STATISTICAL ANALYSIS PLAN

Study Title:	A DOSE-RANGING STUDY OF THE EFFICACY AND SAFETY OF BARDOXOLONE METHYL IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION
Name of Test Drug:	Bardoxolone Methyl
Sponsor:	Reata Pharmaceuticals, Inc
Protocol No.:	402-C-1302
Protocol Version/Date	26-Jan-2017 (Protocol Version 7.0)
Author Biostatistician:	Megan O'Grady, PhD
Analysis Plan Version/Date:	Version 3.0 / 14-June-2018

CONFIDENTIAL AND PROPRIETARY INFORMATION

SPONSOR APPROVAL

A DOSE-RANGING STUDY OF THE EFFICACY AND SAFETY OF BARDOXOLONE METHYL IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

Table of Contents

Rationale for Version 3.0

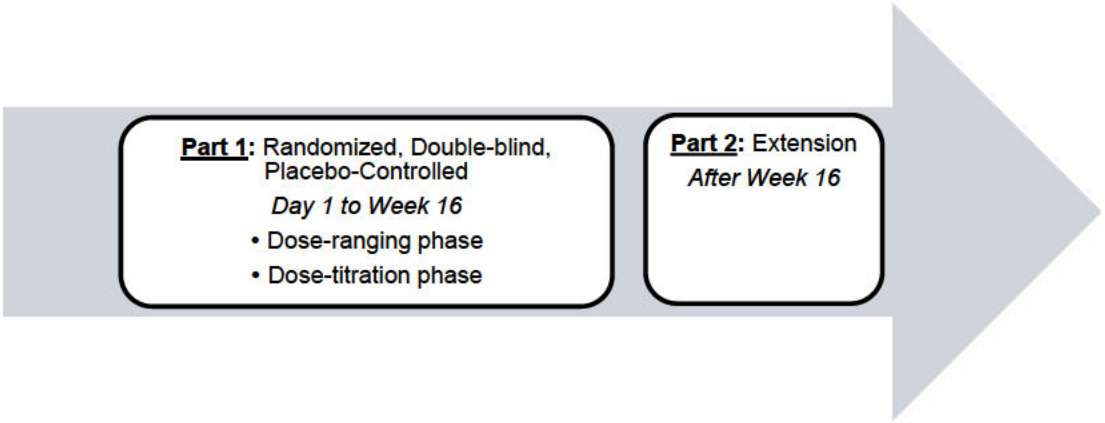
The changes from Version 2.0 to Version 3.0 of the Statistical Analysis Plan were motivated by additional protocol amendments subsequent to the finalization of Version 1 of the SAP. Version 2 was finalized 24 Sept 2015 under protocol Version 5, which included larger expansion cohorts which would be the focus of efficacy analyses. The protocol has been amended two times since Version 2 of the SAP (Protocol Version 6, 01 Jun 2016, and Protocol Version 7, 26 Jan 2017). Additional modifications were made to provide clarity to the statistical methods used in the planned analysis.

In general, the notable modifications include:

- Clarification of a modified Intent-to-Treat subset of patients to exclude patients without sufficient treatment or who have no post-baseline data for the primary endpoint, patients who did not have at least 28 doses of study treatment, or who had a heart or lung transplant over the course of the 16 week study
- Clarify that the primary object of this study is to identify appropriate doses to be used for further study, and that this will be done through assessing the totality of data rather than a single endpoint
- Provide more guidance associated with the methods used in the primary efficacy analysis
- Specify the pooling strategy for the primary analysis
- Specify additional subgroup analyses of 6MWD
- Updated visit windows for unscheduled and end of treatment visits
- Added visit windows for unscheduled and end of treatment visits in Part 2
- Updated appendices to only include information not found in external documentation
- Added specifications for calculating estimated glomerular filtration rate (eGFR)

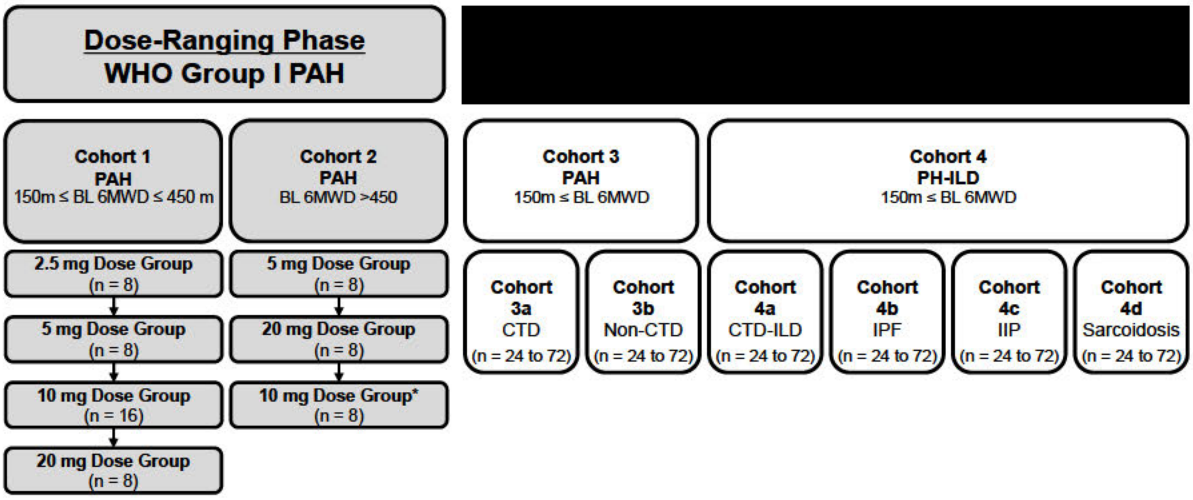
1. INTRODUCTION

This two-part trial will study the safety, tolerability, and efficacy of bardoxolone methyl in patients with pulmonary hypertension (PH). Part 1 will be a double-blind, randomized, dose-ranging, placebo-controlled treatment period and Part 2 will be an extension period. Part 1 and Part 2 may be repeated for additional cohorts at the discretion of Reata.



