COVER PAGE

Official Title:	A Phase 3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease
NCT Number:	NCT03918447
Document Date:	27 Jul 2023

STATISTICAL ANALYSIS PLAN

VERSION 3.0

DATE OF PLAN:

27 JUL 2023

BASED ON:

Protocol Version 7.0 (25 May 2022)

STUDY DRUG:

RTA 402, BARDOXOLONE METHYL

PROTOCOL NUMBER:

402-C-1808

STUDY TITLE:

A PHASE 3 TRIAL OF THE EFFICACY AND SAFETY OF BARDOXOLONE METHYL IN PATIENTS WITH AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

SPONSOR:

Reata Pharmaceuticals, Inc.

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Plano, Texas 75024

(972) 865-2219

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

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Reata Pharmaceuticals, Inc.

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	**Page:**	
Name of Active Ingredient: Bardoxolone methyl		
Title of Study: A Phase 3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease		
Studied period: ~6 years (Estimated based on enrollment of the first patient [May 2019] and the estimated date of last patient last visit [November 2025])	**Phase of development:** 3	

Study Endpoints:

Primary Efficacy Endpoint

- Off-treatment change from baseline in estimated glomerular filtration rate (eGFR) at Week 108.

Secondary Efficacy Endpoint

- Change from baseline in eGFR at Week 100.

[redacted]

- [redacted]
- The off-treatment change from baseline in eGFR at Week 112.
- [redacted]
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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: vital sign measurements, 12-lead electrocardiograms (ECGs), clinical laboratory measurements, pediatric growth (height and weight), and sexual maturity using Tanner staging.

Methodology:

This international, multi-center randomized, double-blind, placebo-controlled Phase 3 trial will study the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with ADPKD. Approximately 850 patients will be enrolled.

Patients will be randomized 1:1 to either bardoxolone methyl or placebo. Randomization will be stratified by eligibility eGFR category (30 to <60; ≥60 to 90), concomitant tolvaptan use (yes, no), and screening albumin to creatinine ratio (ACR; ≤300 mg/g, >300 mg/g). Patients randomized to placebo will remain on placebo throughout the study, undergoing sham titration. Patients with eGFR 60 to 90 mL/min/1.73 m^2 at screening should not comprise more than approximately 40% of enrolled patients.

The maximum bardoxolone methyl dose will be determined by baseline proteinuria status. Patients with baseline ACR≤300 mg/g will be titrated to a maximum dose of 20 mg, and patients with baseline ACR >300 mg/g will be titrated to a maximum dose of 30 mg. Patients receiving bardoxolone methyl will start with once-daily dosing at 5 mg and will dose-escalate to 10 mg at Week 2, to 20 mg at Week 4, and then to 30 mg at Week 6 (only if baseline ACR >300 mg/g) unless contraindicated clinically and approved by the medical monitor. Dose de-escalation is permitted during the study if indicated clinically, and subsequent dose re-escalation is also permitted to meet the dosing objective of the highest tolerated dose.

All patients in the study will follow the same visit and assessment schedule. Following randomization on Day 1, patients will be assessed during treatment in person at Week 1, 2, 4, 6, 8, 12, 24, 36, 48, 52, 64, 76, 88, and 100 and by telephone contact on Day 3, 10, 21, 31, 38, and 45. Patients will continue study drug treatment through Week 100. Patients will also be scheduled to be assessed at an in-person follow-up visit at Weeks 103, 104, 108, and 112 after the end of treatment, respectively.

Efficacy endpoints will be analyzed after final database lock.

The conduct of the study, according to protocol specifications, was impacted by the COVID-19 (Coronavirus Disease 2019) pandemic. As a result, and as of Version 4 of the protocol, modifications intended to address access to and administration of study drug, and adherence to protocol-specified visits and laboratory assessments were implemented. These modifications are described in Appendix 1 of the protocol (COVID-19 Mitigations), Appendix 2 of the protocol (Use of Home Healthcare), and throughout the protocol.

Number of Subjects (planned and analyzed):

Planned: Approximately 850

Diagnosis and main criteria for inclusion:

1. Male and female patients 12≤age≤70 upon study consent;
2. Diagnosis of ADPKD:
    a. For adult (18≤age≤70) diagnosis of ADPKD by modified Pei-Ravine criteria:
        i. at least 3 cysts per kidney by sonography or at least 5 cysts by CT or MRI with family history of ADPKD; or
        ii. at least 10 cysts per kidney by any radiologic method and exclusion of other cystic kidney diseases if without family history;
    b. For adolescent (12≤age<18) diagnosis of ADPKD by:
        i. the presence of family history and/or genetic diagnosis and the presence of at least 1 cyst of 0.5 cm on ultrasound or MRI; or
        ii. patients without a family history or genetic diagnosis must have at least 10 bilateral renal cysts in total, and exclusion of other cystic kidney diseases.
3. eGFR must:
    a. Have a percent difference ≤25% at screening (the values at Screen A and Screen B) and;
    b. Have an average (the values at Screen A and Screen B) ≥30 to ≤90 mL/min/1.73 m^2 for patients 12 to 55 years or ≥30 to ≤44 mL/min/1.73 m^2 for patients 56 to 70 years and;
    c. Support ADPKD disease progression (i.e., average yearly eGFR decline of ≥2.0 mL/min/1.73 m^2 for the past 2 years) for patients with either screening eGFR ≥60 to ≤90 mL/min/1.73 m^2 or age 56 to 70 years;
4. ACR ≤2500 mg/g at Screen B visit;
5. Systolic blood pressure ≤140 mmHg and diastolic blood pressure ≤90 mmHg at Screen A or Screen B visit after a period of rest. Patients receiving an angiotensin-converting enzyme (ACE) inhibitor and/or an angiotensin II receptor blocker (ARB) must be on a stable dose for at least 6 weeks prior to the Screen A visit;
6. Adequate bone marrow reserve and organ function at the Screen A visit as follows:
    a. Hematologic: Absolute neutrophil count >1.5× 10^9/L, platelets >100× 10^9/L, hemoglobin (Hgb) ≥9 g/dL;
    b. Hepatic: Total bilirubin (TBL), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) ≤ the upper limit of normal (ULN);
7. Able to swallow capsules;
8. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
9. Evidence of a personally signed and dated informed consent/assent document indicating that the patient has been informed of all pertinent aspects of the study prior to initiation of any protocol-mandated procedures.
10. Patients receiving an sodium glucose co-transporter 2 inhibitor must be on a stable dose for at least 4 weeks prior to the Screen A visit

Major exclusion criteria:

1. Prior exposure to bardoxolone methyl;
2. Use of tolvaptan within 2 months prior to Screen A. Initiation of concomitant tolvaptan use during the study is not permitted;
3. History of administration of polycystic kidney disease-modifying agents (somatostatin analogues) within 2 months prior to the Screen A visit;
4. B-type natriuretic peptide (BNP) level >200 pg/mL at Screen A visit;

5. Uncontrolled diabetes (HbA1c >11.0%) at Screen A visit;
6. Serum albumin <3 g/dL at Screen A visit;
7. History of intracranial aneurysms;
8. Kidney or any other solid organ transplant recipient or a planned transplant during the study;
9. Acute dialysis or acute kidney injury within 12 weeks prior to Screen A visit or during Screening;
10. History of clinically significant left-sided heart disease and/or clinically significant cardiac disease, including but not limited to any of the following:
    a. Clinically significant congenital or acquired valvular disease;
    b. Left ventricular ejection fraction <40% (based on echocardiogram performed at Screen A visit or within 6 months prior to Day 1);
    c. Pericardial constriction (based on echocardiogram performed at Screen A visit or within 6 months prior to Day 1);
    d. Restrictive or congestive cardiomyopathy (based on echocardiogram performed at Screen A visit or within 6 months prior to Day 1);
    e. Symptomatic coronary disease (prior myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or angina);
    f. History of hospitalization for heart failure;
    g. Cardiac insufficiency, defined as New York Heart Association Class III or IV;
    h. History of untreated atrial fibrillation;
    i. History of unstable arrhythmias;
11. Systolic BP <90 mm Hg at Screen A visit after a period of rest;
12. BMI <18.5 kg/m^2 at the Screen A visit;
13. History of malignancy within 5 years prior to Screen A visit, with the exception of localized skin or cervical carcinomas;
14. Systemic immunosuppression for more than 2 weeks, cumulatively, within the 12 weeks prior to randomization or anticipated need for immunosuppression during the study;
15. Untreated or uncontrolled active bacterial, fungal, or viral infection;
16. Participation in other interventional clinical studies within 30 days prior to Day 1;
17. Unwilling to practice acceptable methods of birth control (both males who have partners of child-bearing potential and females of childbearing potential) during Screening, while taking study drug, and for at least 30 days after the last dose of study drug is ingested;
18. Women who are pregnant or breastfeeding;
19. Known hypersensitivity to any component of the study drug;
20. Any abnormal laboratory level that, in the opinion of the investigator, would put the patient at risk by trial enrollment;
21. Patient is, in the opinion of the investigator, unable to comply with the requirements of the study protocol or is unsuitable for the study for any reason;
22. Coronavirus disease 2019 (COVID-19) pneumonia, related acute kidney injury, or related hospitalization within 6 months prior to Day 1.

Test product, dose and mode of administration:
Bardoxolone methyl will be administered orally at 5, 10, 20, or 30 mg once daily (QD).

Duration of treatment:
Bardoxolone methyl or placebo will be administered through Week 100.

Reference therapy, dose and mode of administration:
Placebo will be administered orally through Week 100, QD.

Criteria for evaluation (see protocol section 6.2, 11.0):

Efficacy: Change from baseline in eGFR; [redacted]

Safety: Results of laboratory results (clinical chemistry, hematology, urinalysis, and microscopy), vital sign measurements, ECG results, pediatric growth (height and weight), [redacted], AEs, and SAEs.

Statistical methods:

With 850 patients enrolled, the study will have approximately 80% power to detect a difference between the 2 treatment groups in change from baseline eGFR of 2.3 mL/min/1.73 m^2. The power calculation was based on a 2-sample t-test as an estimate for the planned analysis of covariance (ANCOVA) analysis and assumes the following:

- Overall two-sided Type I error rate total of 0.05;
- Standard deviation of change from baseline in eGFR of 12 mL/min/1.73 m^2;
- Analyses are based on the intent-to-treat (ITT) population;
- Missing data will be imputed using multiple imputation.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. LIST OF ABBREVIATIONS

The following abbreviations and special terms are used in this statistical analysis plan (SAP).

