COVER PAGE

Official Title:	An Extended Access Program to Assess Long Term Safety of Bardoxolone Methyl in Patients With Chronic Kidney Disease (EAGLE)
NCT Number:	NCT03749447
Document Date:	25 Aug 2023

STATISTICAL ANALYSIS PLAN
402-C-1803

VERSION: 3.0

DATE OF PLAN:

25 AUG 2023

BASED ON:

Protocol Version 4.0 (09 Nov2022)

STUDY DRUG:

RTA 402, BARDOXOLONE METHYL

PROTOCOL NUMBER:

402-C-1803

STUDY TITLE:

An Extended Access Program to Assess long term safety of Bardoxolone Methyl in patients with Chronic Kidney Disease ("EAGLE")

SPONSOR:

Reata Pharmaceuticals, Inc.

5320 Legacy Drive

Plano, Texas 75024 (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 by:

[redacted], MS
[redacted]
Reata Pharmaceuticals, Inc.

Signature _____ Date _____

This document has been reviewed and accepted by:

[redacted], MS
[redacted]
Reata Pharmaceuticals, Inc.

Signature _____ Date _____

[redacted], PharmD
[redacted]
Reata Pharmaceuticals, Inc.

Signature _____ Date _____

TECHNICAL SUMMARY REPORT (TSR)

Name of Sponsor/Company Reata Pharmaceuticals, Inc.	**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 Assess Long-Term Safety of Bardoxolone Methyl in Patients with Chronic Kidney Disease		
Study Center(s): Approximately 230		
Studied period (years): Actual date first patient first visit: March 2019 Estimated last patient last completed: Patient will remain in the study until bardoxolone methyl is available through commercial channels or until patient withdrawal, whichever is sooner The end of the study is defined as the last visit of the last patient.		**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 will assess the long-term safety and tolerability of bardoxolone methyl in qualified patients with chronic kidney disease who previously participated in a qualifying, clinical study with bardoxolone methyl. The CARDINAL study (402-C-1603, NCT03019185, EudraCT 2016-004395-22) and FALCON study (402-C-1808, NCT03918447, EudraCT 2018-004651-20) are the only qualifying clinical studies at this time. The Day 1 visit of EAGLE is not required to be the same day as the End of Study visit of the prior qualifying study. Lab assessments from the qualifying study will be used for EAGLE eligibility and maximum treatment dose assignment (Week 100 for CARDINAL or FALCON protocol versions 1 through 5, and Week 108 [B] for FALCON versions 6 and newer) if those assessments were done ≤ 8 weeks before Day 1. In the event that the eligibility lab assessments were obtained > 8 weeks before the planned EAGLE Day 1 visit, a screening visit will be required for EAGLE enrollment. The maximum bardoxolone methyl dose will be determined by the proteinuria status based on the albumin/creatinine ratio (ACR) value from the eligibility lab assessments from the prior qualifying study, or for patients requiring a screening visit, the maximum bardoxolone methyl dose will be determined based on the ACR values from the screening labs. Patients with eligibility ACR ≤ 300 mg/g will be titrated to a maximum dose of 20 mg, and patients with		

eligibility ACR > 300 mg/g will be titrated to a maximum dose of 30 mg. Adult patients (≥ 18 years of age) 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 eligibility ACR > 300 mg/g) unless contraindicated clinically and approved by the medical monitor. Patients under the age of 18 enrolling from CARDINAL will start dosing at 5 mg every other day during the first week (from Day 1 through the Week 1 visit) and begin once-daily dosing with 5 mg during the second week of the study (following the Week 1 visit through the Week 2 visit), and then continue with once-daily dosing following the same aforementioned dose-titration scheme based on eligibility ACR at Weeks 2, 4, and 6. Patients under the age of 18 enrolling from FALCON will follow the adult dose titration schedule. Dose de-escalation is permitted during the study if indicated clinically, and subsequent dose re-escalation is also permitted.

All patients in the study will follow the same visit and assessment schedule. Patients will be scheduled to be assessed in person during treatment at Day 1, Weeks 1, 2, 4, 6, 8, 12, 24, and every 24 weeks thereafter. Patients will also be assessed by telephone contact on Days 3, 10, 21, 31, 38, and 45. If the Day 1 visit for EAGLE is the same as the end-of-study visit for CARDINAL (all versions) or FALCON (protocol version 5 and older), the laboratory assessments required for both visits should only be completed once. If the Day 1 visit for EAGLE is the same as the end-of-study visit for FALCON (protocol version 6 and newer), the lab assessments required for both visits should be completed for each study individually. If the Day 1 visit of EAGLE is not on the same day as the end-of-study visit from prior qualifying study, lab assessments will be performed for Day 1 through the EAGLE central lab.

The conduct of the study, according to protocol specifications, was impacted by the COVID-19 pandemic. As a result, and as of Version 3 of the protocol, modifications intended to address access to and administration of investigational product, and adherence to protocol-specified visits and laboratory assessments were implemented. These modifications are described in the protocol Appendix 1 (COVID-19 Mitigations).

Number of Patients (planned): Patient numbers will be determined by those who are currently participating or have previously participated in a qualifying clinical study with bardoxolone methyl and meet eligibility requirements.

