Protocol A1481324

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

Statistical Analysis Plan (SAP)

Version: PPD (Clinical Statistics, PPD) - Version 1

PPD (Clinical Statistics, PPD) - Version 2

Dates: 22 April 2014 – Version 1
24 March 2021 - Version 2

TABLE OF CONTENTS

APPENDICES

1. AMENDMENTS FROM PREVIOUS VERSION(S)

Version	Date	Author(s)	Summary of Changes/Comments
2	March 24, 2021	PPD	As of protocol amendment 1, dated 18 Nov 2014 the following changes have been incorporated: • Added definition of on-treatment deaths to Section 8.1. As of Blind Data Review (BDR1), dated 19 Aug 2019 the following changes have been incorporated: • Updated Section 4.1 to include secondary hypotheses/treatment comparisons for 80 mg vs. 20 mg, and 20 mg vs. 5 mg. • Clarified text for Safety population (Section 5.3). For this study Safety population is the same as ITT population. • Added rules for randomization stratification misallocations in Section 5.5. • Updated Section 6.1 categories labels for Change from Baseline in 6MWD 6 Month Walking Distance). • Updated Section 6.2 to include reference to protocol section referring to non-efficacy endpoints screening definitions. • Updated Section 8.1 to include secondary treatment comparisons for 80 mg vs. 20 mg, and 20 mg vs. 5 mg as secondary analysis of primary efficacy endpoint (time-to-death). • Updated Section 8.2 to include 6MWD change from baseline at Month 6 as a secondary endpoint. • Added 6MWD change from baseline at Month 6 as a secondary analysis to Table of summary of efficacy analyses in Section 8.3. • Added a super script “2” to Table 3 to refer to the Borg Score analysis for change from baseline, by randomization stratification factors (Subgroup column).

			• Added two new references to Section 10. • Added algorithm for calculation of PAH at treatment stratification in Appendix 11.1. • All SAS & StatExact Codes are presented in Appendix Sections 11.2.1-11.2.6. • Updated Appendix 11.2.1 and 11.2.4 on SAS code for the Cox Proportional Model and MMRM analysis models, respectively. • Added visit window for secondary and tertiary endpoints to Appendix 11.3. As of protocol amendment 2, dated 28 August 2020 the following changes has been incorporated: • Added to Section 8.2 a sensitivity analyses for time to first adjudicated clinical worsening events. • Added a new Section 9 for DMC review of unblinded interim analysis and its recommendation. This recommendation led to an update regarding study conduct and currently includes a new safety sensitivity analysis for death and SAEs. • Added sensitivity safety analysis for subjects who were switch from 5 mg to 20 mg treatment (Section 9.1).

2. INTRODUCTION

This document describes the planned data summaries and statistical analyses for Protocol A1481324, entitled "A Multi-national, Multicenter Study to Assess the Effects of Oral Sildenafil on Mortality in Adults with Pulmonary Arterial Hypertension (PAH)". It is meant to supplement the study protocol which should be referred to for details regarding the objectives and design of the study. Any deviation to this analysis plan will be described in the Clinical Study Report.

Note: in this document any text taken directly from the protocol is ***italicised***.

2.1. 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.

2.2. Study 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.

3. INTERIM ANALYSES, FINAL ANALYSES AND UNBLINDING

An independent Data Monitoring Committee (DMC) will be engaged to review efficacy endpoints 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.

Interim analyses with statistical analyses on hypotheses testing will be performed for primary comparison of 80 mg vs 5 mg 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.

Treatment unblinding to study team members, investigators and subjects and final analyses will be done after the database lock.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

The primary objective for the study is to test for the non-inferiority of sildenafil 80 mg TID vs. 5 mg TID for mortality; mortality rate with the 80 mg TID is no worse than double the mortality rate for the 5 mg TID.

The hypotheses for the primary endpoint of mortality are:

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

The hypotheses will be tested at an overall level of 2.5% (1-sided).

Additional treatment comparisons for 80 mg vs 20 mg, and 20 mg vs. 5 mg will be performed where these will be considered secondary comparisons. There will be no p-value adjustment for multiplicity.

4.2. Statistical Decision Rules

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.

5. ANALYSIS SETS

5.1. Full Analysis Set

The intent-to-treat population (ITT) will consist of all randomized patients treated with study treatment. The primary efficacy analysis will be conducted using ITT population.