The study includes an initial dose-ranging phase followed by a dose-titration phase. Within the dose-ranging phase, the effects of bardoxolone methyl in two cohorts of WHO Group I PAH (cohort 1: baseline 6MWD ≤ 450 m; cohort 2: baseline 6MWD > 450 m) will be explored to identify an appropriate dose range to be used in the dose-titration phase. Each sequential dose group enrolled in the dose-ranging phase will include 8 patients randomized 3:1 (bardoxolone methyl:placebo).

Within the dose-titration phase, the effects of titration dosing bardoxolone methyl in WHO Group I PAH (Cohort 3 with 2 sub-cohorts: (1) 3a: CTD-PAH; (2) 3b: non-CTD-PAH) as well as subsets of WHO Group III/V PH (Cohort 4 with four sub-cohorts: (1) 4a: CTD-ILD; (2) 4b: IPF; (3) 4c: NSIP/IIP; (4) 4d: Sarcoidosis). Each sub-cohort in the dose-titration phase is expected to enroll up to a maximum of 72 patients, randomized 2:1 (bardoxolone methyl:placebo).



This version of the SAP describes the analyses planned throughout the course of this study. Some analyses may be performed prior to database lock. Any substantive changes made to the statistical analysis plan after any formal interim reviews will be clearly documented and a justification will be given in the CSR.

This SAP is based on Version 7 of the study protocol dated January 26, 2017. If the protocol is subsequently amended, this SAP may be amended as well. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing. All analyses will be conducted using SAS version 9.2 or higher.

1.5 Study Objectives

The objectives of the study are as follows:

1.5.2 Primary Objectives

The primary objective of this study is to determine the recommended dose range for further study of bardoxolone methyl.

Rather than specifying a single rule, clinical judgement and totality of information from the analyses described below will be used to recommend a dose range for further study. Clinical judgment will be guided by the balance of maximized efficacy within the range of doses viewed as having acceptable safety profiles based on available data. Thus, no single endpoint will be used to assess the primary objective.

1.5.3 Secondary Objectives

The secondary objectives of this study are:

- To assess the change from baseline in 6-minute walk distance (6MWD) in those patients treated with bardoxolone methyl versus patients given placebo for 16 weeks.
- To assess the safety and tolerability of 16 weeks of treatment with bardoxolone methyl versus 16 weeks of administration of placebo.

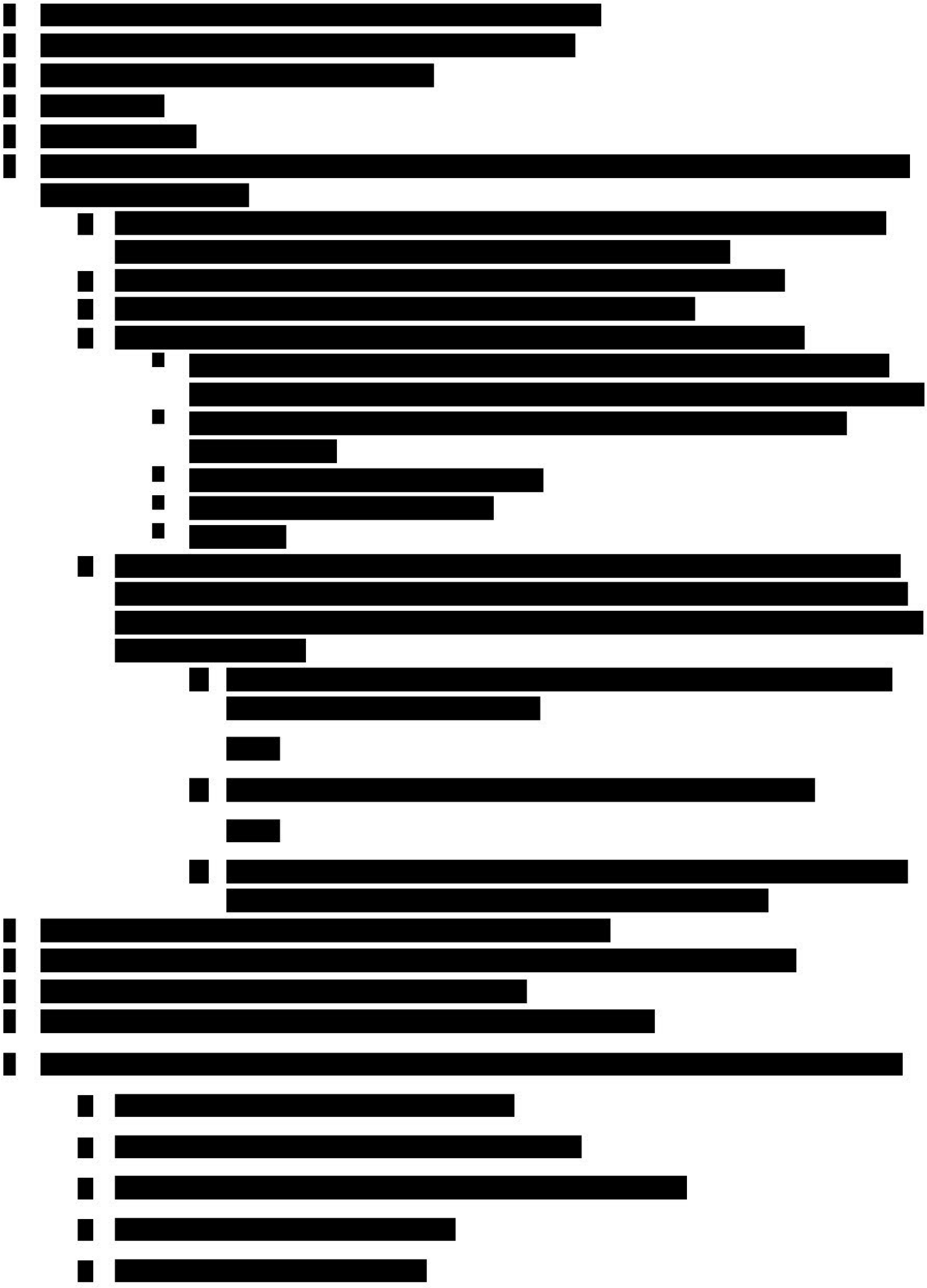
1.6 Endpoints

1.6.2 Primary Efficacy Endpoint

The primary efficacy endpoint is an overall change from baseline in 6MWD through Week 16 for bardoxolone methyl compared to placebo.