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

1. Patients who are participating (or who have participated) in qualifying studies and who have not been required to discontinue study treatment for protocol or safety reasons and who have completed required End-of-Treatment and/or Follow-up visits in a prior clinical study with bardoxolone methyl and who, according to the assessment of the investigator, have a potential positive benefit-risk assessment for participating in the trial.
2. Meets the following eligibility criteria based on assessments from the prior qualifying study or from a screening visit, if applicable.
    a. Not expected to reach end-stage kidney disease or nephrotic syndrome within 12 weeks of study enrollment, in the investigator's judgement; subjects with estimated glomerular filtration rate < 20 ml/min/1.73m^2 should be discussed with the medical monitor before enrollment (eg, such subjects with an average rate of estimated glomerular filtration rate decline > 1.0 ml/min/1.73m^2 per month in the 3 months prior to eligibility assessment may not be eligible);

b. B-type natriuretic peptide < 200 pg/mL at the last on-treatment visit in the prior qualifying study or at a new screening visit, if applicable.

c. No occurrence of a cardiovascular serious adverse event in the prior qualifying study or in the interval between the end of the qualifying study and the screening visit, if applicable.

3. Willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures;
4. Evidence of a personally signed and dated informed consent document (and assent form if necessary) indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study prior to initiation of any protocol-mandated procedures.

Diagnosis and main criteria for exclusion (see protocol Section 8.2):

1. Participation in other investigational clinical studies involving interventional products being tested or used in a way different from the approved form or when used for an unapproved indication;
2. Patients who have an ongoing serious adverse event from a clinical study that is assessed by the investigator as related to bardoxolone methyl.
3. Unwilling to practice acceptable methods of birth control (both males who have partners of childbearing potential and females of childbearing potential) while screening, taking study drug and 30 days after the last study drug dose.
4. Women who are pregnant or breastfeeding.
5. 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.
6. Known hypersensitivity to any component of the study drug.

Test product, dose and mode of administration: Bardoxolone methyl will be administered at oral doses 5, 10, 20, or 30 mg. Each dose of study drug is administered at approximately the same time each day, preferably in the morning.

Duration of treatment: Until bardoxolone methyl is available through commercial channels or until patient withdrawal or study termination, whichever is sooner.

Reference therapy, dose and mode of administration: No reference therapy

Criteria for evaluation (see protocol Section 6.2): Safety: Results of physical examination, laboratory results, ACR, vital sign measurements, weight, AEs, and SAEs.

Statistical methods:

Sample size: The aim of this long-term extended access study is primarily to provide continuing bardoxolone methyl treatment to patients and to assess long-term safety and tolerability, hence no single primary variable has been identified. Patient numbers will be determined by those who are participating (or who have previously participated) in a qualifying clinical study with bardoxolone methyl and meet eligibility requirements.

Primary analysis of safety: As the extension is an open-label design with no comparator group, all statistical analyses will be descriptive. The summary tables will be presented for the overall group of patients and split by previous treatment groups (ie, bardoxolone methyl or placebo) in prior bardoxolone methyl clinical studies.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. LIST OF ABBREVIATIONS

Abbreviation	Term
ACR	albumin/creatinine ratio
ADPKD	autosomal dominant polycystic kidney disease
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (drug classification system)
AYAME	name for study RTA 402-006
BARD	Bardoxolone methyl
Bard	bardoxolone methyl
BNP	B-type natriuretic peptide
CARDINAL	name for Study 402-C-1603
CSR	clinical study report
DBL	database lock
EAGLE	name for Study 402-C-1803
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
FALCON	name for Study 402-C-1808
FMV	first morning void
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
LLD	lower limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
PT	preferred term
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCr	serum creatinine
SDT	study drug termination
SOC	System Organ Class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

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-1803.

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 final analysis, as defined in this SAP document, will be made prior to the initial database lock (DBL) of the study data. Since the trial is an open-label extension 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 SAP is based on:

- Protocol 402-C-1803, Version 4, dated 09 NOV 2022
- ICH guidelines E4 (Dose-Response Information to Support Drug Registration) 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-1803 study. Should the SAP and the protocol be inconsistent with respect to the planned analyses, the language of the SAP is governing.

The SAP version 1 dated 12 SEP 2019 was finalized and placed on file before the 1st DBL on 22 NOV 2019. This current version of the SAP describes the analyses planned prior to the DBL. Unless otherwise specified, these analyses are summarized in the CSR. The CSR will describe any deviations from the planned analyses.

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 mg 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 kidney disease (ESKD) events between the 2 groups. Based on the AYAME (402-006) efficacy results, Kyowa Kirin and Reata Pharmaceuticals, Inc. 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 Objective

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.

3.2. Study Endpoints

3.2.1. Primary 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, weight, urine albumin/creatinine ratio (ACR), and laboratory results.