5.2. 'Per Protocol' Analysis Set

The Per-protocol population (PP) will consist of randomized subjects who receive at least 1 dose of study treatment and contribute at least 1 post-baseline visit. The time to event endpoint for this PP will consist of all events that occur while the subjects are on study treatment without major protocol deviations/violations through 35 days after the last dose of the study treatment, since randomization. This collection period (from randomization to

35 days after the last dose of the study treatment) will also be applied to other efficacy endpoints with PP analyses.

The efficacy analyses of primary and secondary endpoints will be conducted using the per-protocol (PP) population as sensitivity analyses.

5.3. Safety Analysis Set

The safety analysis set will include all randomized subjects treated with study treatment (same as ITT population).

5.4. Treatment Misallocations

If a subject is:

- Randomized but not treated, then they will be reported under their randomized treatment group but will not be included in the efficacy analyses and safety analyses as actual treatment is missing.
- Treated but not randomized, then by definition they will be excluded from the efficacy analyses since randomized treatment is missing but will be reported under the treatment, they actually received for all safety analyses.
- Randomized but took incorrect treatment, then they will be reported under their randomized treatment group for all efficacy analyses but will be reported under the treatment they actually received for all safety analyses.

5.5. Randomization Stratification Misallocations

- Randomized as PAH Treatment Naïve but should have been randomized as On PAH Treatment.
- Randomized as On PAH Treatment but should have been randomized as PAH Treatment Naive.

Classification of a patient into these stratums will be done programmatically and is presented on Appendix 1.

Subjects will be put in the stratum that reflects clinical reality and will be analyzed under the correct determined stratum, ie, stratum determined by clinical data that they should have been randomized. A data listing will be provided for subjects with randomization stratification error.

5.6. Protocol Deviations

Significant protocol deviations may include, but not limited to:

- Failure to meet significant inclusion/exclusion criteria.

- No evidence of adequate compliance to study medication (See Protocol Section 5.3.4 for definition of compliance).

- Receiving excluded concomitant medication.

Protocol deviations (including list of excluded concomitant medications) which lead to exclusion of subjects from PP analyses will be specified before database lock.

6. ENDPOINTS AND COVARIATES

6.1. Efficacy Endpoint(s)

1. Primary Efficacy Endpoint: Time to death (Overall Survival)

For a subject with death reported, time to death will be calculated as (Death Date) – (First Dose Date) +1.

Otherwise, survival time will be calculated as (Censoring Date) – (First Dose Date) +1, with censoring date determined as the following:

- For subjects who complete the study, they will be censored at their last visits.

- For subjects who discontinue but are believed to be alive at the end of study or are lost to follow-up, they will be censored at the later of the last known date in the study, and the date the subject was last known to be alive from the latest survival follow-up.

2. Secondary and Tertiary Efficacy Endpoints:

   A. Time to First Event of Clinical Worsening (secondary endpoint)

Clinical worsening for the purpose of this study is defined[1] as:

- All-cause mortality;

- Non-elective hospital stay for worsening PAH (including but not limited to right heart failure [RHF], initiation of IV prostanoids, lung transplantation, or septostomy); or

- Disease progression (defined as a reduction from baseline in the 6MWD test by 15%, confirmed by *2nd test* done within 2 weeks (cannot be performed on same day), and worsening functional class).

For a subject with clinical worsening, time to first event will be calculated as (First Event Date) – (First Dose Date) +1.

For a subject either completes the study or discontinues from the study without clinical worsening, time to first event will be censored at the last date on which clinical worsening is assessed, and time to first event will be calculated as (Censoring Date) – (First Dose Date) +1.

Events of clinical worsening will be reported on a CRF form. These events will also be evaluated by a Clinical Endpoints Adjudication Committee (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 means a positive change from baseline and worsening refers to a negative change from baseline. In addition, for each subject at each visit, 6MWD will be categorized as the following:

- <380 m, but not missing;
- >=380 m.
    - Maintenance of >=380 m for subjects who had baseline value >=380 m;
    - Achievement of >=380 m for subjects who had baseline value <380 m (non missing).

