STATISTICAL ANALYSIS PLAN

RANGER

VERSION: 2.0

DATE OF PLAN:

05-Jun-2020

BASED ON:

Protocol Version 3.0 (July 16, 2018)

STUDY DRUG:

RTA 402, BARDOXOLONE METHYL

PROTOCOL NUMBER:

402-C-1602

STUDY TITLE:

An Extended Access Program to Access Long-term Safety of Bardoxolone Methyl in Patients with Pulmonary Hypertension ("RANGER")

SPONSOR:

Reata Pharmaceuticals, Inc.

2801 Gateway Drive, Suite 150

Irving, Texas 75063

(972) 865-2219

This study is being conducted in compliance with good clinical practice, including the archiving of essential documents.

SIGNATURE PAGE

This document has been prepared and/or reviewed by:

[redacted]

This document has been reviewed and accepted by:

[redacted]

TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company **Reata Pharmaceuticals**	**Individual Study Table Referring to Part of the Dossier:** **Volume:**	***(For National Authority Use Only)*:**
Name of Finished Product: Bardoxolone methyl capsules	**Page:**	
Name of Active Ingredient: Bardoxolone methyl		
Title of Study: An Extended Access Program to Access Long-term Safety of Bardoxolone Methyl in Patients with Pulmonary Hypertension ("RANGER")		
Investigators: [redacted] **Study Center(s): approximately 150**		
Studied period (years): Until bardoxolone methyl is available through commercial channels or until patient withdrawal, whichever is sooner	**Phase of development:** 3a	
Objectives: To provide continuing open-label treatment with bardoxolone methyl as part of this extended access program while collecting ongoing safety and tolerability data of bardoxolone methyl.		

Methodology: This extended access study assesses the long-term safety and tolerability of bardoxolone methyl in qualified patients with pulmonary hypertension (PH) who previously participated in controlled clinical studies with bardoxolone methyl.

Qualified patients will start dosing at 10 mg of bardoxolone methyl every other day, then begin once daily dosing at Week 4 (unless contraindicated clinically) and continue until the drug is available through commercial channels (including reimbursement) or until patient withdrawal, whichever is sooner. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.

All patients in the study follow the same visit and assessment schedule. Patients are scheduled to be assessed in person during treatment at Day 1, Week 1, Week 2, Week 4, Week 6, Week 8, Week 24, and every 24 weeks thereafter. Patients are also assessed by telephone contact on Days 3, 10, 21, 31, and 38. Day 1 for this extended access study should occur on the same day as the last visit in the controlled clinical study. Patient status should be carefully monitored by the investigator during the first 8 weeks of study treatment. Assessments required for both the last visit in the controlled study and Day 1 for this study should only be completed once.

Patients from the CATALYST study:

Day 1 of this extended access study coincides with the Week 28 follow-up visit for patients from CATALYST (402-C-1504, NCT02657356, EudraCT 2016-000196-24). If this extended access program is not yet open for enrollment at the time of a patient's Week 28 visit, the Day 1 visit (i.e., enrollment) must occur within 30 days of site activation. Exceptions allowing CATALYST patients who have completed 24 weeks of treatment to schedule their follow-up assessments prior to Week 28 and still be considered eligible for this open-label study should be discussed with the Chief Medical Officer at Reata, or designee, and will be considered on a case-by-case basis.

Patients from the LARIAT study:

Day 1 of this extended access study coincides with the End-of-Study visit for patients from LARIAT (402-C-1302, NCT02036970).

Number of Subjects (planned and analyzed): Up to 366 (LARIAT ($n \leq 166$); CATALYST ($n \leq 200$))

Diagnosis and main criteria for inclusion (see Protocol Section 8.1):

Treatment-compliant patients who are participating in qualifying ongoing studies and have completed required End-of-Treatment and/or Follow-up visits in a prior clinical study with bardoxolone methyl.

Test product, dose and mode of administration:

Bardoxolone methyl capsule will be administered orally (every other day or once daily) at 10 mg until it becomes commercially available. Dose de-escalation (down to 5 mg) is permitted during the study, if indicated clinically.

Duration of treatment: Until the drug is available through commercial channels, or until patient withdrawal, whichever is sooner

Reference therapy, dose and mode of administration:

No reference therapy

Criteria for evaluation (see Protocol Section 6.1): The objective is to provide continuing treatment with bardoxolone methyl as part of this extended access program while collecting ongoing safety and tolerability data of bardoxolone methyl.

Statistical methods: The sample size for the RANGER is limited to the number of treatment-compliant patients having completed a qualifying clinical study with bardoxolone methyl (i.e., LARIAT or CATALYST). The analysis population includes all enrolled patients (Safety Population). Since the RANGER is an open-label design with no comparator group, all statistical analyses will be descriptive. No statistical comparisons will be performed. The study was terminated on March 30, 2020. If the treatment end date or study end date are missing, the date will be imputed as March 30, 2020.