4. STUDY DESIGN

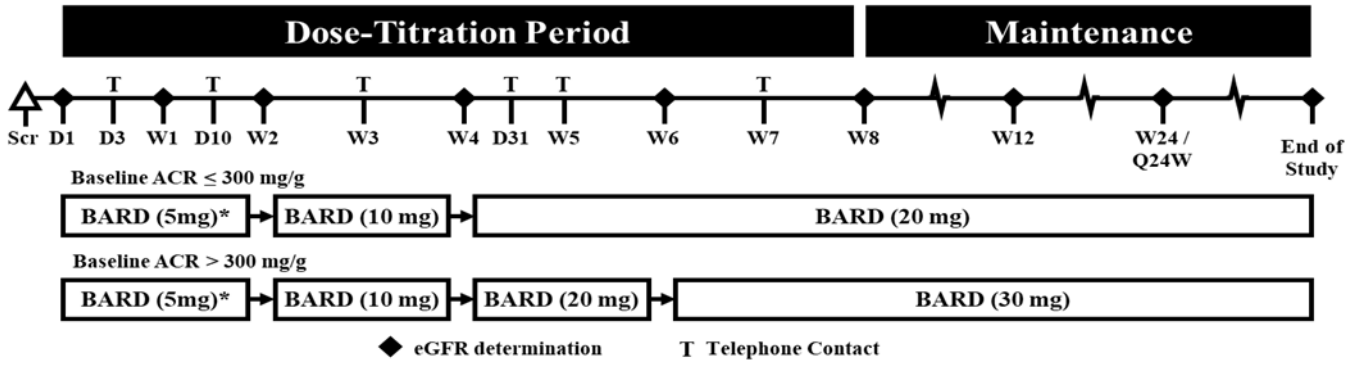
4.1. Summary of Study Design

This extended access study will assess the long-term safety and tolerability of bardoxolone methyl in qualified patients with chronic kidney disease who previously participated in a qualifying clinical study with bardoxolone methyl.

The Day 1 visit of 402-C-1803 is not required to occur on the same day as the last visit of the prior qualifying study (either 402-C-1603 or 402-C-1808). Details for determining eligibility and lab assessment requirements are provided in Protocol Section 7.

All patients in the study will follow the same visit and assessment schedule (Figure 1). Patients will be assessed in person during treatment at Day 1, Weeks 1, 2, 4, 6, 8, 12, 24, and every 24 weeks thereafter. Patients will also be assessed by telephone contact on Days 3, 10, 21, 31, 38, and 45. If the Day 1 visit for 402-C-1803 is the same as the end-of-study visit from the prior qualifying study, the assessments required for both visits should only be completed once. If the Day 1 visit of 402-C-1803 is not on the same day as the end-of-study visit from prior qualifying study, lab assessments are performed for Day 1 through the 402-C-1803 central lab.

Figure 1: Schema for Study 402-C-1803 (EAGLE)



Abbreviations: ACR=albumin to creatinine ratio; D=day; W=week; eGFR=estimated glomerular filtration rate; Scr=screening
*Patients in CARDINAL (402-C-1603) that are under the age of 18 will receive bardoxolone methyl every other day during Week 1. Patients in FALCON (402-C-1808) that are under the age of 18 will receive bardoxolone methyl every day during Week 1.
Note: Screening visit will be scheduled for subjects whose last lab assessments are more than 4 weeks old. Refer to protocol Section 8.3 for additional details. Subjects requiring visit will be consented on the same visits

4.2. Definition of Study Drugs

Capsules containing bardoxolone methyl at the 5 mg, 10 mg, 15 mg, and 20 mg strengths will be used to titrate to a maximum dose of 20 or 30 mg/day are used in this study.

4.3. Sample Size Considerations

The 402-C-1803 study is not powered to show efficacy or safety effects, and there is no placebo comparator in this open-label trial. Patient numbers are determined by those who are participating (or who have previously participated) in a qualifying clinical study with bardoxolone methyl and meet eligibility criteria.

4.4. Randomization

This is a non-randomized, open-label study that includes patients who completed previous qualifying clinical study. The CARDINAL study (402-C-1603, NCT03019185, EudraCT 2016-004395-22) and FALCON study (402-C-1808, NCT03918447, EudraCT 2018-004651-20) are the only qualifying clinical studies at this time.

As no randomization or blinding is performed, all patients enrolled in 402-C-1803 are assigned to bardoxolone methyl.

4.5. Treatment Analysis Group Assignment

The treatment analysis groups for the 402-C-1803 study consist of:

1. Placebo → Bardoxolone (Bard): placebo-bardoxolone methyl patients (patients previously randomized to placebo in 402-C-1603 Phase 3 or 402-C-1808 who started receiving bardoxolone methyl in 402-C-1803),
2. Bard → Bard: bardoxolone methyl patients (patients previously randomized to bardoxolone methyl in 402-C-1603 Phase 3 or 402-C-1808 who started receiving bardoxolone methyl in 402-C-1803). Data from 402-C-1603 or 402-C-1808 must be unblinded to be included in either treatment analysis group.

4.6. Clinical Assessments

All patients in the study follow the same visit and assessment schedule for the duration of the trial. Table 1 lists the overall schedule of assessments for the study.