Table 1. LIST OF ABBREVIATIONS

Abbreviation	Term
ABPM	ambulatory blood pressure monitoring
ACEi	angiotensin converting enzyme inhibitor
ACR	albumin/creatinine ratio
ACR_STRAT	ACR strata used in randomization
ADPKD	autosomal dominant polycystic kidney disease
[redacted]	[redacted]
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
BARD	bardoxolone methyl
BMI	body mass index
BNP	B-type natriuretic peptide
[redacted]	[redacted]
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CSR	clinical study report
CT	computed tomography
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
eGFR_STRAT	eGFR strata used in randomization
ESKD	end stage kidney disease
FDA	Food and Drug Administration (US)
FMV	first morning void
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation	Term
INR	international normalized ratio
ITT	intent-to-treat
IWRS	Interactive Web Response System
KDIGO	Kidney Disease: Improving Global Outcomes
LLD	lower limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MRI	magnetic resonance imaging
NCS	Not clinically significant
NT-ProBNP	N-Terminal Pro-Brain Natriuretic Peptide
OTAE	off-treatment adverse event
[redacted]	[redacted]
pH	potential of hydrogen
PK	pharmacokinetic(s)
PT	preferred term
QTcF	corrected QT interval using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SD	standard deviation
SOC	system organ class
STD	Study Termination Date
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TLFs	tables, listings, and figures
ULD	upper limit of detection
ULN	upper limit of normal
US	United States
WOCBP	women of childbearing potential

2. INTRODUCTION

This statistical analysis plan (SAP) describes the planned analyses and data displays to be included in the Clinical Study Report (CSR) for Study 402-C-1808. This SAP was developed in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E9 guidelines. All decisions regarding the final analysis, as defined in this SAP document, were made prior to Database Lock (unblinding) of the study data.

The SAP is based on:

- Protocol 402-C-1808, Version 7.0, dated 25 May 2022
- ICH guidelines E4 (Dose-Response Information to Support Drug Registration) and E9 (Statistical Principles for Clinical Trials)
- Feedback received from FDA throughout clinical development, including the following communications:
  - FDA End of Phase 2 Meeting Minutes [redacted] for the 31 October 2018 meeting
  - FDA Advice/Information Request [redacted] dated 16 July 2019
  - FDA Advice/Information Request [redacted] dated 08 October 2020
  - FDA Type B Meeting Minutes [redacted] for the 23 July 2021 meeting
  - FDA Type A Meeting Minutes [redacted] for the 08 April 2022 meeting

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 from Study 402-C-1808. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing.

This version of the SAP describes the analyses as planned prior to the final database lock. This SAP will be finalized, approved by the Reata Pharmaceuticals, and placed on file before the database lock. Unless otherwise specified, the final CSR will summarize these analyses. Any deviations from the final approved SAP will be documented in the CSR. Any analyses in addition to those specified in the SAP prior to the database lock are considered ad hoc and will be documented in the CSR.

In May 2023, Kyowa Kirin Co., Ltd. (Kyowa Kirin) announced results from AYAME (402-006), a Phase 3, multi-center, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of bardoxolone methyl (bardoxolone) for patients with diabetic kidney disease. The study enrolled 1013 patients who were treated with 5 to 15 mg of bardoxolone or placebo for 3 to 4 years.

The AYAME (402-006) study met the primary endpoint and key secondary endpoint; however, there was no separation in the occurrence of end-stage renal disease events between the 2 groups. Based on the AYAME (402-006) efficacy results, Kyowa Kirin and Reata have decided to discontinue clinical development of bardoxolone.

This decision was communicated to all sites on 10 May 2023, which is referred to as the study drug termination (SDT) date.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1. Study Objectives

3.1.1. Primary Objectives

- To assess the off-treatment change from baseline in estimated glomerular filtration rate (eGFR) at Week 108.
- To assess safety and tolerability.

3.1.2. Secondary Objective

- To assess the change from baseline in eGFR at Week 100.

[redacted]

- [redacted]
- To assess the off-treatment change from baseline in eGFR at Week 112.
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3.2. Study Endpoints

In patients with autosomal dominant polycystic kidney disease (ADPKD), the study will compare those receiving bardoxolone methyl to those receiving placebo with respect to several endpoints. The timing for analyzing study endpoints is described in Section 5. Primary efficacy analyses are described in Section 8 [redacted]

3.2.1. Primary Efficacy Endpoint

- Off-treatment change from baseline in eGFR at Week 108.

3.2.2. Secondary Efficacy Endpoint

- Change from baseline in eGFR at Week 100.

[redacted]

- [redacted]
- The off-treatment change from baseline in eGFR at Week 112.
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3.2.4. 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: vital sign measurements, 12-lead electrocardiograms (ECGs), clinical laboratory measurements, pediatric growth (height and weight), and sexual maturity using Tanner staging.

4. STUDY DESIGN

4.1. Summary of Study Design

This international, multi-center, randomized, double-blind, placebo-controlled Phase 3 trial will study the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with ADPKD. Approximately 850 patients will be enrolled.

Patients will be randomized 1:1 to either bardoxolone methyl or placebo. Randomization will be stratified by eligibility eGFR category (30 to <60; ≥60 to 90), concomitant tolvaptan use (yes, no), and screening albumin to creatinine ratio (ACR; ≤300 mg/g, >300 mg/g). Patients randomized to placebo will remain on placebo throughout the study, undergoing sham titration. Patients with eGFR 60 to 90 mL/min/1.73 m^2 at screening should not comprise more than approximately 40% of enrolled patients.

The maximum bardoxolone methyl dose will be determined by baseline proteinuria status. Patients with baseline ACR ≤300 mg/g will be titrated to a maximum dose of 20 mg, and patients with baseline ACR >300 mg/g will be titrated to a maximum dose of 30 mg. Patients receiving bardoxolone methyl will start with once-daily dosing at 5 mg and will dose-escalate to 10 mg at Week 2, to 20 mg at Week 4, and then to 30 mg at Week 6 (only if baseline ACR >300 mg/g) unless contraindicated clinically and approved by the medical monitor. Dose de-escalation is permitted during the study if indicated clinically, and subsequent dose re-escalation is also permitted to meet the dosing objective of the highest tolerated dose.

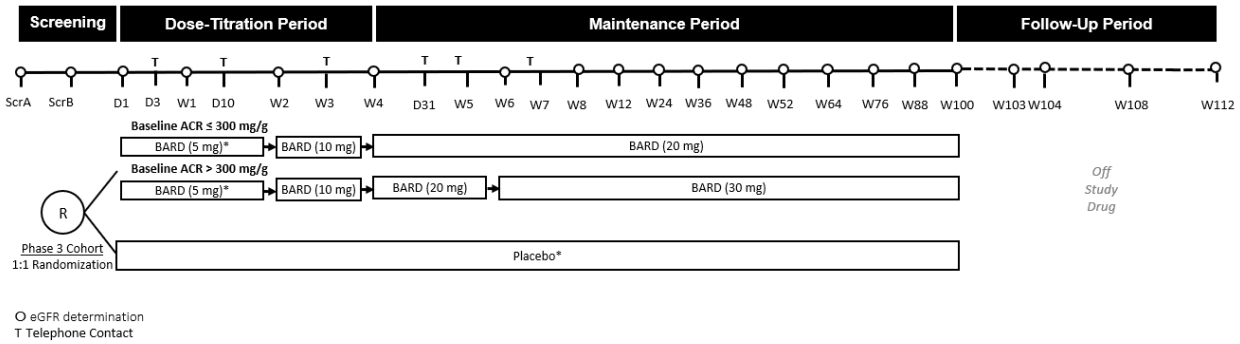
All patients in the study will follow the same visit and assessment schedule. Following randomization on Day 1, patients will be scheduled to be assessed during treatment at Week 1, 2, 4, 6, 8, 12, 24, 36, 48, 52, 64, 76, 88, and 100 and by telephone contact on Day 3, 10, 21, 31, 38, and 45. Patients will continue study drug treatment through Week 100. Patients will also be scheduled to be assessed at an in-person follow-up visit at Weeks 103, 104, 108, and 112, after the end of treatment, respectively. The Data Monitoring Committee performs quarterly reviews of unblinded data for safety throughout the study.

Efficacy endpoints will be analyzed after all enrolled patients have completed the study and the final database lock.

The conduct of the study, according to protocol specifications, was impacted by the COVID-19 (Coronavirus Disease 2019) pandemic. As a result, modifications intended to address access to and administration of investigational product (IP), and adherence to protocol-specified visits and laboratory assessments were implemented and are described in Appendix 1 of the protocol (COVID-19 Mitigations), Appendix 2 of the protocol (Use of Home Healthcare), and throughout the protocol. The COVID-19-related impact on study conduct will be summarized as described in Section 10 of this SAP.

Figure 1. STUDY SCHEMA

Schema for Study of Bardoxolone Methyl in Patients with ADPKD



4.2. Definition of Study Drugs

Bardoxolone methyl capsules, 5 mg (size #4), 10 mg (size #2), 15 mg (size #1), and 20 mg (size #0) may be used in this study. The 30 mg dose will be given as two 15 mg capsules. Placebo capsules will have matching capsule sizes to have the same appearance as the active doses.

4.3. Sample Size Considerations

4.3.1. Primary Endpoints

With 850 patients enrolled, the study will have approximately 80% power to detect a difference between the 2 treatment groups in change from baseline eGFR of 2.3 mL/min/1.73 m^2. The power calculation was based on a 2-sample t-test as an estimate for the planned analysis of covariance (ANCOVA) analysis and assumes the following:

- Overall two-sided Type I error rate total of 0.05;
- Standard deviation of change from baseline in eGFR of 12 mL/min/1.73 m^2;
- Analyses are based on the intent-to-treat (ITT) population;
- Missing data will be imputed using multiple imputation.

PASS 13 software was used to calculate sample size.

4.4. Randomization

Patients will be randomized 1:1 to either bardoxolone methyl or placebo. Randomization will be performed using an interactive web response system (IWRS) and will be stratified by eligibility eGFR category (30 to <60; ≥60 to 90 mL/min/1.73 m^2), concomitant tolvaptan use (yes, no), and screening ACR (≤300 mg/g, >300 mg/g). Eligibility eGFR is the average of the screening eGFR visits. Patients randomized to placebo will remain on placebo throughout the study, undergoing sham titration.

4.5. Clinical Assessments

All patients in the study follow the same visit and assessment schedule for the duration of the trial. Table 2 lists the overall schedule of assessments for the study.