1.6.3 [redacted]

[redacted]



1.6.4 **Pharmacokinetic Endpoints**

Analysis of PK data will be described in a separate PK analysis plan and presented in a standalone PK report.

1.6.5 **Safety Endpoints**

The safety endpoints include frequency, intensity, and relationship to study drug of adverse events and serious adverse events, concomitant medications, and change from baseline in the following assessments:

- Physical examinations;
- Vital sign measurements;
- 24-hour ambulatory blood pressure monitoring (ABPM);
- 12-lead electrocardiograms;
- Clinical laboratory measurements;
- Weight.

1.7 Determination of Sample Size

A sample size of 8 patients randomized at a 3:1 (bardoxolone methyl : placebo) assignment ratio in each dose level within cohort includes 6 patients treated with bardoxolone methyl for identification of gross safety signals. A small number of patients at each dose is not expected to fully characterize safety, therefore issues of concern identified in only 1 of 6 patients (16%) treated with bardoxolone methyl may suggest the need to collect additional information before escalating the dose, by either adding more patients at the current dose level or a lower dose as determined by the PSRC. Each additional dose level enrolled at selected doses adds 6 more patients treated with bardoxolone methyl to further characterize safety, tolerability, and efficacy.

[redacted]

All eligible patients from Part 1 will be included in Part 2, and no new patients will be randomized to Part 2 of the study.

1.8 Study Cohorts

As described in Section 1, this study includes 2 cohorts in the dose-ranging phase and 6 sub-cohorts (within 2 overarching cohorts) in the dose-titration phase. Analyses described in this SAP may be performed separately by cohort. The Part 1 and Part 2 safety and efficacy analyses will be summarized by randomized treatment, pooling all placebo patients and all active patients into various subgroups:

- All PAH patients (Cohorts 1, 2, 3a, and 3b patients)
- All CTD-PAH patients (CTD-PAH patients in Cohorts 1, 2, and 3a)

- All Non-CTD PAH patients (Non-CTD PAH patients in Cohorts 1, 2, and 3b)
- All PH patients (Cohorts 4a, 4b, 4c, 4d)

In addition to the subgroups listed above, the eGFR, six-minute walk test, and pulmonary function testing results will be summarized by individual cohort.

All patients enrolled in the study will follow the same schedule of assessments, including a placebo-controlled period (Part 1) followed by an extension period (Part 2).

1.9 Timing of Analysis

Analyses of Part 1 and Part 2 may be performed as data accumulate to allow for planning of future studies. Timing of analyses will be determined solely by the Sponsor. As this is an exploratory study, no statistical adjustments will be made for repeating an analysis.

1.9.2 Protocol Safety Review Committee

A Protocol Safety Review Committee (PSRC) will assess the starting dose and each new dose level of bardoxolone methyl for safety and tolerability based on review of all available data for this study at the time of each review. PSRC reviews will occur after the Week 4 data are available for the first eight patients enrolled at each new dose level combined across both the $\leq$ 450 m and > 450 m cohorts.

1.9.3 Part 1 (placebo-controlled period) Results

For a particular cohort, the primary analysis of Part 1 will be performed after all patients enrolled in that cohort have completed Part 1.

1.9.4 Part 2 (extension period) Results

In addition to the final reporting of Part 2 data for each cohort, analysis of Part 2 data will be performed for regulatory interactions as determined by the Sponsor. The final analysis of Part 2 data for a particular cohort will be performed after all enrolled patients complete their last Part 2 visit.

1.10 Changes from Protocol

The primary efficacy endpoint was defined in Version 1 of the protocol as change from baseline in 6MWD at Week 16. The primary objective of this longitudinal phase 2 study is to identify the appropriate dose range for further study of bardoxolone methyl in PAH patients. Each dose level includes 6 active and 2 placebo patients within each cohort. Therefore, to maximize the information attained from each patient in the estimate of treatment effect on an endpoint known to have large variability, the primary efficacy endpoint was modified. The original endpoint as defined in the protocol (i.e., treatment effect at Week 16) will also be estimated, along with estimates at other timepoints. The totality of the results will be considered in dose range selection for future studies.

Quality of life, oxygen use and pulse oximetry were not defined in the protocol as exploratory endpoints. These four endpoints will be analyzed using approaches described later in this SAP.

2. STUDY CONDUCT

2.1 Randomization

Eligible patients in Cohorts 1 and 2 will be assigned a dose cohort type based on baseline 6MWD, as described in the study design section in the protocol. Eligible patients in Cohorts 3and 4 will be assigned a dose cohort type based on PAH etiology, as described in the study design section in the protocol. Based on the determined cohort, patients will be randomized to bardoxolone methyl or placebo for Part 1 of the study according to the treatment assignment regimen.

In this double-blind study, all patients, investigators, site personnel, laboratories and central readers with direct involvement in the conduct of the study and their designees will be blinded to treatment assignments. Appropriate measures will be taken to ensure the blind is maintained for the patients and personnel mentioned previously to reduce potential bias. To maintain the blind, investigators will distribute blinded study drug kits to patients as directed by the IWRS system.

Treatment assignments will be managed by an IWRS system. The only people with direct access to treatment assignments will be those individuals who develop and maintain the randomization code, the individuals involved in the implementation and operation of the IWRS system, and the PSRC. Some Sponsor personnel will be unblinded to individual treatment assignments.