Table 1: Schedule of Assessments

Assessment / Study Week (Day±Days)	Screening Visit[a]	Day 1 [a,c]	Week 1 (Phone) Day 3 ± 2 Days	Week 1 Day 7 ± 3 Days	Week 2 (Phone) Day 10 ± 2 Days	Week 2 Day 14 ± 3 Days	Week 3 (Phone) Day 21 ± 2 Days	Week 4 Day 28 ± 3 Days	Week 4 (Phone) Day 31 ± 2 Days	Week 5 (Phone) Day 38 ± 2 Days	Week 6 Day 42 ± 3 Days	Week 7 (Phone) Day 45 ± 2 Days	Week 8 Day 56 ± 3 Days	Week 12 Day 84 ± 3 Days	Week 24 ± 3 Days, Every 24 Weeks ± 3 Days	End of Study Visit[b]
Informed consent	X[c]	X[c]														
Inclusion/Exclusion	X	X														
Demographics[d]	X	X														
Prior and Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical History	X	X														
Height	X	X		X		X		X			X		X	X	X	X
Weight at home		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Weight in-clinic	X	X		X		X		X			X		X	X	X	X
Dispense Weight & Study Drug Diary		X				X		X			X		X	X	X	
Collect/Review Weight & Study Drug Diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital sign measurements	X	X		X		X		X			X		X	X	X	X
Physical examination	X	X		X		X		X			X		X	X	X[e]	X[e]
Pregnancy test[f]		X													X	
Dispense study drug		X				X		X			X		X	X	X	
Collect study drug						X		X			X		X	X	X	X
Telephone contact			X		X		X		X	X		X				
Adverse event collection		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Basic Lipid Panel		X													X	X
Clinical Chemistries (includedeGFR)[g]	X	X		X		X		X			X		X	X	X	X
BNP and NT-proBNP	X	X		X		X		X			X		X	X	X	X
Hematology	X	X		X		X		X			X		X	X	X	X
Urine collection for ACR[h]	X	X						X					X	X	X	X
Tanner Staging[i]		X													X	X

Abbreviations: ACR=albumin/creatinine ratio; AE=adverse event; BNP=B-type natriuretic peptide; CARDINAL=name for Study 402-C-1603; EAGLE=name for Study 402-C-1803; eGFR=estimated glomerular filtration rate; FALCON=name for Study 402-C-1808; IEC=Independent Ethics Committee; IRB=Institutional Review Board; NT-proBNP=N-terminal prohormone B-type natriuretic peptide

[a] A screening visit will be conducted for subjects whose planned EAGLE Day 1 visit is not within 8 weeks of the eligibility lab assessments from the prior qualifying study. Subjects requiring a screening visit will be consented prior to the start of any screening assessments. All other subjects will be consented at the start of the Day 1 visit, before any procedures are performed for this, or the prior study.

[b] After the Week 24 visit, subjects will continue to be assessed in person every 24 weeks until the study ends. The End-of-Study visit should occur within 30 days after bardoxolone methyl becomes available to the subject through commercial channels. Subjects who will be discontinued from the study prior to commercial availability of bardoxolone methyl must also complete all End-of-Study assessments as soon as possible (if possible, within 30 days of discontinuation).
[c] On Day 1, all procedures should be performed before study drug administration. AE assessment on Day 1 should be performed following study drug administration. If the Day 1 visit for EAGLE is the same as the end-of-study visit for CARDINAL (all versions) or FALCON (protocol version 5 and older), the laboratory assessments required for both visits should only be completed once.
If the Day 1 visit for EAGLE is the same as the end-of-study visit for FALCON (protocol version 6 and newer), the lab assessments required for both visits should be completed for each study individually.
[d] Demographics are to be performed on the earliest study visit, whether it be Day 1 or a Screening visit, if necessary.
[e] Assessment should include a complete physical examination as described in the protocol.
[f] 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/IECs.
[g] eGFR will not be calculated by the central lab.
[h] Urine ACR will be measured by first morning void spot urine collection. Appropriate containers for the collection will be provided to the subject at the visit prior to collection.
[i] Adolescent patients from the FALCON (402-C-1808) ($12 \leq$ age < 18 years at consent) will be assessed by Tanner staging at all specified timepoints.

5. PLANNED ANALYSES

5.1. Planned Interim Analyses

Interim analyses are based on locked data. A DBL plan will describe the details of each DBL. 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.

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

Results are 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. 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 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, figures, and listings. All tables, figures, and listings use ICH numbering conventions.

Analyses described in this SAP are based on data collected in 402-C-1803 and data collected in 402-C-1808 and 402-C-1603 per eligibility requirements described in Protocol Section 7.1. All analyses and summaries are produced using Statistical Analysis Software® 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, 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 presented when reporting mean and quartiles; and 2 more decimal places than in the observed value is presented when reporting SD.

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 (ie, 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 402-C-1803 study.

6.3.1. Safety Population

The safety population includes all patients who received at least 1 dose of bardoxolone methyl in 402-C-1803 study. The safety population is used for evaluation of safety variables.

6.3.2. 402-C-1603 to 402-C-1803 Safety Population

The 402-C-1603 to 402-C-1803 safety population includes all patients previously enrolled in 402-C-1603 study who received at least 1 dose of bardoxolone methyl in 402-C-1803 study.

6.3.3. 402-C-1808 to 402-C-1803 Safety Population

The 402-C-1808 to 402-C-1803 safety population includes all patients previously enrolled in 402-C-1808 study who received at least 1 dose of bardoxolone methyl in 402-C-1803 study.

Subgroup analyses will not be conducted due to termination of the bardoxolone methyl program. However, summaries based on the parent studies (402-C-1808 and 402-C-1603) will be provided along with a pooled analysis.

6.4. Baseline Definition

The last measurement on or prior to the date of first study drug administration is considered the 402-C-1803 Day 1 measurement for the calculation of baseline. If baseline is missing, the last available value in prior qualified studies will be used as baseline.

6.5. Derived and Transformed Data

6.5.1. Baseline Age

Subject's age in years is the age collected at 402-C-1803 Day 1.