B. BORG Score (tertiary endpoint)

BORG will be measured at Screening, Day 1 and every 6 months during the study, and at the end of study treatment. Measurement taken on Day 1 will be considered as Baseline value. If Day 1 value is missing and the one taken at Screening is non-missing, then the value taken at Screening will be considered as the baseline value. Change from baseline at each study visit will be calculated as (Result at Post Baseline Study Visit) – (Baseline Value). The visit windows defined for 6MWD above will also apply to BORG score (see Appendix 3).

C. WHO pulmonary hypertension functional class (tertiary endpoint)

WHO pulmonary hypertension functional class will be measured at Screening, Month 3, 6, 9, 12 and every 6 months subsequently during the study, and at the end of study treatment. Measurement taken at Screening will be considered as Baseline value. Change from baseline at each study visit will be calculated as (Result at Post Baseline Study Visit) – (Baseline Value). Visit windows for this tertiary endpoint are defined in Appendix 3.

6.2. Safety Endpoints

A. Treatment-emergent Adverse Events (AE)

A treatment-emergent AE is an AE with an onset after initiation of study treatment, or an AE present at initiation of study treatment that subsequently worsens (ie, increases in severity or relationship to study treatment).

A 3-tier approach will be used to summarize treatment-emergent AEs. Under this approach, AEs are classified into 1 of 3 tiers. Different analyses will be performed for different tiers (See Section 8.4).

Tier-1 events: These are pre-specified events of clinical importance and are maintained in a list in the product's Safety Review Plan.

Tier-2 events: These are events that are not tier-1 but are "common". A MedDRA PT is defined as a tier-2 event if there are at least 5% in any treatment group.

Tier-3 events: These are events that are neither tier-1 nor tier-2 events.

B. Other Safety Endpoints

- Serious AE (SAE);
- Death;
- Concomitant medication;
- Subject discontinuation;
- Vital signs;
- Laboratory results;
- Physical examination;
- Duration of treatment.

For non-efficacy endpoint, study follows protocol screening definition (see Section 6.1 in protocol).

6.3. Covariates

The analyses of the primary and secondary endpoints will be performed using the following two randomization stratification factors as covariates:

- PAH treatment at entry (PAH-treatment naïve vs. on PAH-treatment);
- Etiology of PAH (idiopathic vs. secondary to CTD/surgical repair).

The analyses of 6MWD will also include baseline results as a covariate.

7. HANDLING OF MISSING VALUES

Missing data will not be imputed. For 6MWD at Month 6 and 12, mixed model for repeated measure method (MMRM) will be used for statistical analyses for treatment comparisons. For MMRM, all available data in Month 6 and 12 will be included in the analyses and any missing data are assumed missing at random. Details of the analyses are described in Section 8.

8. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1. Primary Efficacy Analyses

For time to death, treatment comparison will be conducted using Cox proportional hazard regression model.[4,5] The estimate of the hazard ratio for treatment (sildenafil 80 mg TID/5 mg TID, 80 mg/20 mg TID, and 20 mg TID/5 mg TID) together with its confidence interval (CI) and p-value will be provided. Significance level will be determined using the O'Brien-Fleming approach at each interim analysis and the final analysis. The overall significance level is set at 2.5% (1-sided).

The Cox proportional hazard regression model described above will be conducted using PP population as sensitivity analysis.

Time to death analysis will be conducted 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) based on ITT population and PP population.

The duration of overall survival will be summarized graphically using Kaplan-Meier plots for each of the treatment group. Tabular summaries of the Kaplan-Meier curves giving the median, quartiles, mean, standard error of the mean and range of overall survival will also be provided for each treatment group. Number of events and survival rate at each year will also be tabulated by treatment groups where on-treatment deaths are defined as deaths <=7 days post last study dose.

Analyses will be done based on ITT and PP population. Similar analyses will also be conducted for each level of randomization stratification factors.

For treatment comparison, the exact Logrank test will be conducted as sensitivity analysis using ITT and PP populations.

As described in Section 4.1, time to death secondary analyses will be conducted for treatment comparisons for 80 mg vs. 20 mg, and 20 mg vs. 5 mg. All above analyses/methods will be performed for these two treatment comparisons and are considered secondary analyses of the primary efficacy endpoint (time-to-death).

8.2. Efficacy Analyses for Secondary and Tertiary Endpoints

There will be no p-value adjustment for secondary and tertiary data analyses.