TABLE OF CONTENTS

LIST OF TABLES

1. LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation	Term
6MWD	6-minute walk distance
6MWT	6-minute walk test
AE	Adverse Event
ATC	Anatomical/Therapeutic/Chemical
ATS	American Thoracic Society
BMI	Body mass index
BNP	B-type natriuretic peptide
bpm	Beats per minute
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cm	Centimeters
CRF	Case Report Form
CSR	Clinical Study Report
CTD	Connective Tissue Disease
DBP	Diastolic blood pressure
EC	Ethics Committee
eCRF	Electronic case report form
ERA	Endothelin Receptor Antagonist
FC	Functional Class
FDA	Food and Drug Administration (US)
Hb	Hemoglobin

HLT	high level term
hrs	hours
ICH	International Conference on Harmonization
ICH E9	International Conference on Harmonization Tripartite Guideline for Good Clinical Practice E9
IRB	Institutional Review Board
Kg	Kilogram
LLD	lower Limit of Detection
LOAEs	late-onset AEs
M	meter
MedDRA	Medical Dictionary for Regulatory Activities Terminology
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeter of mercury
N	Total Sample Size
NT-Pro BNP	N-Terminal Pro-Brain Natriuretic Peptide
NYHA FC	New York Heart Association Functional Classification
PAH	pulmonary arterial hypertension
PH	pulmonary hypertension
PD5i	Phosphodiesterase inhibitors
pH	potential of hydrogen
PK	Pharmacokinetic
PT	Preferred term

RTA 402	BARDOXOLONE METHYL
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard Error
SOC	System Organ Class
SR	Sustained Release
TBL	Total bilirubin
TEAE	Treatment Emergent Adverse Events
ULD	Upper Limit of Detection
US	United States
WHO	World Health Organization

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Protocol 402-C-1602 (i.e., the RANGER trial).

Protocol Revision Chronology:		
Protocol Version 1	27-Oct-2016	Original
Amendment 1 (Protocol version 2)	05-Jan-2017	• Clinical study manager and contact information is updated. • Estimated study date is updated. • Study schema figure is updated. • Weight in clinic collection is added at Week 24 and End of Study Visit. • Number of dispensed kits are updated. • Week 4 visit is made uniform for all countries.
Amendment 2 (Protocol version 3)	16-Jul-2018	• Visit Schedule is revised with additional monitoring during first 8 weeks. • Dose-titration scheme is changed with increased dosing at week 4. • Dose Regiment is revised. • Clinical chemistries and local chemistry are added throughout study. • Additional monitoring for fluid status is included during first 8 weeks of treatment.

This SAP was developed in accordance with ICH E9 guideline. All decisions regarding final analysis, as defined in this SAP document, will be made prior to the initial Database Lock of the study data. Since the trial is an open-label study, analyses will be re-run based on subsequent database locks as needed for regulatory reporting and/or submissions so long as data continue to accrue. Further information can be found in the protocol.

The statistical analysis plan (SAP) is based on:

- Protocol No. 402-C-1602 Extension, Version 3, dated July 16, 2018
- ICH guidelines E4 and E9 (Statistical Principles for Clinical Trials)

This SAP describes the study populations, how variables are derived, how missing data are handled, and details concerning the statistical methods to be used to analyze the safety and efficacy data in the 402-C-1602 study. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing.

The SAP is finalized, approved by the Sponsor, and placed on file before the initial database lock. This version of the SAP describes the analyses planned prior to the database lock. Unless otherwise specified, these analyses are summarized in the clinical study report (CSR). Any substantive changes made to the SAP after the database lock are clearly identified, and any analyses in addition to those specified in the SAP prior to the database lock are considered ad hoc. The CSR will describe any deviations from the planned analyses.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objective

To provide continuing treatment with bardoxolone methyl as part of this extended access program while collecting ongoing safety and tolerability data of bardoxolone methyl.

3.2. Study Endpoints

3.2.1. Primary Safety Endpoints:

Frequency, intensity, and relationship to study drug of adverse events (AEs) and serious adverse events (SAEs) and change from baseline in the following assessments: physical examinations, vital sign measurements, BNP, N-terminal pro-brain natriuretic peptide (NT-proBNP), and weight.

4. STUDY DESIGN

4.1. Summary of Study Design

RANGER examines the long-term safety and tolerability of bardoxolone methyl in qualified patients with pulmonary hypertension (PH) following completion of previously controlled clinical studies with bardoxolone methyl. Patients and investigators are not unblinded to study treatment from previously controlled clinical studies upon entering the RANGER study.

Qualified patients receive open label bardoxolone methyl (10 mg) every other day, then begin once daily dosing at Week 4 (unless contraindicated clinically) and continue until the drug is available through commercial channels or until patient withdrawal, whichever is sooner. Dose de-escalation (down to 5 mg) is permitted during the study if indicated clinically. Refer to Protocol Section 7.3.1 for additional details on dose de-escalation.