Upon starting Part 2 of the study (i.e., the extension phase) all patients will receive bardoxolone methyl.

2.2 Data Monitoring

Refer to the PSRC plan for details around the timing and conduct of PSRC meetings. The PSRC will be used to evaluate interim analysis results and to determine dose escalation. All summaries/analyses by treatment arm for the PSRC review will be prepared by an Independent Data Coordinating Center (IDCC) [redacted]. During the study the PSRC will review, in an unblinded manner, available safety data through at least Week 4 for all patients in each recently opened cohort and available data from prior cohorts in order to determine if escalation to the next highest dose is warranted.

2.3 Data Sources

Refer to the data management plan for Electronic Case Report Form (eCRF) data specifications and the non-eCRF guidelines for details around data sources external to the eCRF. All data collected in the eCRF and external data sources will be presented in by-patient data listings.

3. STATISTICAL METHODS

The analyses outlined in this SAP will supersede those specified in the protocol for the purpose of a regulatory filing.

Screen failure patients will be summarized by reason for screen failure. Screen failure patients will not be included in any other analyses described in this document. Statistical methods in study Part 1 (Section 3.4) and study Part 2 (Section 3.5) are described separately.

All analyses will be presented by cohort. There are no pre-planned analyses to combine same dose levels across multiple cohorts. Titration cohorts (cohort 3 and cohort 4) will not examine individual dose levels. Summaries of titration cohorts will be grouped according to the randomized treatment: bardoxolone methyl or placebo.

3.1 Analysis Populations

Populations for primary analyses of efficacy and safety from Part 1 of the study are described below. Based on results of the primary analyses, additional populations for sensitivity analyses may be performed as post-hoc analyses.

3.1.2 Intent-to-treat (ITT) Population

The ITT population includes all randomized patients. The ITT analysis will be done by randomized treatment, pooling all placebo patients within each cohort. No data will be imputed for ITT analyses. The ITT population will be used for analyses of exploratory endpoints except 6MWD. The ITT analysis will be summarized by randomized treatment, pooling all placebo patients and all active patients into various subgroups:

- All PAH patients (Cohorts 1, 2, 3a, and 3b patients)
- All CTD-PAH patients (CTD-PAH patients in Cohorts 1, 2, and 3a)
- All Non-CTD PAH patients (Non-CTD PAH patients in Cohorts 1, 2, and 3b)
- All PH patients (Cohorts 4a, 4b, 4c, 4d)

In addition to the subgroups listed above, the eGFR and pulmonary function testing results will be summarized by individual cohort.

All 6MWD analyses will use the mITT population.

3.1.3 Modified Intent-to-treat (mITT) Population

The purpose of this Phase 2 study is to estimate the treatment effect of bardoxolone methyl on 6MWD in patients with PAH, and to identify an appropriate dose for further development. Estimated treatment effect from this study will be used to power future trials of bardoxolone methyl in PAH patients.

The mITT population will include all randomized patients who received at least 28 doses of study treatment, did not undergo heart or lung transplantation during the treatment period, and performed at least one post-baseline 6MWT assessment. The primary population for efficacy analyses of the primary endpoint will be the mITT population. The mITT analysis will be done by randomized treatment, pooling all placebo patients and all active treatment patients.

Since treatment effect is expected to be observed within the first few weeks of treatment and sustained over time, missing data will be imputed using last observation carried forward (LOCF) for mITT analyses. Missing data will only be imputed for the 6MWD analysis.

3.1.4 **Safety Population**

The safety population includes all randomized patients who were dispensed any dose of study drug during the study treatment period. Patients who received one or more doses of bardoxolone methyl will be assigned to the corresponding bardoxolone methyl treatment arm even if it was given in error. If a patient is dispensed bardoxolone methyl at more than one dose, the patient will be included in the safety population at the highest dose dispensed. All safety data will be analyzed for the safety population according to the medication actually dispensed.

3.2 Analysis of Study Conduct

Study enrollment, study treatment exposure and compliance, reasons for study termination will be summarized by treatment arm for all randomized patients within each cohort. Major protocol deviations, including violations of inclusion/exclusion criteria, based on information captured in the eCRFs will be reported and summarized by treatment arm. Any inclusion/exclusion violations will be listed separately, and will only be summarized if it is considered a major protocol deviation.

3.3 Analysis of Treatment Group Comparability

Demographic information (age, sex, ethnicity, race), baseline characteristics (baseline BMI, weight) and baseline disease characteristics (including PAH classification and details, time since diagnosis, baseline PAH concomitant medications, thromboembolic disease assessment, pulmonary function testing, oxygen use during 6MWTs and available baseline right heart catheterization data) will be summarized by treatment arm for all randomized patients.

Descriptive baseline summaries of continuous data will present the group mean, standard deviation, median, minima, and maxima. Descriptive summaries of discrete data will present the category counts as frequencies and percentages.

Unless otherwise stated, the baseline value of any variable will be defined as the last available value recorded prior to the first administration of bardoxolone methyl/placebo. Missing values will not be imputed, unless otherwise noted, and will be tabulated as missing.

3.4 Analysis of Part 1

Part 1 data will be analyzed using the analysis populations defined in Section 3.1. Separate analyses will be performed by each cohort. Part 1 analyses will only include data from the placebo controlled portion of the study. If a subject does not complete Part 1, or chooses not to enter Part 2, then all their data will be used in Part 1. If a subject enters Part 2, then all data up to and including the Week 16 visit will be included in Part 1.

3.4.2 Exposure of Study Medication and Patient Adherence

Patient disposition, study treatment exposure, and compliance will be summarized for each treatment arm with descriptive statistics.

The overall exposure (days) is calculated as [(Week 16 visit date) – (date of first dose) + 1].

If a subject discontinues treatment prior to Week 16, the date of last dose will be used for calculating overall exposure.