A. Time to First Event of Clinical Worsening

Cox proportional hazard model, analyses using Kaplan-Meier method described above will be used for time to first event of clinical worsening. The analyses will be done using ITT population and PP population for overall subjects and by randomization stratification factors.

In addition, a summary table will be presented showing n(%) of subjects with first qualifying clinical worsening event by event (none, all-cause mortality, non-elective hospital stay for worsening PAH or disease progression) for each study treatment group using ITT and PP population for overall subjects and by randomization stratification factors.

Sensitivity analysis for the secondary endpoint time to first event of clinical worsening will be performed for adjudicated clinical worsening events. All the above described analysis will be conducted.

B. 6MWD

For change from baseline, descriptive summaries (n, mean, SD, 95% CI of the mean, median, and range) will be tabulated at each study visit for each treatment group using ITT and PP population for overall subjects and by randomization stratification factors.

Percent of subjects in each category of 6MWD and change will be tabulated at each study visit for each treatment group using ITT and PP population for overall subjects and by randomization stratification factors. The 95% CI of the percentage will also be tabulated (except for the category of 'missing').

For change from baseline at Month 6 and Month 12, treatment comparisons will be conducted using MMRM with covariates of baseline value, treatment and randomization stratification factors. Least square mean difference, its 95% CI and p-value will be tabulated for each treatment comparison (sildenafil 80 mg TID vs. 5 mg TID, 80 mg TID vs. 20 mg TID and 20 mg TID vs. 5 mg TID).

Analyses will be done based on ITT and PP populations for overall subjects and subgroups by randomization stratification factors.

Figures will be provided for the least square mean change from baseline and 95% CI at Month 12 for each study treatment group for ITT population and PP population for overall subjects and by randomization stratification factors.

C. BORG Score

For change from baseline, descriptive summaries will be tabulated at each study visit for overall and by randomization stratification factors for each treatment group.

The BORG assessment will only be valid for analysis at any specific timepoint if a 6MWT has been performed on the same day. If a BORG assessment is recorded on a different day from the 6MWT then the BORG results for that timepoint will be considered missing.

A non-parametric analysis using stratified Wilcoxon (Van-Elteren) method will be used for treatment comparison at Month 12. The stratified Wilcoxon test will include randomization stratification factors. The median difference and its 95% CI calculated using the Hodges-Lehmann estimator will be presented along with the p-value for the Van-Elteren test for each treatment comparison (sildenafil 80 mg TID vs. 5 mg TID, 80 mg TID vs. 20 mg TID and 20 mg TID vs. 5 mg TID). The analyses will be done for ITT population for overall subjects.

D. WHO Pulmonary Hypertension Functional Class

The number and percentages of subjects with each WHO pulmonary hypertension functional class will be tabulated by study visit, for overall and by randomization stratification factors for each treatment group. In addition, a table will be presented by study visit showing number and percentages of subjects improving by at least 2 classes, improving by 1 class, not changing, worsening by 1 class, worsening by at least 2 classes, discontinued, died or missing. The table will be presented for overall and by randomization stratification factors for each treatment group.

The analyses will be done for ITT population for overall subjects and by randomization stratification factors.

8.3. Summary of Efficacy Analyses

Endpoint	Analysis Set	Subgroup Analyses[2]	Statistical Method
Time-to-death[1]	ITT and PP	Yes	Cox proportional hazard regression
Time-to-death	ITT and PP	Yes	Kaplan-Meier for overall survival
Time-to-death	ITT and PP	Yes	Exact LogRank
Time-to-first event of clinical worsening	ITT and PP	Yes	Cox proportional hazard regression
Time-to-first event of clinical worsening	ITT and PP	Yes	Kaplan-Meier
Clinical worsening	ITT and PP	Yes	Descriptive: n (%) of each qualifying first event
6MWD change	ITT and PP	Yes	MMRM for Month 6 and 12
6MWD change	ITT and PP	Yes	Descriptive: summary statistics by study visit
6MWD change	ITT and PP	Yes	Descriptive: n (%) of each change category
6MWD	ITT and PP	Yes	Descriptive: n (%) of each category
BORG score change	ITT	No	Stratified Wilcoxon & Hodge-Lehmann estimates for Month 12
BORG score change	ITT	Yes	Descriptive: summary statistics by study visit
WHO pulmonary hypertension functional class	ITT	Yes	Descriptive: n(%) of each class and n(%) by each change category by study visit

[1] Primary analysis.