All patients in RANGER follow the same visit and assessment schedule. RANGER Day 1 is defined as the first day treatment is dispensed to the patient for this trial, following completion of previously controlled clinical studies. All other RANGER visits are relative to RANGER Day 1. Patients are scheduled for in-person assessments during treatment in RANGER at Day 1, Week 1, Week 2, Week 4, Week 6, Week 8, Week 24, and every 24 weeks thereafter. Patients are also assessed by telephone contact on Days 3, 10, 21, 31, and 38.

Since patients from previously controlled clinical studies will be followed continuously within the study (i.e., seamless rollover), eligibility for the RANGER study is assessed at the follow-up visit or End-of-Treatment visit and a separate screening visit is not required.

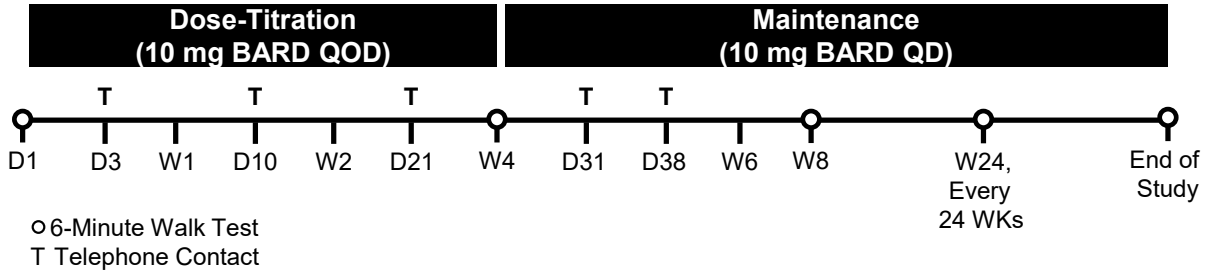
Patients from the CATALYST study:

Day 1 of this extended access study coincides with the Week 28 follow-up visit for patients from CATALYST (402-C-1504, NCT02657356, EudraCT 2016-000196-24). If this extended access program is not yet open for enrollment at the time of a patient's Week 28 visit, the Day 1 visit (i.e., enrollment) must occur within 30 days of site activation. Exceptions allowing CATALYST patients who have completed 24 weeks of treatment to schedule their follow-up assessments prior to Week 28 and still be considered eligible for this open-label study should be discussed with the Chief Medical Officer at Reata, or designee, and are considered on a case-by-case basis.

Patients from the LARIAT study:

Day 1 of this extended access study coincides with the End-of-Treatment visit for patients from LARIAT (402-C-1302, NCT02036970). Treatment-compliant patients who have completed Part 2 (Week 32) of the study are eligible to continue receiving bardoxolone methyl through an extended access program (Study 402-C-1602). Once bardoxolone methyl is available through the extended access program, LARIAT patients in Part 2 who have completed at least 32 weeks of the study complete an End of Treatment Visit.

RANGER Schema for Patients with Pulmonary Hypertension



4.2. Definition of Study Drugs

Capsules containing bardoxolone methyl at the 5 mg and 10 mg strength are used in this study.

4.3. Sample Size Considerations

The sample size for the RANGER study is limited to the number of patients having completed CATALYST (402-C-1504, NCT02657356, EudraCT 2016-000196-24) or LARIAT (402-C-1302, NCT02036970). The study is not powered to show efficacy or safety effects, and there is no placebo comparator in this open-label trial. A maximum of 366 patients will be enrolled in this study, with 200 from CATALYST and 166 from LARIAT.

4.4. Randomization

This is the non-randomized, open-label study that includes patients who previously completed CATALYST or LARIAT. As a result, no randomization or blinding is performed, and patients enrolled in the RANGER are assigned to bardoxolone methyl 10 mg.

4.5. Treatment Analysis Group Assignment

While the CATALYST is ongoing, prior treatment for those patients is considered blinded, and patients enrolling in RANGER from CATALYST are in the blinded-to-bardoxolone methyl treatment analysis group (i.e., "Blinded → BARD"). Once the CATALYST trial is complete and unblinded, patients from CATALYST will be summarized according to their randomized treatment in CATALYST (i.e., "BARD → BARD" or "PBO → BARD").

Because patients in LARIAT received bardoxolone methyl treatment before enrolling in RANGER, all patients enrolling in RANGER from LARIAT are in the bardoxolone methyl study group in RANGER (i.e., "BARD → BARD").

Therefore, before CATALYST unblinding has occurred, the treatment analysis groups consistent of:

1) Blinded → BARD: blinded patients receiving bardoxolone methyl (patients previously enrolled in CATALYST),
2) BARD → BARD: bardoxolone methyl patients (patients previously enrolled in LARIAT), and

After CATALYST is complete and unblinding has occurred, the treatment analysis groups consistent of:

1) PBO → BARD: placebo-bardoxolone methyl (placebo patients previously enrolled in CATALYST),
2) BARD → BARD: bardoxolone methyl patients (patients previously enrolled in LARIAT and bardoxolone methyl patients previously enrolled in CATALYST)

4.6. Clinical Assessments

All patients in RANGER follow the same visit and assessment schedule. RANGER Day 1 is defined as the first day treatment is dispensed to the patient for the RANGER, following completion of CATALYST or LARIAT. All other RANGER visits are relative to RANGER Day 1. Patients are scheduled for in-person assessments during treatment in the RANGER at Day 1, Week 1, Week 2, Week 4, Week 6, Week 8, Week 24, and every 24 weeks thereafter. Patients are also be assessed by telephone contact on Days 3, 10, 21, 31, and 38.