6.5.2. Study Day

Study day is the day relative to the date of first study drug kit dispensation in 402-C-1803, which may precede the date of first dose of study drug.

Assessments that occur after 402-C-1803 study drug dispensation, but on or before the date of first study drug administration are considered to occur on study Day 1.

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 AEs) the quantity 'days since first (or last dose)' is defined as:

- Days since first dose = event date – date of first dose + 1
- 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 will be defined as days divided by 7 and months as days divided by 30.4.

6.5.3. Change from Baseline

Change from baseline is calculated as the result minus baseline, using the baseline value (Section 6.4) and the result assessed closest to the target study day for each analysis visit (Section 6.5.4).

6.5.4. Visit Windows

Table 2: Visit Window (Days)

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
12	Week 12	84	71 ≤ Study Day ≤ 126
24	Week 24	168	127 ≤ Study Day ≤ 210
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 × 7	([Analysis Visit × 7] - 28) ≤ Study Day ≤ ([Analysis Visit × 7] +28)
FU	Follow-up	28 days after last dose	14 ≤ Days after last dose[a] ≤ 35

[a] For safety analyses, last dose for patients completing the treatment or permanently discontinuing study drug that occur on the date of last dose or less than 14 days after last dose are considered on treatment.

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 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 (ie, "retested") result will be ignored. Records from visits not closest to the target study day, and therefore not used in analyses, are presented in by-subject data listings.

6.5.5. Laboratory Evaluations

Any laboratory assessments less than the lower limit of detection (LLD) are imputed as LLD/2. If no LLD is available, then the imputed value is the minimum numeric value listed divided by 2 (eg,

< 25 is 25/2=12.5). Laboratory assessments above the upper limit of detection are imputed as the upper limit of detection. If the lab result is qualitative but presented as > X, then the value X is used in the analysis.

6.5.6. Estimated Glomerular Filtration Rate

The formula used to calculate estimated glomerular filtration rate (eGFR) is based on the patient's age at the date of 402-C-1803 consent. The formula will not change throughout the study. However, note that the formula used in the prior study may be different if the patient was < 18 in prior study and at least 18 in 402-C-1803. The Chronic Kidney Disease - Epidemiology Collaboration equation is used for adult patients (age at consent at least 18 years):

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

The Bedside Schwartz equation is used for pediatric patients (age at consent of 12 to 17):

- eGFR (mL/min/1.73 m^2) = (0.41 × *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* indicates age at time of serum creatinine collection. *Height* indicates height at time of serum creatinine collection. Estimated glomerular filtration rate (eGFR) will not be calculated by the central lab.

6.5.7. Urine Albumin to Creatinine Ratio (ACR)

Albumin/creatinine ratio 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 reported in the central laboratory database as missing when the FMV urine albumin result is < LLD. Urine albumin results < LLD and the corresponding ACR missing values is 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.

6.5.7.1. Baseline Urine Albumin to Creatinine Ratio Categorical Status

Baseline ACR status will also be grouped by the following categories using baseline ACR:

- < 30 mg/g
- 30 mg/g ≤ ACR ≤ 300 mg/g
- 300 mg/g < ACR ≤ 1000 mg/g
- 1000 mg/g < ACR ≤ 3500 mg/g

- ACR > 3500 mg/g

6.5.7.2. ACR Category used in Stratification

The ACR category used for stratification with the following categories:

- ACR ≤ 300 mg/g
- ACR > 300 mg/g

6.5.8. Natural log (ACR)/eGFR

To evaluate ACR after adjusting for filtration rate, ln(ACR)/eGFR (Section 6.5.7 and Section 6.5.6) is calculated.

6.6. Handling of Missing Data

6.6.1. Missing Endpoints

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 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 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

Data are summarized for the safety population (Section 6.3.1)

7.1. Subject Disposition

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

- Patients with prior participation in 402-C-1603 phase 2
- Patients with prior participation in 402-C-1603 phase 3 and randomized to placebo
- Patients with prior participation in 402-C-1603 phase 3 and randomized to bardoxolone methyl
- Patients with prior participation in 402-C-1808 phase 3 and randomized to placebo
- Patients with prior participation in 402-C-1808 phase 3 and randomized to bardoxolone methyl
- Patients completed study when the study was terminated
- Continuing (or complete) treatment
- Terminate early from the treatment
  - Reason for terminating treatment
  - Terminated early from the treatment due to COVID-19
- Continuing (or complete) study
- Terminate early from the study
  - Reason for terminating study
  - Terminated early from the study due to COVID-19
  - Study week at study termination
  - Terminated prior to SDT
  - Terminated after SDT

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

7.2. Screen Failures

Lab assessments from the qualifying study will be used for EAGLE eligibility and maximum treatment dose assignment (Week 100 for CARDINAL or FALCON protocol versions 1 through 5, and Week 108 [B] for FALCON versions 6 and newer) if those assessments were done ≤ 8 weeks before Day 1. In the event that the eligibility lab assessments were obtained > 8 weeks before the planned EAGLE Day 1 visit, a screening visit will be required for EAGLE enrollment. Subjects who previously were ineligible due to previous eGFR requirements may be rescreened once.

Screen failures are not summarized.

7.3. Protocol Deviation

Protocol deviations for major protocol deviations and protocol deviations related to COVID-19 are summarized.