[2] By randomization stratification factor.

8.4. Safety Analyses

The following data will be summarized and listed by treatment and in accordance with the current Pfizer data standards: adverse events (all causality and study treatment related), concomitant medication, discontinuation, laboratory data, vital signs, and physical examination.

The following data will be listed by treatment and in accordance with the current Pfizer data standards: serious adverse events, death, ECG, and pregnancy test.

For treatment duration, descriptive summary statistics (n, mean (standard deviation), and median (range)) will be tabulated. In addition, n(%) of subjects will be calculated for the following categories of treatment duration:

- <1 year;
- 1-<2 years;
- 2-<3 years;
- 3-<4 years;
- 4-<5 years;
- 5-<6 years;
- 6-<7 years;
- >7 years.

For tier-1 and tier-2 treatment emergent adverse events, the risk assessment will be based on incidence proportions. For a given treatment group and event type, the incidence proportion is defined as the number of subjects having at least one event divided by total number of subjects in the safety population. In the case of events with zero counts, the incidence proportion will be zero.

Incidence proportion and its 95% CI will be tabulated for each tier-1 and tier-2 event by treatment group. For each treatment comparison (sildenafil 80 mg TID vs. 5 mg TID, 80 mg TID vs. 20 mg TID and 20 mg TID vs. 5 mg TID), difference in incidence proportion (risk difference [RD]) and its 95% CI will be produced. For tier-1 events, proportion in each treatment, 95% CI and p-values for treatment comparison will also be produced for each of the following safety topics (eye disorders, deafness, cardiovascular (rhythm abnormalities, cardiac failure, and myocardial infarction), cerebrovascular, and pregnancy-related). The specific MedDRA PTs describing each of these safety topics are contained in the Revatio Safety Review Plan (Target Medical Event [TME] List). The p-value and 95%CIs of the RD will be estimated using unconditional exact binomial methods.

The p-values and 95% CIs will not be adjusted for multiplicity (this should be noted via a footnote in the tables). Caution in interpreting the results should be taken for this reason and given the exploratory nature of these analyses.

In addition, a two-panel plot will be presented for tier-1 and tier-2 events. The left panel gives the proportions of AEs observed in each treatment group while the right panel displays 95% CI for the risk difference for each AE for each treatment comparison.

For the graphic display for tier-1 events, proportions of each safety topic in each treatment, its 95% CI and P-Value for each treatment comparison will be added.

8.5. Other Analyses

The following data will be summarized and listed by treatment and in accordance with the current Pfizer data standards: demographics, subject disposition, primary diagnosis, medical history, previous and concomitant medications.

Baseline characteristics will be summarized and tabulated, including the following data:

- PAH treatment at entry: n(%) for PAH-treatment naïve and on PAH-treatment;
- Etiology of PAH: n(%) for idiopathic, and secondary to CTD/surgical repair;
- WHO pulmonary hypertension functional class: n(%) for each class;
- Descriptive summary statistics (n, mean, SD, median and range) for:
    - 6MWD;
    - BORG score.

Number (%) of subjects with at least 80% compliance will be tabulated by study treatment and subject dosing records will be listed.

Baseline PAH background therapy and changes in the PAH background therapy will be listed and summarized.

If appropriate, exploratory analyses of primary and secondary endpoints by subgroup of gender, race, or ethnicity will be performed.

9. INTERIM ANALYSIS AND DMC RECOMMENDATION

Protocol Sections 9.5 and 9.6 pre-specified two interim analyses after 50% and 75% of the required number of events (143 deaths) have occurred and detailed on DMC responsibilities/recommendations, respectively.

A planned interim analysis was conducted after 50% of the required number of events (72 deaths) occurred. The Data Monitoring Committee (DMC) reviewed the results of the interim analysis based on the primary efficacy endpoint of time to death. DMC provided recommendation that the study be stopped as the primary objective (non-inferiority of the 80 mg TID arm vs 5 mg TID arm) had been met. The DMC also expressed a concern regarding the mortality in the 5 mg TID arm. Pfizer accepted the DMC recommendation; all participating sites were notified of DMC recommendation and the end of study activities were initiated.