Table 2: RANGER Schedule of Assessments

Assessment \ Study Week (Day)	Day 1[a]	Week 1 (Phone) Day 3±2	Week 1 Day 7±3	Week 2 (Phone) Day 10±2	Week 2 Day 14±3	Week 3 (Phone) Day 21±2	Week 4 Day 28±3	Week 4 (Phone) Day 31±2	Week 5 (Phone) Day 38±2	Week 6 Day 42±3	Week 8 Day 56±3	Week 24±3, Every 24 Weeks	End of Study Visit[b]
Informed consent	X												
Inclusion/Exclusion	X												
Prior and Concomitant medications	X[c]	X	X	X	X	X	X	X	X	X	X	X	X
Current background medications	X[c]	X	X	X	X	X	X	X	X	X	X	X	X
Weight at home	X	X	X	X	X	X	X	X	X	X	X		
Weight in clinic	X[c]		X		X		X			X	X	X	X
Vital sign measurements	X[c]		X		X		X			X	X	X	X
Physical examination	X[c]		X		X		X			X	X	X	X
Pregnancy test[d]	X[c]											X	
Dispense study drug	X						X					X	
Collect study drug							X					X	X
Telephone contact		X		X		X		X	X				
Adverse event collection	X[e]	X	X	X	X	X	X	X	X	X	X	X	X
Clinical Chemistries[f]	X[c]		X		X		X			X	X	X	X
BNP and/or NT-Pro BNP	X[c]		X		X		X			X	X	X	X
6-min walk test	X[c]											X	X
Dyspnea and fatigue[g]	X[c]											X	X
WHO functional class	X[c]											X	X

Abbreviations: BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro B-type natriuretic peptide; WHO, World Health Organization; AE, adverse event; 6MWT, 6-minute walk test

[a] On Day 1, all procedures should be performed before study drug administration for patients who are treatment-compliant and have previously participated in clinical studies with bardoxolone methyl.

[b] After the Week 24 visit, patients will continue to be assessed in person every 24 weeks until bardoxolone methyl becomes commercially available. The End-of- Study visit should occur within 30 days after bardoxolone methyl becomes available through commercial channels. Patients who will be discontinued from the study prior to commercial availability of bardoxolone methyl must also complete all End-of-Study assessments.

[c] Day 1 assessments should be performed as part of End-of-Treatment or Follow-up visit procedures from a prior study with bardoxolone methyl.

[d] A serum pregnancy test will be performed at any point in time if a pregnancy is suspected. All other pregnancy assessments will be urine pregnancy tests. Additional pregnancy assessments will be performed more frequently if required by local law or requested by local health authorities or IRBs/ECs.
[e] AE assessments on Day 1 should be performed following study drug administration.
[f] Clinical chemistries will be analyzed locally.
[g] Dyspnea and fatigue must be assessed prior to beginning and immediately following completion of the 6MWT using the Borg scale.

5. PLANNED ANALYSES

5.1. Planned Interim Analyses

Interim analyses are based on locked data and performed as appropriate to support commercial approval of bardoxolone methyl. A database lock plan will describe the details of each database lock. All outputs identified in this SAP and planned for the final analysis will be prepared for each interim analysis, and an interim CSR will be prepared.

At the time of each planned interim analysis, no individual patient's data are considered fully locked; therefore, interim results are interpreted as preliminary.

5.2. Final Analyses and Reporting

All final, planned analyses identified in this SAP will be performed after the last patient has completed the study and the database has been locked. A final CSR will be prepared based on the final analyses.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

Results will be summarized by the treatment analysis groups described in Section 4.5.

Patient listings of all analysis data that support summary tables and figures are provided. Measurements from patients excluded from the pre-defined analysis sets are not included in summary tables unless specified otherwise, but they are included in the patient listings. Missing data are not imputed, unless otherwise specified. In general, patient listings are sorted by patient number and assessment date (time and parameter, as applicable).

6.1. General Summary Table and Individual Subject Data Listing Considerations

Results of statistical analyses are reported using summary tables, listings, and figures (TLFs). All TLFs will use ICH numbering conventions.

Results will be pulled from RANGER analysis datasets.

All analyses and summaries are produced using SAS® version 9.3 (or higher).

6.2. General Post Text Summary Table and Individual Subject Data Listing Format Considerations

Unless otherwise specified, descriptive statistics for continuous variables include the number of patients with data (N), mean, standard deviation (SD), median, minimum, and maximum. The same number of decimal places as in the observed value are presented when reporting minimum and maximum; 1 more decimal place than in the observed value is generally presented when reporting mean; and 2 more decimal places than in the observed value are presented when reporting SD. When calculating the minimum and maximum of average baseline values, the same number of decimal places as in the observed value will be presented when reporting minimum and maximum. For imputed values and the average of baseline values, the average values will be rounded to the same number of decimal places as the source value.