Major protocol deviations include but not limited to:

- Protocol deviations for patients who entered the study even though they did not satisfy all entry criteria.
- Patients who received an incorrect dose.

All protocol deviations are listed.

7.4. Demographic and Baseline Characteristics

Summaries of demographic and other baseline characteristic data are presented by treatment analysis group (Section 4.5) for all the safety populations.

The demographic and other baseline characteristics include:

- Age, Age category at the date of informed consent (< 18, ≥ 18)
- Race
- Ethnicity: Non-Hispanic/Latino; Hispanic/Latino
- Sex: (female; male)
- Weight (kg), body mass index (kg/m^2)
- Geographic location: United States; Other
- Diastolic and systolic blood pressure (mmHg), Heart rate (bpm)
- SCr, eGFR, eGFR categorical status (< 60, ≥ 60 mL/min/1.73 m^2)
- ACR (geometric mean), ACR categorical status (< 30 mg/g; ≤ 300 mg/g; > 300 mg/g;
- > 1000 mg/g),
- Angiotensin converting enzyme-inhibitor treatment and/or Angiotensin II receptor blocker (yes/no)
- Genetic subtype: X-linked Alport syndrome; Non-X-linked Alport syndrome (for Alport patients only)
- Chronic kidney disease etiology: Alport syndrome; autosomal dominant polycystic kidney disease (ADPKD)
- Family history of ADPKD (for ADPKD patients only)
- Use of tolvaptan (for ADPKD patients only)
  - Currently using tolvaptan
  - Previously used tolvaptan
  - Never received tolvaptan

- Prior study: 402-C-1603 phase 2, 402-C-1603 phase 3, 402-C-1808

7.5. Listing of Subject Inclusion and Exclusion Criteria

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

7.6. Medical History

Medical history is summarized by treatment analysis group (Section 4.5). If medical history values are not recorded in 402-C-1803, then medical history values recorded at the 402-C-1603/402-C-1808 screening visit are used for analysis. Medical history is coded using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history items are summarized by MedDRA System Organ Class (SOC) and preferred term (PT). Patient listings are also provided.

8. SAFETY AND TOLERABILITY

Safety and tolerability are evaluated by AEs, SAEs, clinical laboratory test results, body weight, vital signs, and physical examination. All analyses of the safety data are performed using the safety analysis set. Descriptive statistics are presented by treatment analysis group (Section 4.5) assignment in the all analysis populations. No formal statistical testing is performed for safety analyses. Any results not included in summaries based on analysis visit window definitions are presented in data listings.

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

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

- Multiple events by PT and SOC are counted once only per patient for summaries of AE incidence.
- For summaries of AE incidence by severity, only the most severe event is counted per patient.
- For summaries of AE incidence by relationship, only the most related event is counted per patient.
- 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 TEAEs are included in summaries.

Adverse events are coded using MedDRA version 21.1. In MedDRA, each verbatim term is mapped to a PT and high-level term, which is then mapped to an SOC. Tables and listings will present data at the SOC and PT level.

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

- Have a date of onset on or after the date of the first dose in the 402-C-1803 study and not more than 30 days after the date of the last dose of study drug in the 402-C-1803 study, 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 or stop date

Adverse events with a date of onset in a prior study that continued during the 402-C-1803 study are not considered TEAEs.

In addition, AEs that occurred >30 days after the date of last dose of study drug are summarized as late-onset AEs. These are AEs that had a date of onset more than 30 days after the date of the last dose of study drug in 402-C-1803 study.

The investigator grades the severity of the AEs as mild, moderate, or severe as defined in the study protocol Section 11.5. The investigators graded association or relatedness to the study medication according to criteria specified in Section 11.4 of the study protocol.

As defined in the protocol, an SAE is an AE that results in any of the following:

- Death;
- A life-threatening adverse drug experience;
- Patient reaches ESKD (defined as the initiation of maintenance dialysis for 12 weeks or more or kidney transplant)
- 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.

8.1.1. Missing and Partial AE Onset Dates

Rules for handling missing or partial AE onset dates are included in Section 6.6.3.

8.1.2. Summaries of Adverse Events

For each treatment analysis group, SOC, and PT, the number and percentage of patients reporting an event is calculated. In summary tables, SOC is presented alphabetically and events within SOC are presented by decreasing frequency count.

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

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

Listings are provided showing:

- All AEs
- SAEs (including deaths)
- AEs leading to permanent discontinuation of study drug

8.2. Exposure and Compliance

The duration of study drug exposure is defined as the number of days on treatment from the first dose of 402-C-1803 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, and duration (days) of

exposure during the study treatment period. In addition, a summary of the number and percentage of patients by dose (5 mg, 10 mg, 20 mg, 30 mg) and by visit window (Section 6.5.4) is generated. If a patient received more than one dose during a visit window, the duration of the longest dose exposure is used to calculate study drug dose during a given visit window.

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). Study drug compliance (%) is calculated as 100 × total number of doses received / total number of study days of study participation. 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. Any dispensation of drug after a subject has his or her end of treatment visit will not be used in any calculation.

8.3. Concomitant and Other Medications

Concomitant medications are coded using the World Health Organization drug dictionary (B3 Global September 2018) for anatomical therapeutic chemical (ATC) classification and preferred drug name. Patients who used multiple medications are counted only once for each ATC and preferred drug name. Anatomical therapeutic chemical (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 402-C-1803 study or a medication that was started after the start of 402-C-1803 study drug dosing.