Table 2. SCHEDULE OF ASSESSMENTS

	Screening Period		Treatment Period											
	Screen A[a]	Screen B[b]	Day 1[c]	Wk 1 (Phone)	Wk 1	Wk 2 (Phone)	Wk 2	Wk 3 (Phone)	Wk 4	Wk 4 (Phone)	Wk 5 (Phone)	Wk 6	Wk 7 (Phone)	Week 8
	Up to Day -90	Up to Day -30	Day 1	Day 3 ±2 Days	Day 7 ±3 Days	Day 10 ±2 Days	Day 14 ±3 Days	Day 21 ±2 Days	Day 28 ±3 Days	Day 31 ±2 Days	Day 38 ±2 Days	Day 42 ±3 Days	Day 45 ±2 Days	Day 56 ±3 Days
Informed Consent/Assent	X													
Inclusion/Exclusion	X		X[d]											
Demographics & Baseline Disease Characteristics	X													
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History	X													
Height[e]	X	X	X		X		X		X			X		X
Weight in Clinic	X		X		X		X		X			X		X
Weight at Home			----------X----------											
Dispense Weight & Study Drug Diary			X				X		X			X		X
Collect/Review Weight & Study Drug Diary				X	X	X	X	X	X	X	X	X	X	X
ECG	X													
Echocardiogram[f]	X													
Vital Sign Measurements	X	X[g]	X		X		X		X			X		X
Comprehensive Physical Exam	X		X											
Targeted Physical Exam					X		X		X			X		X
Pregnancy Test for WOCBP[h]	X	X	X						X					X
Study Drug Administration			----------X----------											
Dispense Study Drug			X				X		X			X		X
Collect Study Drug							X		X			X		X
Telephone Contact				X		X		X		X	X		X	
Adverse Event Collection			X[i]	X	X	X	X	X	X	X	X	X	X	X
Kidney Ultrasound[j]	X													
Clinical Chemistry (incl. eGFR)[k]	X	X	X		X		X		X			X		X
BNP and NT-proBNP	X		X		X		X		X			X		X
Hemoglobin A1c	X													
Hematology	X		X				X		X			X		X
Coagulation			X				X		X			X		X
Basic Lipid Panel			X											
Urinalysis and Microscopy	X		X				X		X			X		X
Urine Collection for ACR[l]		X							X					X
[redacted]														
Virus Serology	X													
PK Samples[n]														
SARS-CoV-2 Antibody Test			X											
Ambulatory Blood Pressure Monitoring[o]	X[p]													
Tanner Staging[q]			X											

	Treatment Period								
	Wk 12	Wk 24	Wk 36	Wk 48	Wk 52 (B)	Wk 64	Wk 76	Wk 88	Wk 100 or End of Treatment
	Day 84 ±3 Days	Day 168 ±3 Days	Day 252 ±3 Days	Day 336 ±3 Days	Day 364 ±3 Days	Day 448 ±5 Days	Day 532 ±5 Days	Day 616 ±5 Days	Day 700 -5 Days (+0 Days)
Informed Consent/Assent									
Inclusion/Exclusion									
Demographics & Baseline Disease Characteristics									
Prior and Concomitant Medications	X	X	X	X	X	X	X	X	X
Medical History									
Height[e]	X	X	X	X	X	X	X	X	X
Weight in Clinic	X	X	X	X	X	X	X	X	X
Weight at Home	----------X----------								
Dispense Weight & Study Drug Diary	X	X	X	X	X	X	X	X	
Collect/Review Weight & Study Drug Diary	X	X	X	X	X	X	X	X	X
ECG				X	X				X
Echocardiogram[f]									
Vital Sign Measurements	X	X	X	X	X	X	X	X	X
Comprehensive Physical Exam					X				X
Targeted Physical Exam	X	X	X	X		X	X	X	
Pregnancy Test for WOCBP[h]	X	X	X	X	X	X	X	X	X
Study Drug Administration	----------X----------								
Dispense Study Drug	X	X	X	X	X	X	X	X	
Collect Study Drug	X	X	X	X	X	X	X	X	X
Telephone Contact									
Adverse Event Collection	X	X	X	X	X	X	X	X	X
Kidney Ultrasound[j]									
Clinical Chemistry (incl. eGFR)[k]	X	X	X	X	X	X	X	X	X
BNP and NT-proBNP	X	X	X	X	X	X	X	X	X
Hemoglobin A1c	X			X					X
Hematology	X	X	X	X	X	X	X	X	X
Coagulation	X	X	X	X	X	X	X	X	X
Basic Lipid Panel					X				X
Urinalysis and Microscopy	X	X	X	X	X	X	X	X	X
Urine Collection for ACR[l]	X	X	X	X	X	X	X	X	X
[redacted]									
Virus Serology									
PK Samples[n]	X								X
SARS-CoV-2 Antibody Test					X				
Ambulatory Blood Pressure Monitoring[o]	X			X				X[r]	
Tanner Staging[q]					X				

	Off-Treatment Period[s]						
	Wk 103	Wk 104 (A)	Wk 104 (B)	Wk 108 (A)	Wk 108 (B)	Wk 112 (A)	Wk 112 (B)
Off-Treatment: Patients who continued study drug through Wk 100 (visits based on date of last dose)	Day 21 – 25 after last dose	Day 28 – 35 after last dose	Day 29 – 36 after last dose	Day 56 – 63 after last dose	Day 57 – 64 after last dose	Day 84 – 91 after last dose	Day 85 – 92 after last dose
Follow-Up: Patients who discontinued study drug prior to Wk 100 (visits based on Day 1 date)	Day 721 - 725	Day 728 – 735	Day 729 – 736	Day 756 – 763	Day 757 – 764	Day 784 – 791	Day 785 – 792
Informed Consent/Assent							
Inclusion/Exclusion							
Demographics & Baseline Disease Characteristics							
Prior and Concomitant Medications	X	X	X				
Medical History							
Height[e]	X	X	X	X	X	X	X
Weight in Clinic			X		X		
Weight at Home							
Dispense Weight & Study Drug Diary							
Collect/Review Weight & Study Drug Diary							
ECG			X		X		
Echocardiogram[f]							
Vital Sign Measurements			X		X		
Comprehensive Physical Exam			X		X		
Targeted Physical Exam							
Pregnancy Test for WOCBP[h]			X		X		
Study Drug Administration							
Dispense Study Drug							
Collect Study Drug							
Telephone Contact							
Adverse Event Collection	X	X	X	X	X	X	X
Kidney Ultrasound[j]							
Clinical Chemistry (incl. eGFR) [k]	X	X	X	X	X	X	X
BNP and NT-proBNP			X		X		
Hemoglobin A1c							
Hematology			X		X		
Coagulation			X		X		
Basic Lipid Panel			X		X		
Urinalysis and Microscopy			X		X		
Urine Collection for ACR[l]			X		X		
[redacted]							
Virus Serology							
PK Samples [n]	X		X		X		
SARS-CoV-2 Antibody Test					X		
Ambulatory Blood Pressure Monitoring [o]							
Tanner Staging [q]					X		

Abbreviations: ABPM = ambulatory blood pressure monitoring, ACR = albumin to creatinine ratio, ADPKD = autosomal dominant polycystic kidney disease, AE = adverse event, BNP = B-type natriuretic peptide, [redacted], ECG = electrocardiogram, eGFR = estimated glomerular filtration rate, IRB/EC = institutional review board/ethics committee, IWRS = Interactive Web Response System, NT-proBNP = N-terminal pro-brain natriuretic peptide, [redacted]

[redacted], PK = pharmacokinetic, SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus 2, Wk = week, WOCBP = women of child-bearing potential

[a] Total Screening period should not exceed 90 days.
[b] Screen B visit should be at least 1 day after Screen A and no more than 30 days prior to Day 1.
[c] Day 1 should be the day of randomization and administration of the first dose. Where randomization in the IWRS must occur earlier than Day 1, the Day 1 visit must align with the administration of the first dose. **On Day 1, all procedures must be performed before study drug administration.**
[d] Screening eligibility procedures do not need to be repeated on Day 1; however, a review of any changes in eligibility criteria should be evaluated prior to Day 1 procedures
[e] Height will be recorded in centimeters. Adult patients (18≤age≤70 years at Screen A visit) will be measured at Screen A only. Adolescent patients (12≤age<18 years at Screen A visit) will be measured at all specified timepoints.
[f] An echocardiogram performed during screening or within 6 months prior to Day 1 may be used to determine eligibility.
[g] Screen B vital sign measurements are needed only if re-assessing blood pressure for eligibility.
[h] A serum pregnancy test will be performed at the Screen A visit for WOCBP or 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 regulatory authorities or IRBs/ECs.
[i] AE assessments on Day 1 should be performed following study drug administration.
[j] Kidney ultrasound (historical or one obtained during screening) may be used to diagnose ADPKD for patients without a prior ADPKD diagnosis.
[k] eGFR will be calculated and appear on lab reports for Screen A and Screen B visits, eGFR will no longer be calculated for any visits after the Screening period.
[l] Albumin to creatinine ratio will be measured by first morning void spot urine collection. Appropriate containers for the collection will be provided to the patient at the visit prior to collection.
[redacted]
[n] Patients must refrain from taking study drug prior to coming to the clinic for PK draws at Week 12 and Week 100.
[o] Ambulatory Blood Pressure Monitoring (ABPM) is an optional sub-study for adult patients (18≤age≤70 years at Screen A) who enroll under protocol version 6.0 (or greater) and consent to the procedure prior to randomization. See Protocol Section 9.10.33 for details and timing on ABPM. ABPM will not be performed on adolescent patients (12≤age<18 years at randomization).
[p] For patients who consent to the optional ABPM sub-study, the initial (baseline) 24-hour monitoring assessment must be done during the Screening period prior to Day 1. See Protocol Section 9.10.33 for detailed information.
[q] Adolescent patients (12≤age<18 years at Screen A visit) will be assessed by Tanner staging at all specified timepoints.
[r] For adult patients who consent to the optional ABPM sub-study, the final 24-hour monitoring assessment occurs after Week 88 and prior to Week 100 (last dose). For patients who discontinue study drug prior to Week 100, patients who consented to ABPM should have the assessment at End of Treatment if no ABPM was conducted in the four weeks prior to the date of last dose.
[s] See Protocol Section 8.3.3 and Protocol Section 8.5.1 for details on the Off-Treatment Period.
[t] Unless permitted in the protocol, all study activities, including assessments and sample collection, are expected to be completed on the same day (i.e., day of the visit).

5. PLANNED ANALYSES

The final analyses are based on final locked data and performed after all enrolled patients have completed the end of study visit. A separate database lock plan will describe details of the database lock.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

The efficacy and safety analyses use the analysis sets defined in Section 6.3. Patient listings (as appropriate) of all analysis data that support summary tables and/or figures are provided along with their source data. The summary tables do not include measurements from patients excluded from the pre-defined analysis sets or extra measurements (such as unscheduled or repeat assessments) not closest to the target study day unless specified otherwise, but the patient listings do include these data. Missing data are not imputed, unless otherwise specified. In general, patient listings are sorted by treatment group, patient number and assessment date (time and parameter, as applicable).