Each study drug kit contains 4 bottles (Bottle A, B, C, D). Each bottle contains 30 capsules at the time of dispensing, and the number of capsules remaining in each bottle is recorded in the drug return CRF. Administered doses will be estimated for each bottle based on the number of capsules dispensed minus the number returned. The compliance is calculated for each bottle (bottle ‘X’) as: [((Total number of kits dispensed in Part 1) x 30) – (Total Bottle ‘X’ capsules returned)] / (Study part exposure days)

For the disposition summary, a patient who completes part 1 is defined as any patient who completes the Week 16 visit while taking study treatment (i.e., end-of-treatment page is blank or date of last dose is within 2 weeks before Week 16 visit date).

3.4.3 Concomitant Medications

The WHO Drug Dictionary will be used to classify all medications recorded during this study. Medications taken from 28 days prior to the administration of the first dose of bardoxolone methyl/placebo through the final follow-up visit will be recorded in the concomitant medication forms. The numbers and percentages of patients who had taken any baseline concomitant medications (i.e., start date on or before study Day 1 and stop date after Day 1) will be summarized by medication for each treatment arm. The numbers and percentages of patients who had started taking any post-baseline concomitant medications during Part 1 (i.e., start date after study Day 1 through Week 16) will be summarized by medication for each treatment arm. Study medications with start date after Week 16 will be excluded from the Part 1 summaries of concomitant medications, unless the patient did not continue into Part 2.

In the presence of partial dates, the available data (month and/or year) will be compared to the appropriate study reference dates to identify the most likely study period.

3.4.4 Efficacy Analysis

Analysis of the 6MWD will be performed using the mITT analysis set on all available data. Missing 6MWD data in Part 1 will be imputed using LOCF as described in Section 3.1.2. No imputation will be performed for missing 6MWD data in Part 2.

The CRF nominal study visits (i.e., Week 4, Week 8, Week 12, and Week 16) will be used for all 6MWT efficacy analyses. For subjects that prematurely discontinue treatment before Week 16 with a 6MWT recorded at the End of Treatment (EOT) assessment, that EOT 6MWD will be used in analysis for the nominal protocol visit most closely matching the subject's visit schedule. For all other efficacy analyses, the value closest to the target study day should be used (Section 3.7.2). In Part 1, LOCF will be applied to impute missing 6MWD values after analysis values are obtained taking into consideration the End of Treatment assessment, if applicable. For all other efficacy variables besides 6MWD, LOCF should not be used, and no imputation for missing data should be performed.

Analysis will pool all active doses within cohort for comparison with placebo in Part 1.

The analyses will be repeated for subgroups defined by PAH etiology in Part 1 (i.e., connective tissue disease vs non-connective tissue disease).

Given the exploratory nature of this study, sensitivity analysis may be performed in an ad hoc manner.

Plots will be generated to summarize 6MWT results by randomized treatment, pooling all placebo patients and all active patients into various subgroups:

- All PAH patients (Cohorts 1, 2, 3a, and 3b patients)
- All CTD-PAH patients (CTD-PAH patients in Cohorts 1, 2, and 3a)
- All Non-CTD PAH patients (Non-CTD PAH patients in Cohorts 1, 2, and 3b)
- All PH patients (Cohorts 4a, 4b, 4c, 4d)

3.4.4.1 Primary Efficacy Endpoint

The primary measure of efficacy is the overall treatment effect across Week 4, Week 8, Week 12, and Week 16 for change from baseline in exercise capacity, as measured by the 6MWD, for bardoxolone methyl compared to placebo. The difference in mean overall change from baseline through Week 16 (active – placebo) will be used to assess the effect of bardoxolone methyl on 6MWD in patients with PAH. A lower 6MWD reflects greater PAH severity thus, a positive change from baseline suggests an improvement.

As supportive analysis to the primary endpoint, the mean change from baseline and treatment differences will be estimated for each visit. The actual values and changes from baseline in 6MWD will be summarized using descriptive statistics at each scheduled visit. Walk distances collected at any duration other than 6 minutes will not be included in the analysis of 6MWD unless the reason for not walking 6 minutes is one listed in the ATS guidelines as a reason for stopping the test immediately (i.e., chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, and pale or ashen appearance).

Baseline for 6MWD will be the average of scheduled predose assessments (e.g., Screen A and Day 1) collected prior to the first administration of study drug. Similarly, two 6MWD measurements collected at Week 4 and again at Week 16. Multiple measures are within the Week 4 and Week 16 visits, and the 6MWD value used as at these visits is the calculated average within these visits.

The mean overall treatment effect across all visits for change from baseline in 6MWD will be estimated and compared with placebo through 16 weeks of treatment by mixed-model repeated measures (MMRM), with treatment group, visit, and the interaction between treatment and visit as fixed factors. Visits at Weeks 4, 8, 12, and 16 will be used. A compound symmetry covariance matrix will be assumed. Point estimates and 95% confidence intervals for the mean change from baseline for each treatment as well as the treatment difference (active-placebo) will be provided overall and at each protocol scheduled timepoint.

Separate mixed models will be used to compare (1) pooled bardoxolone methyl doses with placebo and (2) individual dose levels with placebo. The first model contains two treatment groups with data at four timepoints. Example SAS code to obtain estimated treatment differences is provided below.

```
Proc Mixed data=x order=data;
        Class usubjid trt week;
        model cfb =  trt week trt*week /s;
        repeated week / sub = usubjid type = cs;
        Lsmeans trt / diff cl;
        Lsmeans trt*week / diff cl;
Run;
```

SAS ODS output datasets (DIFFS and LSMEANS) can be used to obtain estimated treatment differences overall and at each week.

If the Pearson correlation between baseline BMI and Week 16 change from baseline 6MWD is significant, then baseline BMI will be included as a covariate. Baseline BMI is defined as the last non-missing observation prior to initial dose. Baseline BMI should only be used as a covariate if

the p-value between Week 16 change from baseline 6MWD and baseline BMI is <0.05. Example SAS code to obtain correlation coefficients and p-values is provided below:

```
proc corr data=x pearson;
where visit='Week 16';
var bmi cfb;
ods output PearsonCorr = bmi_corr;
run;
```

Modifications to contrast statements will be required for the model containing individual dose levels. However, ODS output datasets may also be used without modification of SAS code.