Specifically, concomitant medications are medications:

- That are continued from 402-C-1603 or 402-C-1808 and continued after the first study drug dosing, or
- That have start dates within the 402-C-1803 treatment period.

Concomitant medications are summarized for each treatment analysis group by World Health Organization ATC class and preferred name. Patients may have more than 1 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 or prior to the date of first study drug administration in 402-C-1803 study are not considered concomitant medications.

Patients who take the following excluded medications (defined in the Protocol Section 9.3.1) during the study are listed.

- Any other investigational drug
- Tolvaptan (patients on tolvaptan who have already enrolled under Version 3.0 of the protocol may remain in the trial)
- Somatostatin analogues
- Chronic (> 2 weeks) immunosuppressive therapy, or need for corticosteroids, including therapies such as glucocorticoids, oncologic preparations, and anti-tumor necrosis factor α agents [eg, infliximab (Remicade®), adalimumab (Humira®), certolizumab pegol (Cimzia®), etanercept (Enbrel®)]. (Glucocorticoid intra- articular injections, inhaled products, topical preparations, and nasal preparations are allowed.)

In addition, patients who take the following concomitant medications (defined in the Protocol Section 9.3.2) during the study are listed.

- Antibiotics;
- Daily multivitamins or recommended daily supplements;
- Other medications intended to manage concurrent diseases, as authorized by the treating physician;
- Statins, in the Czech Republic and globally
- Pain management medications
- Oral, implantable, or injectable contraceptives

8.3.1. 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

8.4. Clinical Laboratory Evaluations

Laboratory data are summarized at baseline and at each time point by treatment analysis group (Section 4.5).

8.4.1. Continuous Summaries of Laboratory Results

Selected laboratory evaluations and change from baseline are summarized by treatment analysis group (Section 4.5), laboratory category (hematology, chemistry), test, and study visit using continuous statistics. The eGFR results are calculated using formulas described in Section 6.5.6.

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

Due to the nature of urinalysis parameters, summaries of continuous statistics are not provided unless otherwise specified. The one exception is the ACR from the FMV urine collection. Qualitative lab results, including urinalysis, are included in the listings, but are not summarized.

Laboratory results that are above or below normal limits are flagged in the listings.

8.4.1.1. Urine Albumin/Creatinine Ratio

Summaries of ACR (Section 6.5.7) will use the geometric mean 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 reported as the post-baseline/baseline ratios and are summarized by geometric means with 95% confidence intervals at each time point. Summaries of ACR will use the geometric mean instead of the arithmetic mean. Presentations will display ACR results in the original units (mg/g). Changes in ACR are calculated as the ratio of each visit to baseline.

Additionally, ACR is summarized by baseline ACR quartile. Descriptive summaries at each visit include the geometric mean of ACR, SD as well as the geometric mean of percent change from baseline. Summaries of ACR exclude values within the Week 2 and Week 6 visit windows.

8.4.1.2. Continuous eGFR

Any eGFR values collected after starting dialysis or after receiving a kidney transplant are treated as missing. Missing values are not imputed as specified in Section 6.6.1.

The change from baseline in eGFR is summarized by visit and treatment analysis group (Section 4.5). Summary statistics and change from baseline are presented by visit window (Section 6.5.4). Waterfall plots of eGFR change from baseline, labeled by treatment analysis group (Section 4.5) are generated at each visit window. Results are presented in tables and plots.

8.4.1.3. Natural log (ACR)/eGFR

Mean ratios of natural log (ACR)/eGFR (Section 6.5.8) are summarized at each time point for safety. The ratio of natural log (ACR)/eGFR by analysis visit is summarized by arithmetic means for safety.

8.4.2. Categorical Summaries of Laboratory Results

The number and percentage of patients by laboratory normality and abnormality categories at any time during the study (Normal, Low, High) are summarized by treatment analysis group (Section 4.5), laboratory category (hematology, chemistry, and urinalysis), and laboratory test. The worst abnormality values are defined as the maximum values while on study treatment (ie, up to < 14 days after last dose), except for magnesium and hemoglobin. The worst abnormal values for magnesium and hemoglobin are defined as the minimum values while on study treatment.

An initial set of parameters of specific interest (ALT, AST, ACR) are summarized using shift tables, though additional parameters may be added as appropriate. Shift tables summarizing (1) baseline to end of treatment, and (2) baseline to worst on-treatment, (3) baseline to follow-up, and (4) worst on-treatment to follow-up are presented for lab parameters as appropriate. For ACR, summaries will present shifts from/to the categories in Section 6.5.7.1. For ALT and AST, summaries will present shifts from/to the following categories:

- < 3× upper limit of normal (ULN)
- ≥ 3× ULN to < 5× ULN
- ≥ 5× ULN to < 10× ULN
- ≥ 10× ULN to < 20× ULN
- ≥ 20× ULN

In addition, a summary table is provided by treatment analysis group (Section 4.5) 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
- N-terminal prohormone BNP > 1000 pg/mL

8.4.2.1. Transaminases

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

The number and percentage of patients meeting the following thresholds, which are consistent with Food and Drug Administration guidance of Drug-Induced Liver Injury: Premarketing Clinical Evaluation (July 2009 Drug Safety), are summarized by the maximum dosage received.