Any laboratory value (including eGFR), vital sign assessment, or ECG value collected after ESKD is considered invalid and will be treated as missing.

Efficacy and safety data collected while a patient has temporarily discontinued study drug will be included in analyses. All data will be presented in by-patient listings.

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. The strategy for controlling family-wise overall Type I error rate of 0.05 is described in Section 8.3. For endpoints not described in Section 8.4, the reported significance levels are nominal, and the following statistical conventions are used:

- Unless otherwise noted, all statistical testing is two-sided and is performed at the 0.05 significance level.
- Tests are declared statistically significant if the calculated p-value is <0.05.

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

6.2. Data Presentation Conventions

Unless otherwise specified, descriptive statistics for continuous variables include the number of patients with data (N), mean, standard deviation (SD), standard error (SE), first quartile (Q1), median, third quartile (Q3), 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 presented when reporting mean and quartiles; and 2 more decimal places than in the observed value are presented when reporting SD or SE.

Categorical 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., the denominators include only patients with available data), and the number of missing values is presented. For summaries of AEs and concomitant medications, the percentages are based on the total number of patients in each treatment group.

6.3. Analysis Populations

Table 3 lists the analysis populations in the study.

Table 3: ANALYSIS POPULATION DEFINITION

Analysis Population	Definition
ITT (Intent-to-Treat)	All enrolled patients categorized by their randomized treatment group (whether or not they received study drug).
Safety	All enrolled patients who received at least 1 dose of study drug. The safety population is used for evaluation of safety variables. Patients who received 1 dose of bardoxolone methyl will be classified in the bardoxolone methyl group. Patients who received at least 1 dose of placebo and no dose of bardoxolone methyl will be classified in the placebo group.

6.4. Baseline Definitions

Baseline values are defined as the last non-missing assessment prior to the first study drug administration, unless otherwise specified below. If the first study drug administration occurs after the date of randomization, the last measurement prior to the first study drug administration is considered the Day 1 measurement for the calculation of baseline. If the first study drug administration date is not present, the baseline values are the last non-missing assessment on or prior to the Day 1 visit date.

When assessment time is not available, assessments that are collected on the same date as the first date of study drug administration are considered to occur before the first dose of study drug administration.

6.4.1. Age

Baseline age is defined as the age at consent (Screen A).

6.4.2. Estimated Glomerular Filtration Rate

Baseline eGFR is defined as the average of Screening and Day 1 eGFR measurements, calculated as shown below:

- Screening eGFR=average of the last 2 eGFR measurements collected prior to the Day 1 eGFR collection
- Day 1 eGFR=the measurement after screening but on or before the date of first study drug administration
- Baseline eGFR=(0.5×Day 1 eGFR)+(0.5×Screening eGFR)

If there are only 2 observations available, then the average of the 2 values is used as baseline. Since patients must have Screen A and Screen B eGFR values within a percent difference ≤25% to be eligible for enrollment, the variability of Screening eGFR is mediated by the study inclusion/exclusion criteria. Furthermore, the Screening eGFR value may be collected up to

3 months prior to study entry. The Day 1 eGFR value carries greater weight in the baseline eGFR calculation to account for the reduced variability in the screening eGFR values.

6.4.3. Serum Creatinine

Baseline serum creatinine (SCr) is defined in the same way as baseline eGFR (Section 6.4.2).

6.4.4. Safety Assessments

Baseline for continuous safety assessments (i.e., vital sign assessments, weight, body mass index [BMI], and laboratory measurements) is defined as the average value of measurements collected up through the date of, but not after, first study drug administration.

6.4.5. Urine Albumin to Creatinine Ratio

Baseline ACR is defined as the last ACR value prior to the first study drug administration. Baseline ACR is summarized using the geometric mean of ACR values.

6.4.6. Natural log (ACR)/eGFR

Baseline of natural log (ACR)/eGFR is defined as the ratio of the natural log of baseline ACR (Section 6.4.5) divided by baseline eGFR (Section 6.4.2).

6.5. Derived and Transformed Data

6.5.1. Study Day

Study day is the day relative to the date of first dose. Day 1 is defined as the date of first dose.

If date of first dose is not present, then date of randomization is used to calculate the study day.

Assessments without timestamp collected on the same date as the first date of study drug administration are considered to occur before the first dose of study drug administration.

For visits (or events) after first dose, day is calculated as:

- Study day=visit (or event) date-date of first dose+1

For visits (or events) before first dose, day is calculated as:

- Study day=visit (or event) date-date of first dose

The quantity ‘days since first dose’ is defined as:

- Days since first dose=visit (or event) date–date of first dose+1

The quantity ‘days since last dose’ is defined as:

- Days since last dose=visit (or event) date-date of last dose

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

6.5.2. Visit Windows

Analysis visits and their windows are defined using derived study day (Section 6.5.1) instead of relying on visit labels in the clinical database because clinical visits may occur outside protocol-specified windows. Study day and days after last dose are calculated using the actual date of each scheduled and unscheduled assessment and compared to the target for each analysis visit as specified in Table 4 and Table 5. They are included in analyses of safety and efficacy as follows:

- Efficacy analyses for endpoints assessed through Week 100 use the analysis windows in Table 4, irrespective of whether or not a patient is receiving treatment of study drug.
- Efficacy analyses for endpoints assessed during the follow-up period after Week 100 use the analysis window in Table 4 irrespective of how long a patient has been off-treatment.
- Protocol version 6 eliminated the off-treatment period from Week 48 to Week 52. Patients completing the Week 52 visit prior to consenting to protocol version 6 will be considered "off-treatment" at Week 52. All other patients are expected to be on-treatment at Week 52. Week 52 analysis values in Table 4 will not be used in the efficacy analyses unless otherwise specified. Week 52 values are only summarized descriptively because of the mix of on-treatment and off-treatment values.
- Safety analyses use the analysis windows defined in Table 4 so long as the patient is receiving treatment of study drug. Once a patient permanently discontinues study treatment, safety data are summarized according to time since last dose as defined in Table 5.

Unless otherwise specified 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 (i.e., target) is used for the purposes of data analysis and summary.

If 2 assessments are equidistant from a target, the earlier assessment is used. If 2 assessments are on the same day, the average of 2 assessments will be used for non-laboratory parameters. For laboratory parameters, if both an original and retest result are available in the laboratory dataset, the original result will be used and the second (i.e., "retested") result will be ignored.

One exception is that 2 scheduled chemistry values (including eGFR) are collected within the Week 52 (prior to protocol version 6), Week 104, Week 108, and Week 112 analysis windows.

Protocol specified 2 off-treatment chemistry values collected within the Week 52 (prior to protocol version 6), Week 104, Week 108 and Week 112 analysis window at A and B visits. At Week 52, Week 104, Week 108, and Week 112 visits, the 2 off-treatment measurements that are in the analysis window and closest to the target day specified in Table 4 are averaged for the purpose of data summary and analysis. All values included in the Week 103, 104, 108, and 112 analysis windows must also be assessed after last dose.

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

Table 4. ANALYSIS VISIT WINDOWS

Analysis Visit	Label	Target		Analysis Window
		Study Day[a]	Days After Last Dose	
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
12	Week 12	84	-	71≤study day≤126
24	Week 24	168	-	127≤study day≤210
36	Week 36	252	-	211≤study day≤294
48	Week 48	336	-	295≤study day≤350
52	Week 52	364	-	351≤study day≤406
64	Week 64	448	-	407≤study day≤490
76	Week 76	532	-	491≤study day≤574
88	Week 88	616	-	575≤study day≤658
100	Week 100[b]	700	-	659≤study day≤720
103	Week 103[c]	721	21	721≤study day≤727[d] or 21≤after last dose≤27[e]
104	Week 104[c]	728	28	728≤study day≤755[d] or 28≤after last dose<55[e]
108	Week 108[c]	756	56	756≤study day≤783[d] or 56≤after last dose≤83[e]
112	Week 112 [c]	784	84	784≤study day≤806[d] or 84≤after last dose<106[e]

[a] Study Day is relative to the date of first dose (Section 6.5.1).

[b] Week 100 is the end of the dosing interval and should coincide with the last dose.

[c] Including off-treatment values only.

[d] Analysis windows are based on study day for patients who discontinued treatment early. Analysis windows are based on days after last dose for patients who complete treatment. Last dose for analysis is the Week 100 dose.

[e] Analysis windows are based on days after last dose for patients who complete treatment. Last dose for analysis is the Week 100 dose.

6.5.2.1. Off-Treatment Visit Windows Relative to Last Dose for Safety

Patients who permanently discontinue study drug prior to Week 100 are asked to resume the planned assessments according to the study schedule in the protocol. Off-treatment values for clinical laboratory evaluations (Section 9.5), vital signs (Section 9.7), and electrocardiograms (Section 9.9) are those that occur after the last dose date for patients permanently discontinuing study drug prior to Week 100, and are summarized relative to their last dose of study drug. Off-treatment safety assessments (clinical labs, vital signs, and ECGs) are grouped for analyses according to the strategy in Table 5. Assessments that occur on or before the date of last dose through 20 days after last dose are considered on-treatment period.

Table 5: ANALYSIS VISITS FOR OFF-TREATMENT SAFETY FOLLOWING EARLY TREATMENT DISCONTINUATION

Off-Treatment Safety Analysis Visit	**Label**	**Target Study Day** (days after last dose)	**Analysis Window**
0	Last dose (on-treatment)[a]	0	0 (days after last dose ≤20)
4	Off Treatment 4-weeks[b]	28	21≤days after last dose≤35
8	Off Treatment 8-weeks[b]	56	36≤days after last dose≤71
12	Off Treatment 12-weeks[b]	84	72≤days after last dose≤99
24	Off Treatment 24-weeks[b]	168	100≤days after last dose≤252
48	Off Treatment 48-weeks[b]	336	253≤days after last dose≤350
72	Off Treatment 72-weeks[b]	504	351≤days after last dose≤518
96	Off Treatment 96-weeks[b]	672	519≤days after last dose≤686

[a] Last dose for patients permanently discontinuing study drug prior to Week 100. Assessments that occur on the date of last dose or less than 21 days after last dose are considered on treatment and summarized using Table 4 windows.
[b] The off-treatment values indicate the value closest to the date of last dose and at least 21 days after last dose.