As a result of the DMC recommendation, all subjects currently on sildenafil 5 mg TID were to be placed on prescription sildenafil or an alternative PAH treatment at the Investigator's discretion. However, there are sites with subjects who do not have post-study PAH treatment options available, for those subjects, investigators were advised to switch, in a blinded manner, the dose for subjects receiving 5 mg (TID) to 20 mg (TID) until the end the study. (See Protocol Appendix 6 for further details end of study activities and on continuity of study treatment and dose adjustment (5 mg to 20 mg (TID)).

An unblinded team, with no connection to the conduct of study, was created to communicate with DMC and regulatory agency. Study team continued to be blinded until final database lock.

9.1. Sensitivity Safety Analysis

If a subject is switched from 5 mg to 20 mg, they will be reported under their randomized treatment group for all efficacy analyses but will be reported under the treatment they first receive for all safety analyses. In addition, a sensitivity safety analysis for deaths, major AE and SAEs will be conducted on the subgroup of subjects that switched from 5 mg to 20 mg only.

In summary, study analyses tables will present data by treatment as follows:

- All efficacy analysis will be presented with 3 randomized arms (5 mg, 20 mg, 80 mg).
- All safety analysis will be presented with 3 actual treated arms (5 mg, 20 mg, 80 mg).
- Sensitivity analysis for the subgroup of patients who switch from 5 mg to 20 mg, for major safety endpoint (ie, deaths, AEs, SAEs) will be presented with 4 treated arms (5 mg, 20 mg, 80 mg, 5-20 mg).

10. REFERENCES

1. McLaughlin, Vallerie V. *et al* [2009], End Points and Clinical Trial Design in Pulmonary Arterial Hypertension, Journal of the American College of Cardiology, Vol.54, No.1, Suppl S, 2009, S907-107.

2. Longitudinal Data Analysis by Donald Hedeker and Robert D Gibbons Copyright @2006 John Wiley & Sons. Inc.

3. Chan ISF, Zhang Z. (1999). Test-based exact confidence intervals for the difference of two binomial proportions. Biometrics, 55:1201–1209.

4. Allison, P. D. 1995. Survival Analysis Using the SAS System: A Practical Guide. Cary NC: SAS Institute.

5. Cox, D. R. 1972. "Regression Models and Life Tables (with Discussion)." Journal of the Royal Statistical Society, Series B 34:187—220. Cox, D. R. & D. Oakes. 1984. Analysis of Survival Data. London: Chapman and Hall.

11. APPENDICES

Appendix 1. CLASSIFICATION OF PAH TREATMENT AT ENTRY (programmatically)

PAH Treatment Naïve:

Subjects were randomized as PAH Treatment Naïve and data are missing for PREVIOUS DRUG TREATMENT FOR PRIMARY DIAGNOSIS

or

Subjects met one of the criteria below based on data recorded on PREVIOUS DRUG TREATMENT FOR PRIMARY DIAGNOSIS:

- If there are no records for subjects when Con med Class = “"PREVIOUS DRUG TREATMENT FOR PRIMARY DIAGNOSIS"

Or

- Con med Class = “"PREVIOUS DRUG TREATMENT FOR PRIMARY DIAGNOSIS” and the concomitant medication preferred term(CMDECOD) is like ("AMBRISENTAN", "BERAPROST", "EPOPROSTENOL", "ILOPROST", "MACITENTAN", "OPSUMIT", "REVATIO", "SILDENAFIL", "TADALAFIL", "TRACLEER", "VELETRI", VENTAVIS", "ZEPAHEX")

and

- Calculation of duration since start of treatment (tr01sdt-cmstrt)+1 value is <28 days then patient is PAH treatment naïve.

On PAH Treatment:

Subjects met the criterion below based on data recorded on PREVIOUS DRUG TREATMENT FOR PRIMARY DIAGNOSIS:

- if CMCLAS = "PREVIOUS DRUG TREATMENT FOR PRIMARY DIAGNOSIS"

and

- The concomitant medication preferred term is like ("AMBRISENTAN", "BERAPROST", "EPOPROSTENOL", "ILOPROST", "MACITENTAN", "OPSUMIT", "REVATIO", "SILDENAFIL", "TADALAFIL", "TRACLEER", "VELETRI", "VENTAVIS", "ZEPAHEX")

and

- Calculation of the duration since start of treatment (tr01sdt-cmstrt)+1 value is >=28 days then patient is on PAH treatment.