Table 3: Pre-specified Threshold Levels for Transaminases

Lab Parameter	Threshold
ALT, AST	≥ 3 × ULN and < 5 × ULN
	≥ 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
ALP	> 1.5 × ULN

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; TBL=total bilirubin; ULN=upper limit of normal.

A summary table that includes frequencies and percentages of patients that meet any of the above criteria at any time during the study is provided. A listing of subjects with abnormal ALT, AST, or TBL will also be provided.

8.4.2.2. Frequency of End Stage Kidney Disease, eGFR decline ≥ 30%, or eGFR < 15

The kidney failure composite outcome is defined as reaching one of the following:

- 30% decline from baseline in eGFR; or
- eGFR < 15 mL/min/1.73 m^2; or
- ESKD (initiation of maintenance dialysis or kidney transplant).

A ≥ 30% decline or eGFR < 15 is considered confirmed when the threshold is achieved at ≥ 2 visits. Patients who achieved the threshold at their last visit, and did not have a second confirmatory visit, are considered confirmed. The analysis uses initiation of maintenance dialysis or kidney transplant as reported prior to the end of the follow-up window in the database by the investigator. Any initiation of maintenance dialysis or kidney transplant that occurs after the follow-up window will be listed separately. Patients with a decrease from baseline in eGFR of ≥ 30% at the last on-treatment visit will be considered to have a ≥ 30% decrease from baseline eGFR. In the event a patient has both an increase from baseline in eGFR of ≥ 30% and a decrease from baseline in eGFR of ≥ 30%, only the decrease from baseline will be considered in composite endpoint analyses.

The proportion of patients with ESKD (dialysis/transplant), eGFR decline ≥ 30%, or eGFR < 15 will be summarized, and the composite of all these criteria will be evaluated. The frequency analyses will be performed for all visits. No off-treatment eGFR values are included in the analysis.

As a sensitivity analysis, the analyses are repeated for the frequency of patients with ESKD (dialysis/transplant), eGFR decline ≥ 30%, or eGFR < 15 with all-cause death added to the kidney failure composite.

8.5. Vital Signs

Vital signs assessments include systolic blood pressure (mmHg) and diastolic blood pressure (mmHg), body temperature (°C), heart rate (bpm), height (cm), weight (kg), and body mass index (kg/m^2). Vital signs are summarized at baseline and at each time point (Section 6.5.4) along with the change from baseline by treatment analysis group (Section 4.5). Line graphs of change from baseline over time for blood pressure are plotted.

All data are listed.

8.5.1. Body Weight

Body weight, as collected during each in-office visit in 402-C-1803, is summarized using descriptive statistics for observed results and change from baseline at each time point. In addition, number and percentage of patients experiencing a 5 pound (2.3 kilogram) or greater increase in weight are summarized by time point. Boxplots and line graphs of change from baseline over time for weight are plotted.

8.6. Pregnancy

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

9. PHARMACOKINETICS

There are no pharmacokinetic samples collected in 402-C-1803.

10. COVID-19 IMPACT

10.1. Operational Impact

The COVID-19 pandemic has impacted the conduct of the study per protocol. The mitigation strategies are adopted to protect the health of participants in the 402-C-1803 study, while maintaining compliance with good clinical practice and minimizing the risk to trial integrity (Protocol Appendix 1). These measures apply to United States and rest of the world. An eCRF form is updated to collect data for COVID-19 impact.

The number and percentage of patients impacted by COVID-19 are summarized by visit and treatment analysis group for the following categories:

- Visit impact
  - Visit not done
  - Visit conducted out of window
  - One or more procedures could not be performed
  - Rollover delayed
- Data collection methods
  - No change (occurred as expected per protocol)
  - Telephone visit
  - Video conference visit
  - Home health care visit
  - Local lab
  - Other
- Drug dispensation methods
  - No change (office visit)
  - Investigational product 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 impacted by COVID-19 are summarized by treatment analysis group (Section 4.5) for the following categories:

- 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 investigational product supply, other)

Patient narratives are provided for all patients who test positive for SARS-CoV-2, the causative agent of COVID-19.

Early discontinuations of treatment or study due to COVID-19 are summarized and listed (specified in Section 7.1).

All deviations due to the impacts of COVID-19 are identified and documented accordingly by the site and the sponsor. The failure to complete a protocol visit is not considered as a reason for study discontinuation and/or a major deviation. All COVID-19–related deviations will be identified in the protocol deviation listing (Section 7.3).

10.2. Safety

For continued patient safety oversight, patients should continue with protocol-specified visits. Where inadvisable for the patient to be seen for an in-person clinic visit or if a patient is unwillingly to come to the clinic, alternate visit completion methods should be considered, such as by phone, telemedicine, home health visits and/or local laboratory monitoring of safety labs.

Patients affected by COVID-19 with visits not done, visits outside the window, one or more procedures not performed, and other impact to study assessments or procedures are listed.

Patients with changes in safety data collection methods due to COVID-19 including telephone, video conference, home health, local lab, and other methods are listed.

APPENDIX 1

Programming Specifications

Continuous data are listed corresponding to the precision measured or calculated. Measures of central tendency are presented using 1 more decimal place than the precision of the data.

Summaries of variability are presented using 2 significant digits more than the precision of the underlying data. Minimum and maximum are presented using the precision of the data.

All percentages are to be expressed as integers with 1 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