6.5.3. Laboratory Evaluations Imputations

Any laboratory assessments less than the lower limit of detection (i.e., < LLD) are imputed as LLD/2 (e.g., <25 is 25/2=12.5). Laboratory assessments above the upper limit of detection (ULD) are imputed as the ULD. If the lab result is qualitative but presented as >X and X is 10 times greater than the ULN, then the value X is used in the analysis.

6.5.4. eGFR

The eGFR is calculated using the formula below according to patient's age at the date of consent. The formula will not change throughout the study. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation is used for adult patients (age at consent at least 18 years):

- eGFR (mL/min/1.73 m^2)=$141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times$ 1.018 [if female]×1.159 [if black]

For Adolescents (≥12 and <18 years age old at consent) - the eGFR value will be calculated by using Bedside Schwartz equation:

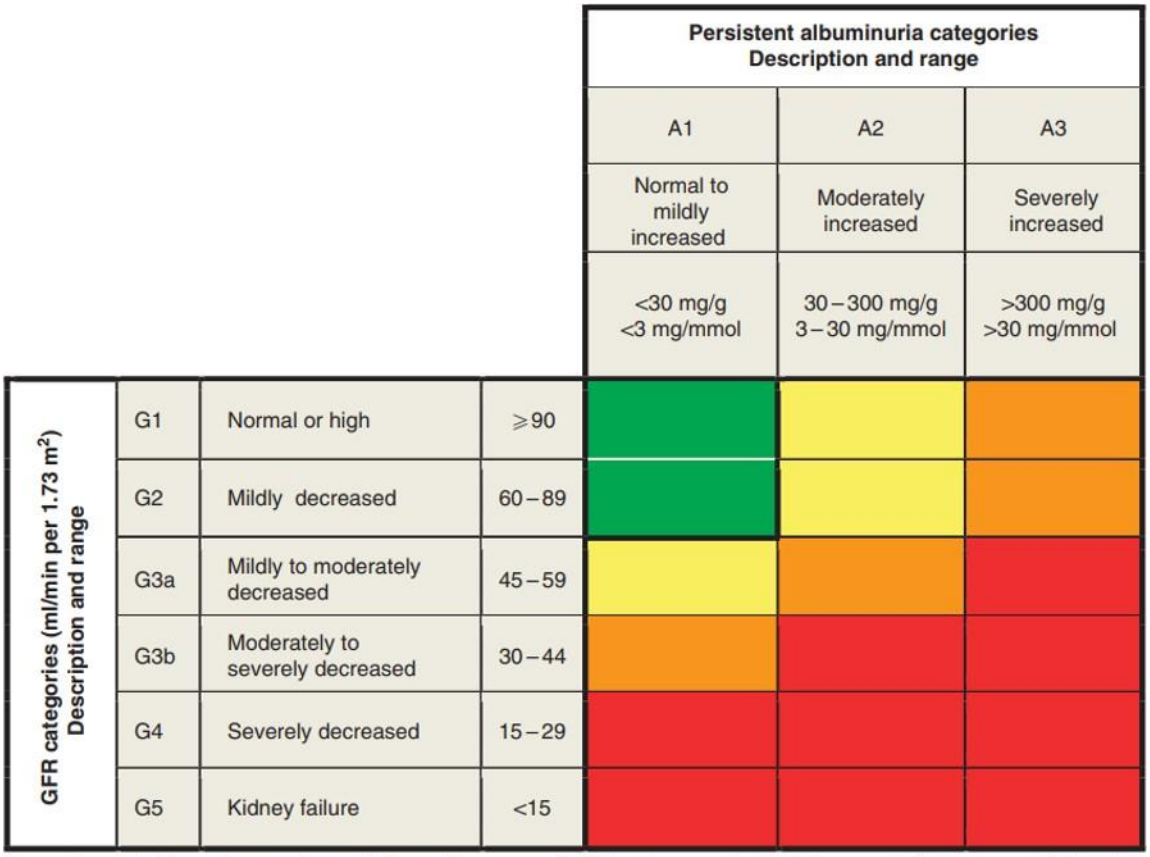
- eGFR (mL/min/1.73 m^2)=$(0.41 \times$ Height in cm$)/S_{cr}$

where S_{cr} is serum creatinine (mg/dL), κ is 0.7 for females or 0.9 for males, and α is -0.329 for females or -0.411 for males. Min indicates the minimum of S_{cr}/κ and 1, and max indicates the maximum of S_{cr}/κ and 1. Age and height indicates at time of serum creatinine collection as collected in the associated case report form (CRF).

6.5.4.1. Prognosis of CKD by eGFR and Albuminuria Category

Prognosis of chronic kidney disease (CKD) is determined by the intersection of the following eGFR and albuminuria categories (KDIGO, 2013):

Figure 2: PROGNOSIS OF CKD BY eGFR AND ALBUMINURIA CATEGORIES



Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red, very high risk.

The Prognosis of Kidney Disease: Improving Global Outcomes (KDIGO) CKD progression risk scores is summarized by cell and color (Green, Yellow, Orange and Red).

Table 6. CKD STAGE

CKD[a] Stage	eGFR[b] (mL/min/1.73 m^2)
1	≥90
2	60 to <90
3a	45 to <60
3b	30 to <45
4	15 to <30
5	<15

[a] Chronic kidney disease
[b] Estimated glomerular filtration rate

Table 7. ALBUMINURIA CATEGORY

ACR[a] Category	ACR (mg/g)
1 (normo-albuminuria)	<30
2 (micro-albuminuria)	30 to ≤300
3 (macro-albuminuria)	>300

[a] Urine albumin to creatinine ratio

6.5.5. Urine Albumin to Creatinine Ratio (ACR)

ACR is provided in the central laboratory database as the ratio of urine albumin to urine creatinine from the first morning void (FMV) urine collection. The ACR value is not calculated in the central laboratory database when the FMV urine albumin result is < LLD. Urine albumin results < LLD and the corresponding ACR missing values are imputed as follows:

- If urine albumin result ≤LLD, then
  - Imputed urine albumin result (mg/dL)=LLD/2
  - Imputed ACR (mg/g)=(imputed urine albumin result in mg/dL)/[(urine creatinine in mg/dL)/1000]

The ACR results are log-transformed for analysis to produce data that are more normally distributed. Any imputed ACR result where ACR=0 is considered to be 0.1 mg/g for purposes of calculating the geometric mean.

6.5.5.1. Baseline Urine Albumin to Creatinine Ratio (ACR) Categorical Status

Baseline ACR status will be grouped by the following categories using baseline ACR (see Section 6.4.5):

- ACR ≤300 mg/g
- ACR >300 mg/g

Baseline ACR accounts for screening and Day 1 values and may not match ACR used for stratification based on screening values only.

6.5.5.2. eGFR Category used in Stratification (eGFR_STRAT)

The eGFR category used for stratification (eGFR_STRAT) is determined by the randomization list with the following categories:

- 30 mL/min/1.73 m^2 <eGFR<60 mL/min/1.73 m^2
- 60 mL/min/1.73 m^2 ≤eGFR≤90 mL/min/1.73 m^2

6.5.5.3. ACR Category used in Stratification (ACR_STRAT)

The ACR category used for stratification (ACR_STRAT) is determined by the randomization list with the following categories:

- ACR ≤300 mg/g
- ACR >300 mg/g

6.5.6. Electrocardiogram Fridericia Corrected QT Interval

Electrocardiogram intervals are assessed locally at each site.

The following formula is used to calculate the Fridericia corrected QT interval (QTcF) for analysis from QT and RR intervals:

- $QTcF = QT/\sqrt[3]{RR}$ where RR=60/(Heart Rate)

6.5.7. ACR adjusted for eGFR

To evaluate ACR after adjusting for filtration rate, ln (ACR)/eGFR (Sections 6.5.5 and Section 6.5.4) is assessed.

6.6. Handling of Missing Data

6.6.1. Missing Efficacy Endpoint Data

Missing data will not be imputed for analyses of efficacy endpoints.

6.6.2. Missing Start and Stop Dates for Concomitant Medications

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 defined in Section 9.1.

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 dosing;

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

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

- Day, month, and year are missing;
- 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.

6.6.4. Missing End of Treatment Date

For patients without a full end of treatment date (i.e., missing day, month, or year), the last study drug dispensation date will be used as the end of treatment date for purposes of analysis.

7. STUDY POPULATION

7.1. Subject Disposition

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

- ITT population
- Safety population
- Received at least 1 dose at or after Week 52
- Completed treatment or follow-up through Week 52
  - Week 48 to Week 52 On-treatment
  - Week 48 to Week 52 Off-treatment
- Discontinued treatment prior to Week 100
  - Reason for discontinuing treatment
  - Treatment discontinuation related to COVID-19
- Completed study follow-up through Week 104
  - Completed treatment through Week 100
  - Discontinued treatment early but completed study visits
  - Discontinued treatment early but completed eGFR assessments through Week 104
- Completed study follow-up through Week 108
  - Completed treatment through Week 100
  - Discontinued treatment early but completed study visits
  - Discontinued treatment early but completed eGFR assessments through Week 108
- Completed study follow-up through Week 112
  - Completed treatment through Week 100
  - Discontinued treatment early but completed study visits
  - Discontinued treatment early but completed eGFR assessments through Week 112
- Completed study follow-up through Study Termination Date (STD)
  - Completed treatment through Week 100
  - Discontinued treatment early but completed study visits
  - Discontinued treatment early but completed eGFR assessments through STD
- Terminated from the trial before Week 112
  - Reason for study termination

  - Study termination related to COVID-19
  - Study week at study termination
  - Terminated prior to STD
  - Terminated after STD
- Number of patients by study visit
  - On treatment
  - Off treatment
  - In study follow-up
  - Stopped study

Patients who completed follow-up are defined as those who were in the study through Week 112 visit. A listing of disposition is provided for all enrolled patients.

7.2. Protocol Deviations

All protocol deviations are listed, and the frequency of patients with protocol deviations and major protocol deviations are summarized by deviation type and treatment group.

7.3. Demographic and Baseline Characteristics

Summaries of demographic and other baseline characteristic data are presented by treatment group for all analysis populations. They may also be summarized by randomized dose level (20 mg, 30 mg, or placebo).