Subjects will be put in the stratum that reflects clinical reality. Patients will be analyzed under the correct determined stratum, ie, stratum determined by clinical data that they should have been randomized.

Appendix 2. STATISTICAL METHODOLOGY DETAILS

Appendix 2.1. Sample SAS Code for Cox Proportional Hazards Model - Time-to-death Endpoint

Sample SAS (SAS Institute Inc.) code to fit the Cox proportional hazard model specified in Section 8.1 is given below:

```
proc phreg data= input dataset (where=(trtxn in ("treatment1" "treatment2")));
  class trtxn cohort;
  model Time_to*censor(1)=trtxn ;
    contrast 'treatment2 vs. treatment1' trtxn -1 1(values) / estimate=keyword (e.g.
    exp=exponentiates the contrast that is to be estimated) alpha=0.05;
run;
```

Where,
TX=treatment group
TIME_TO=time to death (survival days)
COHORT= stratification variable (all or by strata)
CENSOR=censoring variable, 1=censored, 0=event

Where the variable 'STRATA' has the following 4 levels:

- PAH-treatment naïve at study entry and disease etiology of idiopathic;
- PAH-treatment naïve at study entry and disease etiology of CTD/surgical repair;
- On PAH-treatment at study entry and disease etiology of idiopathic;
- On PAH-treatment at study entry and disease etiology of CTD/surgical repair.

Appendix 2.2. Sample SAS Code for KM Plots (LIFETEST) - Time-to-death Endpoint

The following SAS codes can be used for Kaplan-Meier plots/analysis:

```
PROC LIFETEST;
   TIME TIME_TO*CENSOR(1);
   STRATA TX;
   RUN;
```

Where,
TX=treatment group
TIME_TO=time to death (survival days)
CENSOR=censoring variable, 1=censored, 0=event

Appendix 2.3. Sample StatXact Code for Exact Logrank Test - Time-to-death Endpoint

The following StatXact (Cytel Inc.) codes can be used for statistical analysis of time to death (overall survival):

```
PROC TWOSAMPL DATA=;
   LO/EX;
   PO  TX;
   RE  TIME_TO;
   CE  CENSOR;
   STRATUM STRATA;
RUN;
```

Where the variable 'STRATA' has the following 4 levels:

- PAH-treatment naïve at study entry and disease etiology of idiopathic;
- PAH-treatment naïve at study entry and disease etiology of CTD/surgical repair;
- On PAH-treatment at study entry and disease etiology of idiopathic;
- On PAH-treatment at study entry and disease etiology of CTD/surgical repair.

Appendix 2.4. Sample SAS Code for MMRM Analyses - 6MWD Endpoint

Sample SAS code to fit the MMRM model specified in 8.1 is given below. The response variable Chg is change from baseline at Month 12, trtxn is treatment group, prev_tx = pah treatment at entry (pah-treatment naïve or on pah treatment) and etiology = etiology (idiopathic or secondary to CTD/surgical repair). The following SAS codes can be used for statistical analysis:

```
PROC MIXED data= input dataset;
CLASS trtxn PREV_TX  ETIOLOGY usubjid avisitn;
MODEL chg = BASE trtxn PREV_TX  ETIOLOGY avisitn trtxn*avisitn/solution;
REPEATED avisitn/TYPE=UN SUBJECT=usubjid(trt_n);
LSMEANS trtxn*avisitn/PDIFF TDIFF alpha=0.05 diff=control ('1' '4');
LSMEANS trtxn*avisitn/PDIFF TDIFF alpha=0.05 diff=control ('2' '4');
ods output lsmeans=lsmeansop  diffs=trtcmp;
RUN;
```

Appendix 2.5. Sample StatXact Code for the Exact Binomial test – Risk Difference AEs

Sample syntax for Proc Binomial in StatXact (Cytel Inc.) syntax for risk difference under Method 1 (Chan and Zhang, 1999):[3]

```
PROC BINOMIAL;
        BY EVENT;
        RISKDIFF / EX ONE STD;
        POPL _TX;
        OUTCOME _EXIST;
RUN;
```