Categorical (qualitative) data are presented using frequency counts and percentages. All percentages are rounded to 1 decimal place, unless otherwise specified. Percentages equal to 100 are presented as 100% and no percentages are presented for zero frequencies. Where individual variable values are missing, summaries of categorical data are based on reduced denominators (i.e., only patients with available data are included in the denominators). For summaries of AEs and concomitant medications, the percentages are based on the number of patients who received study drug within each summary group.

6.3. Analysis Populations

Analysis populations defined in this section pertain to patients enrolled in the RANGER portion of the trial.

6.3.1. Enrolled Population

The enrolled population will include all enrolled patients, regardless of whether a patient took any dose of bardoxolone methyl. A patient is considered enrolled if informed consent form is obtained. The set of enrolled patients will be used for study population summaries.

6.3.2. Safety Population

The safety population includes all patients who received at least 1 dose of bardoxolone methyl.

6.3.3. Subgroups

The 6-minute walk test, Borg dyspnea index, and WHO/NYHA functional class assessment are summarized separately using the following subgroups:

- Geographic location: US; Other
- Sex: female; male
- Race: (White, Non-White)
- Ethnicity: Non-Hispanic/Latino; Hispanic/Latino
- CTD; non-CTD

Safety summaries are summarized by CTD; non-CTD.

6.4. Baseline Definition

Last measurement on or prior to the date of first study drug administration is considered the RANGER Day 1 measurement for the calculation of baseline. If a baseline value is missing, the last available value in the LARIAT or CATALYST study will be used as baseline.

6.5. Derived and Transformed Data

6.5.1. Connective Tissue Disease (CTD) Etiology

Subgroups include summaries by CTD and non-CTD status. In addition, baseline characteristics summaries include connective tissue disease (CTD) etiology (none, scleroderma, lupus, mixed, and other). Patient's etiology is derived from the baseline characteristics in the prior study in which he or she participated (LARIAT or CATALYST). For patients participating in CATALYST or LARIAT, PH etiology values are the values recorded at the CATALYST or LARIAT Screening visit.

Subject's age in years will be calculated based on date of informed consent date using the following formula:

Age (year) = FLOOR (date of informed consent – date of birth)/365.25*12)

where FLOOR () function returns the integer part of the result.

6.5.2. Baseline Age

Subject's age in years is defined as the age at RANGER study consent (RANGER Day 1 for LARIAT patient, RANGER Day 1for CATALYST patient). If no date of RANGER study consent is present, the age at RANGER Day 1 visit is used.

Age (year) = Floor ((date of extension study consent – date of birth)/365.25)

6.5.3. Study Day

Study day is the day relative to the date of first study drug kit dispensation in RANGER study, which may precede the date of first dose of study drug. Day 1 is defined as the date of study drug kit dispensation in RANGER study, unless otherwise specified for the calculation of baseline (Section 6.4).

Assessments that occur after RANGER study drug dispensation but before the first study drug administration are considered to occur on study Day 1. Assessments collected on the same date as the first date of study drug administration will be considered to occur before the first dose of study drug administration.

For visits (or events) after the date of drug dispensing, day is calculated as:

- Study day = visit (or event) date - date of drug dispense + 1

For visits (or events) before the date of drug dispensing, day is calculated as:

- Study day = visit (or event) date - date of drug dispense

For listings (such as for adverse events) the quantity 'days since first (or last dose)' is defined as:

- days since first (or last dose) = event date – date of first (or last dose) + 1

For summaries that present distribution of time expressed in weeks and months, weeks will be defined as days divided by seven and months as days divided by 30.4.

6.5.4. Change from Baseline

Change from baseline is calculated using the baseline value (Section 6.4) and the value closest to the target study day, using the rules defined in Section 6.5.5.

Change from baseline is calculated as (post-baseline result – baseline result).

Percent change from baseline is calculated as (change from baseline/baseline result * 100).

If either the baseline or the post-baseline result is missing, the change from baseline and/or percentage change from baseline is set to missing as well.

6.5.5. Visit Windows

Because clinical visits may occur outside protocol-specified windows, instead of relying on visit labels in the clinical database, analysis visits and their windows are defined using derived study day (Section 6.5.3). Study day is calculated using the actual date for each scheduled and unscheduled assessment and compared to the target study day for each analysis visit. Data analysis and summaries are based on the collection date that is closest to the protocol scheduled target study day (Table 3).