The demographic and other baseline characteristics include:

- Baseline Age, Baseline Age category (<18, ≥18)
- Sex, Race, Ethnicity
- Weight (kg), Height (cm), BMI (kg/m^2)
- Diastolic and systolic blood pressure (mmHg), Heart rate (bpm)
- Serum creatinine, eGFR, eGFR categorical status (<60, ≥60), eGFR Stratum
- ACR, ACR categorical status (≤300; >300), ACR Stratum
- KDIGO CKD progression risk score: color (Green, Yellow, Orange, Red) and cell in Figure 2
- CKD Stage (Table 6)
- Angiotensin converting enzyme inhibitor (ACEi) treatment and/or Angiotensin II receptor blocker (ARB) (yes/no)
- Other baseline variables of interest

ADPKD related information includes:

- Age at ADPKD diagnosis
- Family history of ADPKD
- For patients with family history of ADPKD:
  - Sonography (indicating 3 or more cysts) for adult patients
  - Sonography (indicating 1 or more cyst) for adolescent patients
  - Computed tomography (CT) or magnetic resonance imaging (MRI) (indicating 5 or more cysts)
- For patients without family history of ADPKD:
  - Other cystic kidney diseases present
  - 10 or more cysts
- Use of Tolvaptan
  - Currently using Tolvaptan
  - Previously used Tolvaptan
  - Never received Tolvaptan
- [redacted]

7.4. Listing of Subject Inclusion and Exclusion Criteria

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

7.5. Medical History

Medical history is summarized by treatment. Medical history is coded using MedDRA (Medical Dictionary for Regulatory Activities). Medical history items are summarized by MedDRA system organ class (SOC) and preferred term (PT). A by-patient listing of medical history will be provided.

7.5.1. Historical eGFR

To characterize disease progression prior to trial entry, up to 5 years of historical serum creatinine values are collected for each patient as part of their medical history. Collection of historical serum creatinine is subject to availability of data from medical records; therefore, the number of available values will vary by patient and some patients may have no historical values. Historical serum creatinine values are converted to mg/dL and eGFR is calculated for analysis according to the to the appropriate equation (Section 6.5.4) using the patient age at laboratory collection for adult patients, or patient height at Screening for adolescent patients. Historical serum creatinine values were analyzed at various local laboratories (i.e., not collected as part of central lab data). Therefore, historical serum creatinine and corresponding eGFR values are considered part of a patient's medical history, and distinct from central lab assessments collected as part of the trial.

The eGFR values used in the analysis dataset for the baseline label (Table 8) are the baseline eGFR values for each patient (defined in Section 6.4.2), not the individual Screen A, Screen B, and Day 1 eGFR values.

Historical values are prior to first dose and have a negative Study Day value:

- Study Day=(Date of Historical Lab Collection)–(Date of Screen A)

Summary statistics of eGFR results by historical year (listed in Table 8) will be presented for the ITT population. Summary statistics of available historical eGFR results are based on the following analysis windows:

Table 8: LABELS FOR SUMMARY OF HISTORICAL CHANGE IN eGFR

Analysis Visit	Label	Study Day Windows
-5	Historical Year 5	1825 to 1461 days prior to Screen A
-4	Historical Year 4	1460 to 1096 days prior to Screen A
-3	Historical Year 3	1095 to 731 days prior to Screen A
-2	Historical Year 2	730 to 366 days prior to Screen A
-1	Historical Year 1	365 to 1 days prior to Screen A
0	Baseline	Screen A to Day 1

The summary statistics will include the average eGFR value by patient and analysis time point. For instance, if multiple values are listed in the historical Year 1 results for a given patient, the average of those values is used to calculate the summary statistics.

8. EFFICACY

Analyses of efficacy described in this section are the primary analyses of the efficacy endpoints, and pertain to the ITT population (i.e., all patients randomized in the study), unless otherwise specified. The trial includes endpoints following 2 years of treatment.

Stratification factors including tolvaptan use (yes/no) and screening ACR (≤300 mg/g, >300 mg/g) will only be used in the efficacy models as covariates if the category with the smallest number of patients comprise >20% of patients enrolled in the study. Continuous baseline eGFR will be included as a covariate instead of the categorical eGFR stratification factor. The following abbreviations are used in descriptions of the ANCOVA and MMRM analysis models:

Table 9. MODEL PARAMETER ABBREVIATIONS

Abbreviation	Model Term
BASE_eGFR	Baseline eGFR
*Tolv_STRAT	Concomitant tolvaptan use (yes, no)
*ACR_STRAT	Screening ACR (≤300 mg/g, >300 mg/g)
TRT	treatment group
TRT x VISIT	the interaction between treatment and time
VISIT	analysis visit used as time

* Tolvaptan use (yes/no) and screening ACR (≤300 mg/g, >300 mg/g) will only be used in the efficacy models as covariates if the category with the smallest number of patients comprises >20% of patients enrolled in the study.

8.1. General Considerations

Data collected from individual study centers will be pooled; results will not be presented by individual study center. Analyses are performed for all bardoxolone methyl patients in comparison with all placebo patients. Summary statistics for observed values, change from baseline, and percent change from baseline are presented by randomized treatment group. Missing values are handled as described in Section 6.6.

8.2. Statement of the Null and Alternate Hypotheses

All primary efficacy analyses compare the change from baseline in eGFR for patients randomized to bardoxolone methyl (Δ_{eGFR_BARD}) to the change from baseline in eGFR for patients randomized to placebo (Δ_{eGFR_PBO}) at the endpoint-specified visit according to the following hypotheses:

- Null hypothesis, H_0: $(\Delta_{eGFR\_BARD})-(\Delta_{eGFR\_PBO})=0$ mL/min/1.73 m^2
- Alternative hypothesis, H_1: $(\Delta_{eGFR\_BARD})-(\Delta_{eGFR\_PBO})\neq 0$ mL/min/1.73 m^2

Because eGFR decreases with disease progression, a higher change from baseline in eGFR for bardoxolone methyl relative to placebo is considered evidence of benefit.

8.3. Multiple Comparisons and Multiplicity

All objectives are presented with nominal significance levels for descriptive purposes only.

8.4. Primary Endpoint

8.4.1. Primary Endpoint Analysis

The primary endpoint of this study is the off-treatment change from baseline in eGFR at Week 108. The ITT population will be used for all analyses. For all patients enrolled in the trial, Week 108 is the off-treatment eGFR assessed closest to 108 weeks after Study Day 1. For a patient who completed 2 years of treatment, the 8-week drug treatment withdrawal period occurs at Week 108 (i.e., 56 days after last dose). For a patient who stopped drug treatment early, the eGFR assessment at Week 108 is analyzed, irrespective of how long a patient has been off-treatment. Analysis of Week 108 (after a planned 8-week drug treatment withdrawal period) assesses the preserved drug benefit (relative to placebo) following withdrawal of treatment.

The off-treatment change from baseline eGFR at Week 108 for patients treated with bardoxolone methyl is compared to placebo using an ANCOVA model, with BASE_eGFR as a covariate, and TRT as fixed effects. The ANCOVA analysis uses eGFR values collected in the Week 108 analysis window (Section 6.5.2), which includes the follow-up assessment at Week 108 for patients who discontinued treatment early irrespective of time after last dose.

Missing Week 108 eGFR data will not be imputed.

The difference between bardoxolone methyl and placebo in change from baseline of eGFR is estimated along with the 95% confidence interval at Week 108.

Example SAS code as follows:

```
proc glm data=efficacy;
   class TRT ACR_STRAT;
   model DELT_eGFR=trt ACR_strat base_egfr /solution;
   lsmeans trt / diff stderr pdiff cl alpha=0.05;
run;
```

8.5. Secondary Efficacy Endpoint

The ITT population will be used for all analyses unless otherwise specified.

8.5.1. Secondary Efficacy Endpoint Analyses

The secondary efficacy endpoint of this study is the change from baseline in eGFR at Week 100 (i.e., the end of the first year of drug exposure). The change from baseline in eGFR for patients treated with bardoxolone methyl is compared with placebo at Week 100 using MMRM analysis, with BASE_eGFR as a covariate, and the following fixed factors: treatment group (TRT), time (i.e., VISIT; analysis visit number), and the interaction between treatment and time (TRT x VISIT).

The trial design separates discontinuation of study drug from discontinuation of study follow-up. Therefore, patients may discontinue early from study drug while continuing follow-up with study visits and assessments. The analysis of eGFR at Week 100 uses available eGFR values irrespective of whether or not a patient is receiving treatment. Analyses for Week 100 will not include the Week 52 data due to mix of on-treatment and off-treatment values. The MMRM analysis uses all eGFR values collected through Week 100 according to analysis visits 1, 2, 4, 6, 8, 12, 24, 36, 48, 64, 76, 88, and 100 (Section 6.5.2). An unstructured covariance matrix is used. In the event the MMRM model with an unstructured covariance structure does not converge, the following covariance structures are substituted, in the order listed. Each subsequent covariance structure is used only if each no previous model did not converge.

1. Heterogeneous Toeplitz covariance structure (assuming different variances at each time point and measurements taken closer together in time are more highly correlated than those taken farther apart).
2. Toeplitz covariance structure (assuming measurements taken closer together in time are more highly correlated than those taken farther apart).
3. First order auto-regressive [AR(1)] covariance structure (assuming measurements taken closer together in time are more highly correlated than those taken farther apart, but the correlation is more constrained than the Toeplitz structure).
4. Compound symmetry covariance structure (assuming equal correlation for measurements from a patient, regardless of how far apart in time they were taken).

If the MMRM model does not converge using any of the aforementioned covariance structures, variables from the model statement may be removed in the sequence of 1) Tolv_STRAT, 2) ACR_STRAT.

The difference between bardoxolone methyl and placebo in change from baseline in eGFR is estimated along with the 95% confidence interval at Week 100 for the primary analysis of the secondary endpoint.

Missing eGFR data will not be imputed.

SAS example as follows:

```
proc mixed data=OUT2 method=reml alpha=0.05 covtest;
      class  VISITNUM(ref=LAST)
             TRT(ref=FIRST) SUBJID ACR_STRAT;
```

```
      model DELT_eGFR = BASE_eGFR ACR_STRAT TRT VISITNUM
            TRT*VISITNUM BASE_eGFR*VISITNUM / solution ddfm=kr;
      repeated VISITNUM / subject=SUBJID type=un r;
      lsmeans TRT*VISITNUM / pdiff om cl e;
      estimate 'Estimate at Week 100' TRT 1 -1 TRT*VISITNUM 1 -1 / cl;
      ods output LSMeans=LSM diffs=Diff;

run;
```

A plot of least squared means from the MMRM model at each visit by treatment arm will be created.

