The incidence of epistaxis was higher in patients with pulmonary arterial hypertension secondary to connective tissue disease (sildenafil 12.9 %, placebo 0 %) than in primary pulmonary hypertension patients (sildenafil 3.0 %, placebo 2.4 %) and was higher in sildenafil-treated patients treated with concomitant oral vitamin K antagonist (8.8 % versus 1.7 % not treated with concomitant vitamin K antagonist). This event will be monitored closely in the study.

Co-administration with Bosentan

In a study of PAH patients (primary PAH and secondary PAH associated with CTD) on background bosentan therapy, no incremental benefit (6-minute walk distance (6MWD)) of sildenafil co-administered with bosentan was demonstrated over bosentan alone. The results of the 6MWD were different between primary PAH and PAH associated with CTD. The mean result of the combination of sildenafil and bosentan was numerically worse than bosentan alone in patients with PAH associated with CTD but numerically better than bosentan alone in patients with primary PAH. Therefore, the combined use of sildenafil and bosentan in patients enrolled in this study is not permitted.

CYP3A4 Inhibitors

A population pharmacokinetic analysis of data from patients in clinical trials indicated an approximately 30% reduction in sildenafil clearance when sildenafil was co-administered with mild/moderate CYP3A4 inhibitors. This concentration range covers the increased sildenafil exposure observed in specifically-designed drug interaction studies with CYP3A4 inhibitors (except for potent inhibitors such as ketoconazole, itraconazole, and ritonavir). Concurrent treatment with potent CYP3A4 inhibitors while taking study medication is prohibited during the study.

CYP3A4 Inducers

A population pharmacokinetic analysis of data from patients in clinical trials indicated an approximately 3-fold increase in sildenafil clearance when sildenafil was co-administered with mild CYP3A4 inducers. Concomitant administration of potent CYP3A4 inducers is expected to cause substantial decreases in plasma levels of sildenafil. Concurrent treatment with potent CYP3A4 inducers while taking study medication is prohibited during the study.

Use of Placebo

Subjects will receive blinded placebo tablets with their active treatment to maintain the blind. Since all subjects will be receiving active treatment, no risk from use of placebo has been identified.

2. ADDITIONAL RELEVANT INFORMATION

Not applicable.

3. CONCLUSION

In conclusion, Pfizer considers that the results of the nonclinical toxicity and safety pharmacology studies together with the data from the clinical program confirms that treatment with sildenafil in patients with PAH of various etiologies and severities is associated with improvements in exercise ability and favorable effects on hemodynamics and other measures of efficacy such as BORG Dyspnea Score, WHO Functional Class, QoL, and use of background medication. Additionally, the potential long-term effectiveness of this agent is suggested as demonstrated in open label studies A1481142 and A1481153. Risks to subjects with PAH are minimized through appropriate pre-enrollment screening, specific exclusion criteria, and close safety monitoring throughout the study including the use of an external data safety monitoring committee. Clinical events will be adjudicated by a Clinical Endpoint Adjudication Committee.

Complete information for this compound may be found in the Summary of Data and Guidance for Investigator (Section 7) of the Investigator's Brochure.

Appendix 6: Continuity of study treatment and dose adjustment (5 mg to 20mg (TID)) in Ukraine, Russia, Czech Republic, Bosnia and Herzegovina, and Mexico.

A planned interim analysis was conducted after 50% of the required number of events (72 deaths) occurred (data cutoff 30 May 2020). The Data Monitoring Committee (DMC) subsequently convened on 01 July 2020 to review the results of the interim analysis based on the primary efficacy endpoint of time to death.

The DMC recommended and the formal notification was received by Pfizer on 07 July 2020 to stop the trial for the following reasons:

1. Primary Study Objective - noninferiority of sildenafil 80 mg (TID) vs 5 mg (TID) dose with respect to mortality - was met
2. Safety concern regarding mortality with sildenafil 5 mg (TID) dose

Following acceptance of the DMC recommendation on 08 July 2020, an Investigator's Letter was sent to all participating sites on 13 July 2020 communicating the DMC recommendation. Sites were instructed to initiate the study closeout activities by scheduling an End of Treatment Visit no later than 15 August 2020 for all subjects currently receiving study treatment. After completing the End of Treatment Visit, subjects may continue on prescription sildenafil and/or other available therapies, at the investigator's discretion.

The sites with subjects who do not have post-study PAH treatment options currently available received a second Investigator's letter, on 30 July 2020. For those subjects, sites were instructed to schedule a regular Study Visit before 15 August 2020 to ensure that all subjects receiving sildenafil 5 mg (TID) discontinue their treatment as soon as possible and continue on 20 mg (TID) (the currently approved dose). This needs to be accomplished in a blinded fashion at the scheduled visit as follows:

- Subjects must be informed about the DMC recommendation and their consent to continue in the study obtained.
- Subjects must be informed that if they agreed to continue participation in the study and are currently receiving 5 mg (TID), their dose would be automatically increased to 20 mg (TID); for subjects currently receiving either 20 mg sildenafil (TID) or 80 mg sildenafil (TID), the dose would remain unchanged. Both the investigator and the subject will remain blinded to the study treatment.
- A new blinded study drug kit will be assigned and dispensed to all subjects.

The IVRS/IWRS system will be set to close the sildenafil 5 mg (TID) treatment arm and to replace it with sildenafil 20 mg (TID). This will ensure that all subjects in the 5 mg TID arm will be increased to 20 mg TID in a blinded manner, as follows:

1. Subjects on 5 mg TID will be increased to 20 mg TID and will continue in the study on 20 mg TID until the End of Treatment Visit.
2. For subjects on 20 mg TID or 80 mg TID, the dose will remain unchanged until the End of Treatment Visit.

To ensure continuity of study treatment with sildenafil, subjects are allowed to stay in the study until they can be enrolled into a program that will provide access to prescription sildenafil at the time of the End of Treatment Visit.

After completing the End of Treatment Visit, a 28-day follow-up visit will be scheduled at which time the End of Study CRF page will be completed. This will conclude the subject's participation in the trial.