[redacted]

[redacted]

[redacted]

[redacted]

3.4.5 **Safety Analysis**

Safety data will be summarized using the safety population. Missing data will not be imputed for safety analyses. With the exception of adverse events, safety results will be summarized by the CRF nominal study visits (i.e., Week 1, Week 2, Week 4, Week 8, Week 12, and Week 16). For subjects that prematurely discontinue treatment before Week 16 with an End of Treatment (EOT) assessment, that EOT will be used in analysis for the nominal protocol visit most closely matching the subject's visit schedule. Similarly, for patients with safety results at an unscheduled visit that unscheduled visit will be used in analysis for the nominal protocol visit most closely matching the subject's visit schedule. For all safety listings except adverse events, if a safety result does not fall within a scheduled visit window, that result will be included in the safety listings but not the safety table summaries.

Moreover, if retest values are available, all safety analyses should use the results closest to the target study day (e.g., Day 28 for Week 4, Day 56 for Week 8, etc.). If two values are equidistant from the target study day, the earliest of those values will be used in all safety analyses.

3.4.5.1 Part 1 Treatment Emergent Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) dictionary will be used to classify all adverse events reported during the study by system organ class (SOC) and preferred term

(PT). Analysis of treatment-emergent adverse events from Part 1 (Part 1 TEAE) will include all new or worsening adverse events with date of onset during or after the date of first study drug administration through the end of Part 1. Part 1 TEAE summaries will exclude adverse events with date of onset after the Week 16 visit date or date of onset more than 30 days after the date of last study drug administration for patients who discontinue treatment. Part 2 TEAE summaries will exclude adverse events with date of onset more than 30 days after the date of last study drug administration for patients who discontinue treatment. Adverse events will be summarized by SOC and PT. Tables and listings will summarize adverse events occurring in Part 1 and 2 separately. Drug-related AEs, SAEs, and serious drug-related AEs will be summarized accordingly. Multiple occurrences of the same event will be counted once for each patient at the level of SOC and the level of PT.

Adverse events by SOC, PT, and severity will also be summarized. Multiple occurrences of the same event will be counted once for each patient by preferred term under the highest severity.

In the presence of partial dates, the available data (month and/or year) will be compared to the appropriate study reference dates to identify the most likely study period.

3.4.5.2 Laboratory Data

Laboratory test results include clinical chemistry, hematology, and urinalysis. Continuous lab data, including actual values and changes from baseline, will be summarized using descriptive statistics (including mean, standard deviation, quartiles, median, minima and maxima) for chemistry and hematology parameters. If the scheduled assessment is missing, use the recheck measurement closest in time to scheduled visit (if available).

If a Day 1 laboratory collection occurred after the first dose of study drug, that lab value should not be used as the baseline lab value. The baseline lab value is the last laboratory value collected before study drug administration.

Shift tables will be provided to assess changes from normal to abnormal shifts from baseline to Week 16 for chemistry and hematology parameters.

3.4.5.3 Estimated Glomerular Filtration Rate

For calculation of the eGFR, the 4-variable MDRD equation must be used. The equation is as follows:

eGFR = 175 x standardized serum creatinine (mg/dL) –1.154 x age –0.203 x 1.212 [if black] x 0.742 [if female]

The patient's age utilized in the eGFR calculation will be the age by visit listed in the laboratory dataset.

For the eGFR analysis, the value closest to the target study day should be used (Section 3.7.2). Patients randomized to placebo and converted to bardoxolone methyl in Part 2 should use the Week 16 eGFR value as baseline.

The eGFR analyses will not include eGFR values >=14 days after the patient's last dose of bardoxolone methyl or placebo.

3.4.5.4 Physical Exam Data

Physical examination data is collected as normal/abnormal categories at each time point by body system. Abnormal physical examinations will be listed by patient, body system and visit.

3.4.5.5 Vital Sign Measurement

Vital sign measurements include patient's heart rate, respiration rate, and temperature, weight, BMI, and blood pressure (systolic and diastolic). Actual values and changes from baseline values for vital signs and weight will be summarized using descriptive statistics (including mean, standard deviation, quartiles, median, minima and maxima) by treatment group at all scheduled study visits. If the scheduled assessment is missing, use the recheck measurement closest in time to scheduled visit (if available).

3.4.5.6 24 Hour Ambulatory Blood Pressure Monitoring

Systolic blood pressure, diastolic blood pressure, pulse pressure and heart rate are collected during the 24-hour ambulatory blood pressure monitoring (ABPM) [redacted]. Actual values and changes from baseline values for these four parameters will be summarized using descriptive statistics (including mean, standard deviation, quartiles, median, minima, maxima, and 95% confidence interval) by treatment group at all scheduled study visits. If the scheduled assessment is missing, the recheck measurement closest in time to scheduled visit will be used (if available).

The overall (24 hour) mean for each measure, the day time mean, and the night time mean will be summarized. Appendix A provides more detail of the planned analyses of the 24-hour ABPM data.

3.4.5.7 ECG

Actual values for the 12-lead ECGs collected at each visit and changes from baseline in ECG measures (i.e., RR, PR, QRS, QT/QTc interval) at post-baseline visits will be summarized. Additionally, frequency counts for ECG results (normal, abnormal not clinically significant, abnormal clinically significant, or unable to evaluate) will be summarized at each visit. If the scheduled assessment is missing, use the recheck measurement closest in time to scheduled visit (if available).

3.5 Analysis of Part 2

All patients in Part 2 will receive an active dose of bardoxolone methyl. Patients must be compliant with dosing and complete Part 1 according to the protocol to be eligible for continuation into the extension period (Part 2). Therefore, separate populations for safety and efficacy will not be defined for Part 2 analyses.