[redacted]

[redacted]

[redacted]

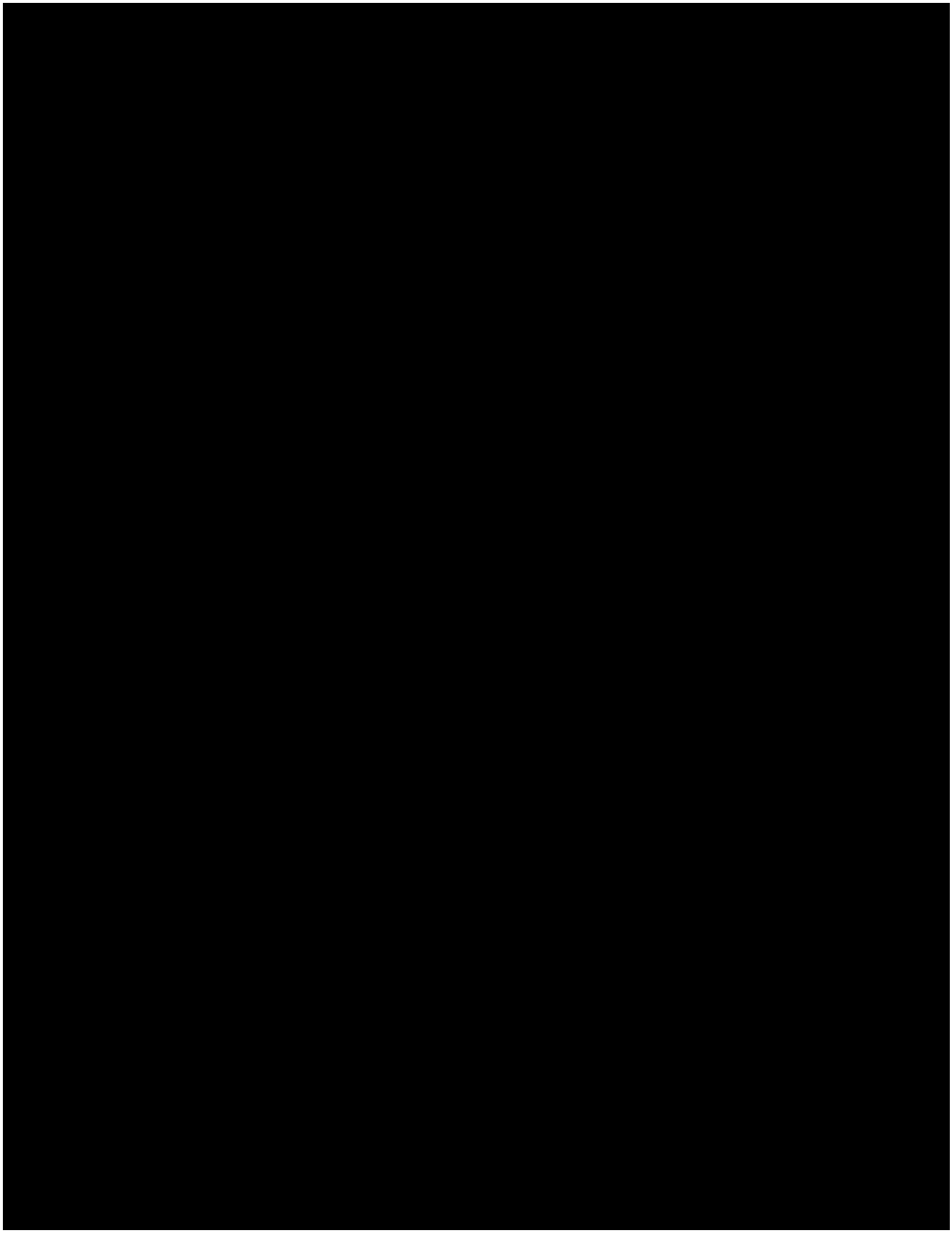
[redacted]

8.6.1.2. Off Treatment eGFR ANCOVA Analyses – No Imputation for Missing Data

The ANCOVA analysis (defined in Section 8.4.1) will be performed by using eGFR values collected at [redacted] Week 112 off-treatment analysis visits (Table 4). Missing eGFR data per visit are not imputed.

The difference between bardoxolone methyl and placebo in change from baseline of eGFR is estimated along with the 95% confidence interval at each off-treatment visits.

[redacted]



[redacted]

9. SAFETY AND TOLERABILITY

Safety and tolerability are evaluated by AEs, SAEs, clinical laboratory test results, body weight, vital signs, 12-lead ECG findings. All analyses of the safety data are performed using the safety analysis set. Descriptive statistics are presented by treatment group assignment in the safety analysis set. Statistical testing is not performed for safety analyses unless otherwise specified. On-treatment values are summarized according to the analysis study windows in Section 6.5.2; Off-treatment values are summarized according to the analysis study windows in Section 6.5.2.1. Safety data summaries are grouped by treatment.

Continuous safety parameters (including selected clinical chemistries and vital signs) may be summarized using the methodology described in Section 8.4.1, and Section 8.5.1. Only the visit windows outlined in Table 4 and Table 5 are included in these analyses.

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

Treatment-emergent adverse events are summarized by treatment as defined by the safety analysis set. In addition to being summarized by treatment year, AEs are also summarized overall.

Treatment-emergent adverse events are events that either:

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

General considerations for TEAE summaries are:

- Multiple events by PT and SOC are counted once only per patient for summaries of TEAE incidence.
- For summaries of TEAE incidence by severity, only the most severe event is counted per patient.
- For summaries of TEAE incidence by relationship, only the most strongly related event is counted per patient.
- A TEAE with a missing resolution date or incomplete date that is not identified as continuing is assumed to be continuing.
- For summaries of the number of TEAEs, all TEAEs are counted.

Off-treatment AEs (OTAEs) are events with a start date more than 30 days after last dose and not considered treatment emergent. Off-treatment AEs will be summarized separately.

Adverse Events are coded using MedDRA. In MedDRA, each verbatim term is mapped to a preferred term and high-level term (HLT), which is then mapped to a SOC.

The investigator grades the severity of the AEs as mild, moderate, or severe as defined in the study protocol. The investigator grades association or relatedness to the study medication according to criteria specified in Section 11.4 of the protocol.

As defined in the protocol, an SAE is an adverse event (occurring at any dose and regardless of causality) that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Is 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 Adverse Event Onset Dates

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

9.1.2. Summaries of Adverse Events

Treatment-emergent adverse events and OTAEs are summarized by treatment. For each treatment, SOC, and PT, the number and percentage of patients reporting an event is calculated. In summary tables, SOC is presented alphabetically and events within each SOC are presented by decreasing frequency count. Additionally, summary tables of events within PTs are presented by decreasing frequency count may be generated.

Summary tables (number and percentage of patients and events) of TEAEs (by SOC and PT) are provided by treatment as follows:

- All TEAEs
- All related TEAEs (definitely, probably, or possibly related)
- All TEAEs by severity
- All serious TEAEs (including deaths)
- All non-serious TEAEs
- All related serious TEAEs (including deaths)
- All TEAEs leading to permanent discontinuation of study drug
- All TEAEs leading to study drug interruption
- All TEAEs leading to dose de-escalation
- TEAEs by time to onset (≤12 weeks and >12 weeks)
- TEAEs exhibited in >5% of patients in either treatment group

Listings are provided showing:

- All AEs
- Deaths
- SAEs
- AEs leading to permanent discontinuation of study drug
- TEAEs leading to study drug interruption
- TEAEs leading to dose de-escalation

9.2. Exposure and Compliance

The duration of study drug exposure is defined as the number of days on treatment from the first dose of study drug until the last dose of study drug (last dose–first dose+1), excluding the off-treatment period between the Week 48 visit and Week 52 visit prior to protocol version 6. 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 (including the number of patients with ≥80% compliance through Week 100, duration (days) of exposure during the study treatment period, and the number and percentage of patients who reached the goal at any point during the study. The overall treatment duration for all placebo patients and bardoxolone methyl patients who completed treatment through Week 100 vs. bardoxolone methyl patients who did not complete treatment through Week 100 is also summarized. In addition, a summary of the number and percentage of patients exposed by dose (placebo, 5 mg, 10 mg, 20 mg, 30 mg) and by visit is generated. If a patient received more than 1 dose during a visit window, the duration of the longest constant dose is used to calculate exposure. A summary of the number and percentage of patients exposed to study drug by treatment will be summarized for the following duration categories:

- ≤16 Weeks
- >16 Weeks
- >24 Weeks
- >48 Weeks
- >72 Weeks
- >96 Weeks

Total number of doses dispensed, and total dose (mg) dispensed is calculated from total number of kits (bottles) recorded on the Study Drug Dispensation electronic case report form (eCRF). Total number of doses received is 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). If a kit is not returned but the patient had a subsequent dispensation, then the non-returned kit is assumed to have been taken in full. However, if a kit is not returned and no kit is subsequently dispensed, then the non-returned kit is assumed to not have been taken. Study drug compliance (%) is calculated as 100 × total number of doses received / total number of

study days of study participation, excluding the off-treatment periods between Week 48 to Week 52 prior to protocol version 6 and Week 100 to Week 104.

The off-treatment periods between Week 48 to Week 52 prior to protocol version 6 and Week 100 to Week 104 will be analyzed by the summary of days since last dose. Indeed, for patients with a Week 52 off-treatment analysis visit, summary statistics of days since last dose are generated. Similarly, for patients with a Week 104 analysis visit, summary statistics of days since last dose are generated.

The number and percentage of patients are summarized by treatment group for Drug Interruption not related to COVID-19:

- Interruption Type (Primary Investigator (PI) initiated, Patient Reported)
- Primary reason for interruption (AE, Elevated Transaminase not clinically significant (NCS), Elevated BNP NCS, Fluid Overload NCS, Weight Gain NCS, Weight Loss NCS, Other)

Drug Interruption due to COVID-19 will also be summarized as specified in Section 11.1.

Patients not at per-protocol dose are listed, including reasons.

9.3. Concomitant Medications

Concomitant medications are coded using the World Health Organization (WHO) drug dictionary for anatomical therapeutic chemical classification (ATC) and preferred drug name. A patient who used multiple medications is 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, WHO ATC class and preferred name. Percentages are based on the number of patients in the safety analysis set. Each summary is ordered by descending order of incidence of ATC class and preferred name within each ATC class. Concomitant medications will be summarized by treatment year and overall.

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

- that are continued from screening and continued after the first study drug dosing, or
- that have start dates or stop dates within the treatment period, or
- that start before treatment end and have no end date.

Medications with an end date on the date of first study drug administration are not considered concomitant medications. Patients who take excluded medications (defined in the Protocol Section 9.3.1) during the study are listed.

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. Prior and Concomitant Procedures and Surgeries

Prior and concomitant procedures and surgeries are listed.

9.5. Clinical Laboratory Evaluations

Laboratory data are summarized at baseline and at each time point by treatment.

9.5.1. Continuous Summaries of Laboratory Results

Laboratory evaluations and change from baseline are summarized by treatment, laboratory category (hematology, chemistry, urinalysis, and microscopy), test, and study visit using continuous statistics. The eGFR results are calculated using formulas described in Section 6.5.4.