Table 3: Analysis Visits

Analysis Visit	Label	Target Study Day	Analysis Window
0	Day 1	1	1
1	Week 1	7	2 ≤ Study Day ≤ 10
2	Week 2	14	11 ≤ Study Day ≤ 21
4	Week 4	28	22 ≤ Study Day ≤ 35
6	Week 6	42	36 ≤ Study Day ≤ 49
8	Week 8	56	50 ≤ Study Day ≤ 70
24	Week 24	168	140 ≤ Study Day ≤ 196
48	Week 48	336	308 ≤ Study Day ≤ 364
72	Week 72	504	476 ≤ Study Day ≤ 532
96	Week 96	672	644 ≤ Study Day ≤ 700
120, 144, etc.	Week 120, Week 144, Every 24 Weeks Thereafter	Analysis Visit x 7	([Analysis Visit x 7] -28) ≤ Study Day ≤ ([Analysis Visit x 7] +28)
FU	Follow-up	28 days after last dose	14 ≤ Days after last dose ≤ 35

The safety follow-up is based on days since last dose. If more than one assessment exists during the follow-up after last dose, the one closest to 28 days following the date of the last study drug administration is used for analysis and summary.

If a parameter is assessed or measured more than once within a visit window, the one that is closest to the protocol-scheduled time point (or target study day) is used for the purposes of data analysis and summary. If two assessments are equidistant from a target study day, the earlier assessment is used. If the visit used for analysis includes two assessments on the same day, the average of the two measurements will be used.

Records from visits not closest to the target study day, and therefore not used in analyses, are presented in by-subject data listings.

6.6. Handling of Missing Data

6.6.1. Missing Data

Missing data are not imputed.

6.6.2. Missing Start and Stop Dates for Prior and Concomitant Medication

Missing start dates for concomitant medications are not imputed.

Concomitant medications with incomplete end dates are considered concomitant medications if:

- Day and month are missing, and the year is equal to or after the year of the first date of study drug administration;
- Day is missing and the year is after the year of the first date of study drug administration;
- Day is missing and the year is equal to the year of the first date of study drug administration and the month is equal to or after the month of the first date of study drug administration; or
- Year is missing.

6.6.3. Missing Start and Stop Dates for Adverse Events

Treatment-emergent adverse events (TEAEs) are events that either:

- Had a date of onset on or after the date of the date of first dose of study drug and not more than 30 days after the date of the last dose of study drug, or
- Had no recorded date of onset with a stop date after the first dose of study drug, or
- Had no recorded date of onset or stop date.

Adverse events with incomplete start dates are considered after the date of first dose if:

- Day and month are missing, and the year is equal to or after the year of the first date of study drug administration;
- Day is missing and the year is after the year of the first date of study drug administration;
- Day is missing and the year is equal to the year of the first date of study drug administration and the month is equal to or after the month of the first date of study drug administration; or
- Year is missing.

Adverse events with incomplete start dates are considered on or within 30 days of last dose, if:

- Day and month are missing, and the year is equal to or before the year of the date of last dose of study drug plus 30 days;
- Day is missing and the year is equal to or before the year of the date of last dose of study drug plus 30 days, and month is equal to or before the month of the date of last dose of study drug plus 30 days;
- Year is missing.

6.6.4. Missing Treatment or Study End Date

The study was terminated on March 30, 2020. If the treatment end date or study end date are missing, the date will be imputed as March 30, 2020. If the treatment end date or study end date are missing and no reason for treatment or study discontinuation are included in the CRF, the reason for treatment or study discontinuation will be study termination.

7. STUDY POPULATION

Data are summarized for the safety population (Section 6.3.2).

7.1. Screen Failures

Screen failures are not summarized.

7.2. Subjects Disposition

A disposition summary includes the number and percentage of patients in the following categories:

- Patients with prior participation in LARIAT
- Patients with prior participation in CATALYST and randomized to placebo (only summarized when unbinding of CATALYST has occurred)
- Patients with prior participation in CATALYST and randomized to bardoxolone methyl (only summarized when unblinding of CATALYST has occurred)
- Continuing (or complete) treatment
- Terminate from the study
  - Reason for terminating study

Results will be summarized by analysis population (Section 6.3). A listing of disposition is provided for all enrolled patients.

7.3. Demographic and Baseline Characteristics

Summaries of demographic and other baseline characteristics summaries are presented by treatment analysis group (Section 4.5) for all analysis populations. Derivation of demographic and other baseline characteristics are described in Section 6.5.

Demographic and other baseline characteristics include the following:

- Age (years) at the date of informed consent
- Sex: female; male
- Race
- Ethnicity: Non-Hispanic/Latino; Hispanic/Latino
- Weight, body mass index (BMI)
- Geographic location: US; Other
- Baseline disease characteristics (WHO functional class, baseline 6MWT)
- Connective tissue disease (CTD) etiology (none, scleroderma, lupus, mixed, and other)
- Number of background medications

- Background medication class (endothelin receptor antagonist, phosphodiesterase type-5 inhibitors, soluble guanylate cyclase, prostacyclins)
  - Background medications (e.g., ambrisentan, bosentan, riociguat, etc.)

7.4. Listing of Subject Inclusion and Exclusion Criteria

A listing of enrolled patients who did not meet inclusion or exclusion criteria is generated.