The Part 2 safety and efficacy analyses will be summarized by randomized treatment, pooling all placebo patients and all active patients into various subgroups:

- All PAH patients (Cohorts 1, 2, 3a, and 3b patients)
- All CTD-PAH patients (CTD-PAH patients in Cohorts 1, 2, and 3a)
- All Non-CTD PAH patients (Non-CTD PAH patients in Cohorts 1, 2, and 3b)
- All PH patients (Cohorts 4a, 4b, 4c, 4d)

Due to the ongoing nature of this study, summary of Part 2 data will be strictly by patients initially randomized to active versus placebo patients that transition to active therapy. The groups will be labeled as BARD or PBO-BARD. All patients randomized to an active dose of bardoxolone methyl in Part 1 will be summarized with the BARD group in Part 2 analyses. All patients randomized to placebo in Part 1 will be summarized with the PBO-BARD group in Part 2 analyses.

Additional by-dose level results may be presented to explore long term trends by dose level, but will be included in an ad hoc manner.

3.5.2 **Patient characteristics and exposure**

Demographics and baseline disease characteristics will be summarized for patients who continue into study Part 2.

Exposure will be summarized using the Part 2 treatment groups (BARD, PBO-BARD) for the following:

- Total time in Part 2: ([last dose date] – [Week 16 visit date] + 1)
- Total time in study: ([last dose date] – [first dose date] + 1)

Discontinuations in Part 2 prior to study termination will be listed.

3.5.3 **Concomitant Medications**

The WHO Drug Dictionary will be used to classify all medications recorded during this study. The numbers and percentages of patients who had started taking any post-baseline concomitant medications during Part 1 (i.e., start date after study Day 1 through Week 16) or Part 2 will be summarized by medication for each treatment arm.

In the presence of partial dates, the available data (month and/or year) will be compared to the appropriate study reference dates to identify the most likely study period.

3.5.4 **Efficacy**

Efficacy analyses described in Section 3.4.3 will not be performed on available data from Part 2. Instead, 6MWD will be summarized using descriptive statistics only (include 95% confidence interval for change from baseline at each visit) using the Part 2 treatment groups (BARD, PBO-BARD) Patients randomized to placebo and converted to bardoxolone methyl in Part 2 should use the Week 16 eGFR value as baseline. If the Week 16 eGFR lab collection occurs after the date and time of first dose at Week 16, then the closest value prior to Week 16 should be used as baseline for patients randomized to placebo and converted to bardoxolone methyl. No inferential statistics will be provided for Part 2 data and missing 6MWD will not be imputed in Part 2.

3.5.4.1 Part 2 Changes from Baseline in 6MWD

Due to the ongoing nature of this study, summary of Part 2 data will be strictly by patients initially randomized to active versus placebo patients that transition to active therapy. The groups will be labeled as BARD or PBO-BARD. All patients randomized to an active dose of bardoxolone methyl in Part 1 will be summarized with the BARD group in Part 2 analyses. All patients randomized to placebo in Part 1 will be summarized with the PBO-BARD group in Part 2 analyses.

In the Part 2 (open-label) portion of LARIAT, all active doses within a cohort will be pooled (including placebo patients randomized to active in Part 2). All active doses within a cohort, the BARD group, and PBO-BARD group will be compared to baseline 6MWD.

Actual values and changes from baseline will be summarized using descriptive statistics (including mean, standard deviation, quartiles, median, minima and maxima).

3.5.5 Safety

Safety analyses described in Section 3.4.4 will be performed on available safety data from Part 2 using the Part 2 treatment groups (BARD, PBO-BARD). Change from baseline summaries of safety described in 3.4.3 will include both change from baseline (Part 1) and change from the end of Part 1 (Week 16) for Part 2.

Analyses of adverse events will count only Part 2 treatment-emergent adverse events (TEAEs), defined as new or worsened events after the Week 16 visit. New or worsened events after Week 16 visit are those events with an AE start date after the Week 16 study visit, or previously recorded AEs with an adverse change in severity (e.g., went from mild to moderate or moderate to serious) after the Week 16 study visit. Similarly, only new onset concomitant medications (date of first dose after the Week 16 visit) will be included in Part 2 summaries.

Shift tables will be provided to assess changes from normal to abnormal shifts from Week 16 to each nominal visit for chemistry and hematology parameters.

Additional details will be provided in the mock Tables, Listings, and Figures.

3.6 Pharmacokinetic Analysis

A separate document contains details regarding the planned pharmacokinetic analyses.

3.7 Missing and Partial Data

For the analysis of safety variables, partial dates may be imputed; otherwise, missing data will be treated simply as missing. However, if an AE onset date is missing, it will be imputed (see Appendix C). The algorithms for imputation of partial dates depend upon the parameter (see Appendix C). The central laboratory uses assays that have lower limits of detection (LLD). Continuous laboratory data results which are less than the lower limit of detection or above the upper limit of quantification will be imputed to the value of the lower or upper limit plus or minus one significant digit, respectively (e.g., if the result of a continuous laboratory test is < 20, a value of 19 will be assigned).

Imputation for missing efficacy data (i.e., 6MWD) is described with the efficacy analysis Section 3.4.4.

3.7.2 Analysis Windows for Part 1

For all Part 1 analyses of 6MWD, scheduled visits will be used regardless of study day, as well as any unscheduled or end of treatment visits within the visit windows listed in Section 3.7.4. If an unscheduled or EOT visit falls within the same window as a nominal study visit, the average of the two will be used. For subjects that prematurely discontinue treatment before Week 16 with a 6MWT recorded at the End of Treatment (EOT) assessment, that EOT 6MWD will be used in analysis for the nominal protocol visit most closely matching the subject's visit schedule.

For all other Part 1 efficacy and safety analyses, if multiple assessments fall within the same analysis visit, the assessment closest to the target study day specified in the protocol will be used. If two assessments are equidistant from a post-baseline target visit day, the earlier assessment will be used. Visits that do not occur in all versions of the protocol (i.e., Week 6) should be treated as unscheduled assessments.