Chemistry values (including eGFR) collected at the following visits will be averaged.

- Week 104 A and Week 104 B
- Week 108 A and Week 108 B
- Week 112 A and Week 112 B

Box plots and line graphs are generated for selected laboratory test results, such as eGFR, ACR, alanine aminotransferase (ALT), aspartate aminotransferase (AST), TBL, BNP, blood urea nitrogen, uric acid, magnesium, creatinine, and creatine kinase (CK). Line graphs include mean ± SE over time for both the observed values and for change from baseline.

Summaries of continuous statistics are provided for the following urinalysis parameters: albumin, creatinine, pH, erythrocytes, and specific gravity. Qualitative lab results are included in the listings but are not summarized. Laboratory results that are above or below normal limits are flagged in the listings. Summaries of ACR (Section 6.5.5) will use the geometric mean (with standard error) with 95% confidence intervals instead of the arithmetic mean and will display ACR results in original units of mg/g. Changes from baseline in ACR are calculated as the ratio of each visit to baseline and reported as the post-baseline/baseline ratios and are summarized by geometric means with 95% confidence intervals at each time point.

9.5.1.1. Natural log (ACR)/eGFR

Mean ratios of natural log (ACR)/eGFR (Section 6.4.6) are summarized at each time point. The ratio of natural log (ACR)/eGFR by analysis visit is summarized by arithmetic means.

9.5.2. Categorical Summaries of Laboratory Results

Select laboratory parameters will be summarized using shift tables. Shift tables are summarized by treatment, laboratory category (hematology, chemistry, urinalysis, and microscopy), and laboratory test and present shifts from baseline status (Normal, Low, High) to worst on study treatment status (Normal, Low, High). The worst abnormality values are defined as the maximum values while on study treatment (i.e., up to <21 days after last dose), with the exception of magnesium and hemoglobin. The worst abnormal values for magnesium and hemoglobin are defined as the minimum values while on study treatment (i.e., up to <21 days after last dose).

Additionally, laboratory parameters of specific interest (ALT, AST, ACR, BNP) are summarized using shift tables that summarize shifts from (1) baseline status to end of treatment status, (2) worst on-treatment status to worst off-treatment status, (3) worst on-treatment status to end of study, and (4) baseline status to worst on-treatment status 5) baseline to worst off-treatment, and (6) worst on-treatment status to best (lowest) off-treatment status. The number and percentage of patients are summarized. For ACR, summaries will present shifts from/to the categories listed in Section 6.5.5.1. For ALT and AST, summaries will present shifts from/to the following categories:

- ≤ ULN
- > ULN to <3× ULN
- ≥3× ULN to <5× ULN
- ≥5× ULN to <10× ULN
- ≥10× ULN to <20× ULN
- ≥20× ULN

For BNP, summaries will present shifts from/to the following categories:

- <100 pg/mL
- ≥100 pg/ml to <200 pg/ml
- ≥200 pg/ml to <400 pg/ml
- ≥400 pg/ml

In addition, a summary table is provided for the number and percentage of patients meeting a following pre-specified threshold level at any time during the study:

- ACR >3500 mg/g
- Magnesium <1.3 mEq/L (0.65 mmol/L)
- BNP >200 pg/mL
- NT-proBNP >1000 pg/mL

9.5.2.1. Transaminases

Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) plots are generated for ALT and AST versus TBL.

The number and percentage of patients meeting the following thresholds (Table 10) at any time during the study are summarized by the maximum dosage received. The pre-specified thresholds are consistent with FDA guidance.

Table 10: PRE-SPECIFIED THRESHOLD LEVELS FOR TRANSAMINASES

Lab Parameter	Threshold
ALT, AST	≥3× upper limit of normal (ULN) and <5× ULN

Lab Parameter	Threshold
	≥5× ULN and <10× ULN
	≥10× ULN and <20× ULN
	≥20× ULN
	≥5× ULN for more than 2 weeks
TBL	≥ULN and ≤1.5× ULN
	>1.5× ULN and ≤2× ULN
	>2× ULN
ALT, AST, TBL	ALT or AST >3× ULN and TBL >1.5× ULN
	ALT or AST >3× ULN and TBL >2× ULN
ALT, AST, TBL, International normalized ratio (INR)	>3× ULN and (TBL >2× ULN **or** INR >1.5)
ALP	>1.5× ULN

A listing of subjects with abnormal ALT, AST, or TBL will also be provided.

[redacted]

9.7. Vital Signs

Vital signs assessments include systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg), body temperature (°C), heart rate (HR, bpm), height (cm), weight (kg), and BMI (kg/m^2). Vital signs are summarized at baseline and at each time point along with the change from baseline by treatment. Boxplots and line graphs of change from baseline over time for blood pressure are plotted.

In addition, a summary table is provided for the number and percentage of patients meeting a following pre-specified post baseline on-treatment blood pressure change categories:

- SBP (mm Hg):
  - Maximum increase from baseline: ≥20; ≥40; ≥60
  - Maximum decrease from baseline: ≥20; ≥40
- DBP (mm Hg):
  - Maximum increase from baseline: ≥20; ≥40
  - Maximum decrease from baseline: ≥20

9.8. 24-hr ABPM Sub-study

A subset of patients who consent to the 24-hour ambulatory blood pressure monitoring (ABPM) sub-study will have systolic blood pressure, diastolic blood pressure, pulse pressure and heart rate collected during 24-hour periods as specified in Table 2. Observed values and change from baseline will be summarized at baseline and at analysis visits Week 12, Week 48 and Week 88 for each 24-hour ABPM assessment using the following 24-hour parameters: overall mean, daytime mean, and nighttime mean. Descriptive summaries will include confidence intervals.

The 24-hour ABPM parameters will be calculated as specified in Table 11. For each 24-hour period, calculation of the average values is the sum of all valid ambulatory blood pressure measurements divided by the number of all valid blood pressure measurements, within the range of time specified for the parameter. Categorical summaries for systolic blood pressure and diastolic blood pressure described in Section 9.7 will also be performed.

Table 11: 24-HOUR ABPM PARAMETERS

Parameter	Calculation
Overall (24-hour) SBP, DBP mean	average of all valid measurements taken from the patient's ambulatory blood pressure monitoring device
Daytime SBP, DBP mean	average of all valid measurements taken from 6 am to 10 pm
Nighttime SBP, DBP mean	average of all valid measurements taken from 10 pm to 6 am next day

9.9. Electrocardiogram

Electrocardiogram (ECG) data, such as clinical interpretation of ECGs, heart rate and interval assessments of PR, QRS, and QT are collected on the eCRF. QTcF is calculated for analysis (Section 6.5.6). Descriptive statistics for observed values and change from baseline at each time point are presented for these 12-lead ECG interval assessments. In addition, number and percentage of patients with any abnormal values (i.e., above a pre-specified threshold) at any time during the study are summarized by time point and overall. The pre-specified levels of ECG QTcF thresholds (Table 12) are consistent with FDA guidance:

Table 12: PRE-SPECIFIED THRESHOLD LEVELS FOR ECG PARAMETERS

ECG Parameter	Pre-Specified Level
PR	>200 msec
QTcF	>450 and ≤480 msec
	>480 and ≤500 msec
	>500
	Change from baseline: >30 and ≤60 msec
	Change from baseline: >60 msec
Heart rate	<40 beats/min
	>100 beats/min

Line graphs of change from baseline over time for ECG parameters are plotted.

9.10. Pregnancy

A listing is provided for serum and urine pregnancy results of all on-study pregnancies.

10. PHARMACOKINETICS

Individual concentration data will be listed by subject, visit and timepoint.

11. COVID-19 IMPACT

11.1. Operational Impact

The COVID-19 pandemic has impacted the conduct of the study per protocol. To minimize study disruptions, alternative drug dispensation methods and remote visit completion methods are available if it is inadvisable for a patient to be seen for an in-person clinic visit or if a patient is unwilling to come to the clinic (further details provided in Appendix 1 and Appendix 2 of the protocol). Any study procedures that cannot be conducted remotely will be noted as missing.

For any visits after 01 March 2020 sites should record if visits, data collection, drug dispensation, and drug administration are impacted by or related to COVID-19.

The number and percentage of patients are summarized by visit and treatment group for the following categories:

- Visit impact by COVID-19
  - Visit not done
  - Visit conducted out of window
  - One or more procedures could not be performed
- Alternative data collection methods
  - No change (occurred as expected per protocol)
  - Telephone visit
  - Video conference visit
  - Home health care visit
  - Local lab
  - Other
- Drug dispensation impact
  - No change (office visit)
  - IP dispense not scheduled (telephone visit)
  - Mailed to patient
  - Home health care provided
  - Dose not escalated
  - Dose de-escalated
  - Other

The number and percentage of patients are summarized by treatment group for Drug Interruption due to COVID-19:

- Tested positive for COVID-19 (yes, no, not tested)
- Primary reason for interruption (medical monitor/sponsor recommendation, site mandate, patient choice, insufficient IP supply, other)

A by-patient listing of all study visits that were affected due to COVID-19 including a description of how the patient's participation was altered will be provided.

Early discontinuations of study drug or study due to COVID-19 will be summarized and listed in disposition summary tables and the disposition listing (described in Section 7.1), respectively.

All deviations due to the impacts of COVID-19 (after 01 March 2020) will be identified and documented accordingly by the site and the Sponsor. The failure to complete a protocol visit will not be considered as a reason for study discontinuation and will not be considered as a major deviation. All COVID-19-related deviations will be identified in the protocol deviation listing (Section 7.2)

11.2. Impact on Efficacy

The primary and key secondary endpoints, as well as the secondary endpoints are lab-based endpoints (i.e, change in eGFR). Home health care visits and/or local laboratories are available to collect labs, including eGFR, for patients who are unable or unwilling to come for in-clinic visits. Central laboratory kits are utilized at in-clinic visits, home health care visits, and local laboratory visits. Therefore, the contingency measures put in place to collect this critical efficacy data are not expected to impact the efficacy results. Missing data due to COVID-19 is handled as described in Section 6.6.

Sensitivity analyses may be performed as appropriate to assess the potential impact of the COVID-19 pandemic on efficacy outcomes.

11.3. Impact on Safety

Patient narratives will be provided for all patients who test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19.

For patients who are unable to complete an in-clinic visit, safety assessments can be performed through alternative remote visit methods. Central laboratory kits are used to assess safety laboratory information regardless of visit method; therefore, the contingency measures put in place to collect this critical safety data are not expected to impact the laboratory results.

Subgroup analyses may be performed as appropriate to assess the potential impact of the COVID-19 pandemic on safety outcomes.

12. REFERENCES

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