7.5. Medical History and Medical Conditions Present at Entry

Medical history is summarized by treatment analysis group (Section 4.5, as well as all patients combined). For patients participating in CATALYST or LARIAT, medical history values are the values recorded at the CATALYST or LARIAT Screening visit. Medical history is coded using MedDRA (Medical Dictionary for Regulatory Activities) version 19.0. Medical history items are summarized by MedDRA SOC and PT. Patient listings are also provided.

8. EFFICACY

Analyses of 6MWT, Borg dyspnea scale include only summary statistics by visit window (Section 6.5.5) Summary statistics for observed values and change from baseline are presented.

8.1. 6-Minute Walk Test

The change from baseline in 6MWT score is summarized by visit and treatment analysis group (Section 4.5). Summary statistics for observed values and change from baseline are presented by visit window (Section 6.5.5). Line plots of change from baseline of 6MWT by visit and treatment analysis group (including overall patients) are generated up to and including study Week 120.

8.2. Borg Dyspnea Index

The change in Dyspnea scale is summarized by visit and treatment analysis group (Section 4.5). Summary statistics for observed values and change from baseline are presented by visit window (Section 6.5.5).

8.3. WHO/ NYHA Functional Class Assessment

WHO functional class assessment values collected at each visit using the appropriate analysis windows (Section 6.5.5) will be used. The number of patients in each class Section 12.2) is summarized at each analysis visit by treatment analysis group (Section 4.5). The categorical summaries for shift from baseline to highest and lowest WHO/ NYHA Functional Class are presented. The shift from baseline values includes WHO/ NYHA Functional Class I, II, III, IV and a category for missing data.

9. SAFETY AND TOLERABILITY

Safety data (including AEs, vital signs, BNP, and NT-proBNP) are listed and summarized for patients in the safety population (Section 6.3.2) by treatment analysis group (Section 4.5).

The analysis visit windows (Section 6.5.5) are used for all safety analyses. Any results not included in summaries based on analysis visit window definitions are presented in data listings.

9.1. Adverse Event Preferred Term and Body/Organ System Summary Tables

AEs are summarized by treatment analysis group as defined by the safety analysis set. General considerations for AE summaries and calculations are:

- Multiple events by preferred term (PT) and system organ class (SOC) are counted once only per patient for each treatment analysis group.
- For summaries by severity, only the most severe event is counted per patient for each treatment analysis group.
- For summaries by relationship, for frequency counts by patient, only the most related event is counted per patient for each treatment analysis group.
- An AE with a missing resolution date or incomplete date that is not identified as continuing is assumed to be continuing and no duration is calculated.
- Only treatment-emergent adverse events (TEAEs) are included in summaries.

AEs are coded using MedDRA (Medical Dictionary for Regulatory Activities) version 19.0. In MedDRA, each verbatim term is mapped to a preferred term and high level term (HLT), which is then mapped to a system organ class. Tables and listings present data at the SOC and PT level.

Treatment-emergent adverse events (TEAEs) are events that either:

- Had a date of onset on or after the date of the date of first dose in the RANGER study and not more than 30 days after the date of the last dose of study drug in the RANGER study, or
- Had no recorded date of onset with a stop date after the first dose of study drug, or
- Had no recorded date of onset or stop date.

Adverse events with a date of onset in LARIAT or CATALYST that continued during the RANGER study are not considered TEAEs.

In addition, adverse events which occurred >30 days after the date of last dose of study drug are listed as late-onset AEs (LOAEs). These are adverse events that had a date of onset more than 30 day after the date of the last dose of study drug.

The investigator grades the severity of the AEs as mild, moderate, or severe as defined in the study protocol Section 11.5.

Association or relatedness to the study medication are graded by the investigator according to criteria specified in Section 11.4 of the study protocol.

As defined in the protocol and captured on the CRF, a serious adverse event (SAE) is an adverse event that results in any of the following:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Results in a congenital anomaly or birth defect in an offspring of a patient taking study drug;
- Is an important medical event.

9.1.1. Missing and Partial AE Onset Dates

Rules for handling missing partial AE Onset Dates are included in Section 6.6.3.

9.1.2. Summaries of Adverse Events for Serious Adverse Events (SAE), Adverse Event Dropouts, and Death

Treatment-emergent AEs are summarized by treatment analysis group at onset of the AEs. For each treatment analysis group, SOC, and PT, the number and percentage of patients reporting an event are calculated. For subgroups, the number and percentage of patients reporting an event within a subgroup are calculated. In summary tables, SOC are presented alphabetically and events within SOC are presented by decreasing frequency count.

Summary tables (number and percentage of patients) of AEs (by SOC and PT) are provided by treatment analysis group as follows:

- All treatment-emergent AEs
- All treatment-emergent related AEs (definitely, probably, or possibly related)
- All treatment-emergent AEs by severity
- All treatment-emergent serious adverse events (including deaths)
- All related treatment-emergent serious adverse events (including deaths)
- All treatment-emergent adverse events leading to permanent discontinuation of study drug.