Appendix 2.6. Sample SAS Code for the Wilcoxon (Van-Elteren) Method & Hodges-Lehmann Estimates - BORG Score Endpoint

```
ODS TRACE ON;
ods output  HodgesLehmann=hodges1_1(outputdata);
proc npar1way hl data=input dataset
      align=strata;
      class trtxn;                  /*only select 2 treatment groups for comparison*/
      strata cohort;                  /*stratification variable*/
      var chg;                       /*Borg score change from baseline at month 12*/
 run;
ODS OUTPUT CLOSE;
ODS TRACE OFF;

ODS TRACE ON;
ods output  WilcoxonStrataTest=Van1_1(outputdata);
proc npar1way wilcoxon data= input dataset;
        class trxn;          /*only select 2 treatment groups for comparison*/
        strata cohort;          /*stratification variable*/
        var chg;               /*Borg score change from baseline at month 12*/
       run;
ODS OUTPUT CLOSE;
ODS TRACE OFF;
```

The following SAS codes can be used to produce p-values from Van-Elteren test:

```
PROC FREQ;
   TABLES PREV_TX * ETIOLOGY * TX*RESULTS
            /CMH2    SCORES=MODRIDIT;
   RUN;
```

Appendix 3. VISIT WINDOWS

Appendix 3.1. Visit Window for 6MWD and Borg Score Endpoints

For by-visit analyses on endpoint of 6 Minutes Walk Distance (6MWD) and BORG score the visit windows are defined as follows:

Visit	Target Day	Window
Screening	Up to 21 Days Prior to Date of Randomization[1]	Day -20 – Day 0
Day 1	Date of Randomization[1]	Day 1
Month 6	Day 183	Day 2-Day 274
Month 12	Day 365	Day 275 – Day 456
Month 18	Day 548	Day 457 – Day 639
Month 24	Day 730	Day 640 – Day 821
Month 30	Day 913	Day 822 – Day 1004
Month 36	Day 1095	Day 1005 – Day 1186
Month 42	Day 1278	Day 1187 – Day 1369
Month 48	Day 1460	Day 1370 – Day 1551
Month 54	Day 1643	Day 1552 – Day 1734
Month 60	Day 1825	Day 1735 – Day 1916
Month 66	Day 2008	Day 1917 – Day 2099
Month 72	Day 2190	Day 2100 – Day 2281
Month 78	Day 2373	Day 2282 – Day 2464
Month 84	Day 2555	Day 2465 – Day 2646
Month 90	Day 2738	Day 2647 – Day 2829
Month 96	Day 2920	Day 2830 – Day 3011

[1] If first dose date is later than randomization date, first dose date will be considered as Day 1.

If there are multiple records within a visit window, the one closest to the target day will be chosen for statistical analyses; for records with equal distance to the target day, the one that occurs at a later time will be selected for statistical analyses.

Appendix 3.2. Visit Windows for WHO Pulmonary Hypertension Functional Class

For by-visit analyses on endpoint of WHO pulmonary hypertension functional class the visit windows are defined as follows:

Visit	Target Day	Window
Baseline	Up to 21 Days Prior to or on Date of Randomization[1]	Day -20 – Day 1
Month 3	Day 91	Day 2 – Day 137
Month 6	Day 183	Day 138 – Day 229
Month 9	Day 274	Day 229 – Day 320
Month 12	Day 365	Day 321 – Day 456
Month 18	Day 548	Day 457 – Day 639
Month 24	Day 730	Day 640 – Day 821
Month 30	Day 913	Day 822 – Day 1004
Month 36	Day 1095	Day 1005 – Day 1186
Month 42	Day 1278	Day 1187 – Day 1369
Month 48	Day 1460	Day 1370 – Day 1551
Month 54	Day 1643	Day 1552 – Day 1734
Month 60	Day 1825	Day 1735 – Day 1916
Month 66	Day 2008	Day 1917 – Day 2099
Month 72	Day 2190	Day 2100 – Day 2281
Month 78	Day 2373	Day 2282 – Day 2464
Month 84	Day 2555	Day 2465 – Day 2646
Month 90	Day 2738	Day 2647 – Day 2829
Month 96	Day 2920	Day 2830 – Day 3011

[1] If first dose date is later than randomization date, first dose date will be considered as Day 1.

If there are multiple records within a visit window, the one closest to the target day will be chosen for statistical analyses; for records with equal distance to the target day, the one that occurs at a later time will be selected for statistical analyses.