3.7.3 **Analysis Windows for Part 2**

Part 2 assessments will be used in efficacy and safety analyses if the assessment was collected within the scheduled window below. Study day will be calculated for each assessment and compared to the protocol defined study day for each visit. In general, analysis in Part 2 will be defined as follows:

Table 1. Visit Windows in Part 2

Analysis Visit	Study Day	Analysis Window
Week 18	126	123 ≤ Study Day ≤ 132
Week 20	140	133 ≤ Study Day ≤ 147
Week 22	154	148 ≤ Study Day ≤ 161
Week 24	168	162 ≤ Study Day ≤ 182
Week 32	224	210 ≤ Study Day ≤ 238
Week 56 and every 24 weeks thereafter	392, every 168 days thereafter	Study Day – 14 days ≤ Study Day ≤ Study Day + 14 days

Records from unscheduled or end of treatment visits that do not fall within an analysis window will be listed, but will not be analyzed. For the 6MWT analysis, if use of the visit windows yields more than one value for a particular visit, the average of the two or more values will be used for analysis. For all other analyses, including the eGFR and safety analyses, the value closest to the target study day should be used Visits that do not occur in all versions of the protocol (i.e., Part 2 visits past week 32 that were changed to phone visits) should be treated as unscheduled assessments.

3.7.4 **Analysis Windows for Unscheduled and End of Treatment Visits (Part 1)**

Additionally, unscheduled assessments and end of treatment assessments will be used in efficacy and safety analyses if the unscheduled assessment was collected within the scheduled window below. Study day will be calculated for each unscheduled assessment and compared to the protocol defined study day for each visit. In general, analysis windows for unscheduled and end of treatment visits in Part 1 will be defined as follows:

Table 2. Visit Windows for Unscheduled and End of Treatment Visits in Part 1

Analysis Visit	Study Day	Analysis Window
Day 1	1	Study Day ≤1
Week 1	7	2 ≤ Study Day ≤ 10
Week 2	14	11 ≤ Study Day ≤ 20
Week 4	28	21 ≤ Study Day ≤ 42
Week 8	56	43 ≤ Study Day ≤ 70
Week 12	84	71 ≤ Study Day ≤ 98
Week 16	112	99 ≤ Study Day ≤ 119

Records from unscheduled or end of treatment visits that do not fall within an analysis window will be listed, but will not be analyzed. Per Section 3.4.4, for the 6MWT analysis, if use of the visit windows yields more than one value for a particular visit, the average of the two or more values will be used for analysis. For all other analyses, including the eGFR and safety analyses, the value closest to the target study day should be used (Table 2).

4. REFERENCES

1. QualityMetric Health Outcomes(tm) Scoring Software

2. http://www2.sas.com/proceedings/sugi29/188-29.pdf

5. APPENDICES

5.1 Appendix A: Ambulatory Blood Pressure Monitoring (ABPM)

Throughout this section, "ambulatory blood pressure" refers to the systolic and diastolic pressures, pulse pressure, and heart rate as collected via 24-hour ABPM. If multiple 24-hour APBM collections occur for a nominal study visit, the last 24-hour APBM collection will be used in the analysis.

Three ambulatory blood pressure parameters will be calculated for each patient using the 24-hour ABPM data.

1. A patient's mean 24-hour ambulatory blood pressure is calculated as the average of all valid measurements taken from the patient's ambulatory blood pressure monitoring device.
2. A patient's mean daytime ambulatory blood pressure is calculated as the average of all valid measurements taken from 6 am to 10 pm.
3. A patient's mean nighttime ambulatory blood pressure is calculated as the average of all valid measurements taken from 10 pm to 6 am next day.

For a given 24-hour period average, the numerator is the sum of all valid ambulatory blood pressure measurements, while the denominator is the number of all valid blood pressure measurements.

Using each of the three ambulatory blood pressure parameters (24-hour, daytime, nighttime) calculated for each patient, actual values and change from baseline values will be summarized descriptively by received study drug at all scheduled study visits for all four ambulatory blood pressure assessments (systolic blood pressure, diastolic blood pressure, pulse pressure, heart rate). Descriptive summaries will include confidence intervals for each treatment group as well as the difference between the treatment group's means. Additionally, blood pressure analyses described in Section 5.1will be performed using the ABPM measurements.

5.2 Appendix B: Listing of Tables Included for Part 2 Analysis

A subset of TLFs in Part 1 will be used in Part 2. Minor modifications are anticipated due to the combined dose levels (BARD vs PBO-BARD). All TLFs in Part 2 will only include data associated with Part 2 of the study. No cumulative summaries or listings will be provided.

Efficacy summaries that include a change from baseline will summarize both change from original baseline as well as change from Week 16. No inferential statistics will be provided for Part 2 data.

5.3 Appendix C: Imputation Rules for Missing Dates

Incomplete diagnosis or treatment date

- If day is missing, day will be set to 15th of the month.
- If month and day are missing, month and day will be set to July 1st.
- If year and month and day are missing, date will be set to missing.

Adverse Event

- If onset date is completely missing, onset date is set to date of first dose.
- If (year is present and month and day are missing) or (year and day are present and month is missing):
  - If year = year of first dose, then set month and day to month and day of first dose
  - If year < year of first dose, then set month and day to December 31st.
  - If year > year of first dose, then set month and day to January 1st.
- If month and year are present and day is missing:
  - If year=year of first dose and month = month of first dose then set day to day of first dose date month < month of first dose then set day to last day of month > month of first dose then set day to first day of month
  - If year < year of first dose then set day to last day of month
  - If year > year of first dose then set day to first day of month
- For all other cases, set onset date to date of first dose.

Concomitant Medications

- If start date is completely missing, start date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to January 1.
- If year and month are present and day is missing, set day to 1st day of month.
- If end date is completely missing, end date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing), set month and day to December 31.
- If year and month are present and day is missing, set day to last day of the month.