Listings are provided showing:

- All AEs
- Serious adverse events (including deaths)
- AEs leading to discontinuation of study drug.

9.2. Exposure and Compliance

The duration of study drug exposure is defined as the number of days on treatment analysis group from the first dose of study drug until the last dose of study drug (last dose - first dose + 1). Study drug exposure is summarized by descriptive statistics. Summaries include the total dose (mg) received (based on the number of pills returned), study drug compliance, the number and percentage of patients receiving study drug by scheduled dispense visit (reference visit window table), and duration (days) of exposure during the study treatment period.

In addition, a summary of the number and percentage of patients on bardoxolone methyl by visit and dose (5 mg, 10 mg) is generated.

Total number of doses dispensed and total dose (mg) dispensed are calculated from total number of kits (bottles) recorded on the Study Drug Dispensation eCRF. Total number of doses received are calculated from information on the eCRF of Study Drug Return and Study Drug Dispensation, as the total number of doses dispensed – total number of doses returned. Study drug compliance (%) is calculated as 100 × total number of doses received / total number of doses dispensed. For patients who remain on study treatment at the time of an interim or final data cut, the last kit dispensed date is considered the date of last dose.

9.3. Concomitant and Other Medications

Concomitant medications are coded using the World Health Organization (WHO) drug dictionary (1 Mar 2016 DDE+HD B2) for anatomical therapeutic chemical classification (ATC) and preferred drug name. A patient who used multiple medications are counted only once for each ATC and preferred drug name. ATC and preferred drug name within each ATC are sorted alphabetically. Coded concomitant medications are summarized by treatment analysis group (Section 4.5). Percentages are based on the number of patients in the safety analysis set.

A concomitant medication is any medication taken at the time of first study treatment during the RANGER study or a medication that was started after the start of RANGER study drug dosing. Specifically, concomitant medications are medications

- that are continued from CATALYST or LARIAT and continued after the first study drug dosing, or
- that have start dates or stop dates within the treatment period.

Concomitant medications are summarized for each treatment analysis group by WHO ATC class and preferred name. Patients may have more than one medication per ATC class and preferred name. At each level of patient summarization, a patient is counted once if he/she reported one or more medications at that level. Each summary is ordered by descending order of incidence of ATC class and preferred name within each ATC class.

Concomitant medications include those with an end date after the first study drug administration as well as medications without an end date. Medications with an end date on the date of first study drug administration are not be considered concomitant medications.

9.3.1. Missing and Partial Concomitant and Other Medication Start and Stop Dates

Missing and partial concomitant medication start and stop dates are detailed in Section 6.6.2.

9.4. Summaries of Laboratory Results

Laboratory data are summarized at baseline and at each time point by treatment analysis group (Section 4.5). Only values obtained within analysis study windows (Section 6.5.5) are included in by-visit summary statistics

Patients falling into the following four clinical meaningful categories are listed.

In addition, the number and percentage of patients in the following four clinical meaningful categories is summarized at each analysis visit by treatment analysis group (Section 4.5).

- BNP > 200 pg/mL
- BNP increase from baseline > 100%
- NT-proBNP > 1000 pg/mL
- NT-proBNP increase from baseline > 100%

9.5. Vital Signs

Vital signs assessments include systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg), body temperature (°C), heart rate (HR, bpm), weight (kg), and BMI (kg/m^2). Only values obtained within analysis study windows (Section 6.5.5) are included in by-visit summary statistics. Vital signs are summarized at baseline and at each time point along with the change from baseline by treatment analysis group (Section 4.5). All data are listed.

Line plots of change from baseline of vital signs by visit and treatment analysis group (including overall patients) are generated up to and including study Week 120. In addition, line plots are generated by: CTD; non-CTD.

Vital signs are summarized by: CTD; non-CTD.

9.6. Pregnancy

A patient listing is provided for all on-study pregnancies.

10. PHARMACOKINETICS

There are no pharmacokinetic samples collected in RANGER study.

11. CHANGES FROM PROTOCOL

Synopsis in the protocol doesn't indicate patients are scheduled to be assessed in person during treatment at Week 1. This SAP includes Week 1 in Section 4.6 Clinical Assessment and Table 3 Analysis Visits to follow protocol Table 3 Schedule of Assessments.

12. APPENDIX

12.1. Programming Specifications

Continuous data are listed corresponding to the precision measured or calculated. Measures of central tendency are presented using one more decimal place than the precision of the data. Summaries of variability are presented using two significant digits more than the precision of the underlying data. Median, Minimum, and the maximum are presented using the precision of the data. For instance, if the raw data are rounded to the 0.001 decimal place, the derived values must be rounded to the 0.0001 decimal place.

All percentages are to be expressed as integers with one decimal place. The convention for rounding percentages is as follows:

- Values greater than or equal to x.x5% are rounded up
- Values between 0 and x.x5% are rounded down

12.2. World Health Organization Functional Assessment Classification

Class I:	Patients with pulmonary hypertension (PH) 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 near 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.