Statistical Analysis Plan
for
Phase 2 Portion of
402-C-1603

[redacted]

EUDRACT NUMBER: 2016-004395-22

A Phase 2/3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Alport Syndrome

Version: 5.0

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SPONSOR APPROVAL AND SIGNATURE PAGE

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

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

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ACE	angiotensin converting enzyme
ACR	albumin to creatinine ratio
AE	adverse event
ALT	alanine aminotransferase
AR	auto-regressive
ARB	angiotensin II receptor blocker
AST	aspartate aminotransferase
ATC	Anatomical/Therapeutic/Chemical
AUC	area under the plasma concentration curve
BARD	Bardoxolone methyl
BCVA	best corrected visual acuity
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CM	concomitant medication
C_{max}	maximum drug concentration in plasma
CSR	clinical study report
eCRF	electronic case report form
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ESKD	End stage kidney disease
EOT	end of treatment
FAS	full analysis set
FDA	Food and Drug Administration (US)
GFR	glomerular filtration rate
Hgb	hemoglobin
ICH	International Conference on Harmonization
IGF-1	insulin-like growth factor-1
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
LLD	lower limit of detection
LS	least squares
MCH	mean corpuscular hemoglobin

Abbreviation or Specialist Term	Explanation
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
NT-Pro BNP	N-Terminal Pro-Brain Natriuretic Peptide
pH	potential of hydrogen
PK	pharmacokinetic
PTA	Pure tone audiometry
PT	preferred term
QTc	corrected QT interval
RBC	red blood cell
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SCr	serum creatinine
SD	standard deviation
SOC	system organ class
TBL	total bilirubin
TEAE	treatment-emergent adverse event
TLFs	tables, listings, and figures
T_{max}	time when maximum drug concentration in plasma is achieved
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO	World Health Organization
WHO DD	World Health Organization Drug Dictionary
WOCBP	women of child bearing potential

2. REVISION HISTORY AND RELEVANT DOCUMENTS

Below is a list of revision summaries of this statistical analysis plan.

Version Date	Document Owner	Revision Summary
1.0 dated 28 FEB 2017	[redacted]	Initial version.
2.0 dated 21 AUG 2017	[redacted]	Updated the handling of missing data for efficacy and sensitivity analyses, and the handling of baseline eGFR and SCr values. Specifically: • Primary efficacy analysis will have no data imputed for missing eGFR • There will be no pre-planned sensitivity analysis for the primary efficacy variable • Baseline eGFR and SCr will use the average of the last 2 assessments collected prior to Day 1 as screening values for the baseline value derivations Added SAS pseudo-code for MMRM analysis. Added categorical analysis of CKD stage. Phase 2 objectives and the Schedule of Assessments were updated according to Protocol V2. The Audiology Assessment definition of non-adults was also updated to exclude 18 year olds (i.e., updated to <18) for consistency with other age categorizations in this study. Typographical errors were also corrected.

Version Date	Document Owner	Revision Summary
3.0 dated 04 DEC 2017	[redacted]	Modified data handling rules for urine albumin levels >ULD or <LLD to be applied to all visits. Specifically: • Urine albumin results reported as <LLD will be imputed with LLD/2; • Urine albumin results reported as >ULD will be imputed with the ULD; • Where the ACR value is missing due to urine albumin results <LLD or >ULD, the imputed urine albumin result will be used to calculate ACR. Clarification that baseline eGFR is equal to the screening eGFR if no pre-dose, Day 1 value exists. The same clarification was added for serum creatinine. The definition of baseline for vitals sign assessments was defined as the average of pre-dose measurements collected through Day 1. The off-treatment analysis set was modified to require minimum dosing compliance. Added clarification for calculation of study drug compliance. Added clarification for CKD stages. Added clarification that sensitivity analyses may be performed as appropriate. Added table of laboratory parameters to be used for categorical laboratory summaries.
4.0 dated 19 JUL 2018	[redacted]	Modified data handling rules for patients who discontinue study drug Added analysis methods for natural log (ACR)/eGFR Added geometric mean analysis for ACR values Added description of analysis for Patient Global Impression of Change and Clinical Global Impression of Change Added analysis of covariance calculation of historical change in eGFR Added comparison of eGFR before and after participation in CARDINAL Added detailed calculation of study drug compliance

Version Date	Document Owner	Revision Summary
5.0 dated 05 JUN 2019	[redacted]	Clarification that additional efficacy analyses conducted after database lock at Week 52 will not update efficacy tables results for visits at or before Week 52. Change in INR pre-specified threshold levels for categorical laboratory summaries Add analysis of frequency and time-to-first kidney failure event Phase 2 objectives were updated according to Protocol V4

The analysis plan is based on the information from the following document:
Protocol Version 4.0, 22 April 2019.

3. PURPOSE OF THE ANALYSIS PLAN

The purpose of this statistical analysis plan (SAP) is to pre-specify statistical analysis methods for supporting the completion of the clinical study report (CSR) of the Phase 2 portion of Protocol 402-C-1603 for the investigational product bardoxolone methyl (BARD). This SAP will be used to analyze the safety, tolerability, and efficacy data collected during Phase 2 portion of the study. This SAP complies with the International Conference on Harmonisation (ICH) guidance and relevant Food and Drug Administration (FDA) guidances. The analyses described in this plan are considered *a priori*, in that they have been prospectively defined prior to clinical database lock. The planned analyses identified herein may be included in regulatory submissions and/or future manuscripts.

This plan may be amended for reasons such as, but not limited to, protocol amendments, interim analysis results, and internal data reviews that take place prior to clinical database lock of the Phase 2 portion of the study. Exploratory analyses, which are not defined in this SAP, may be performed to support the clinical development program. Any post-hoc or unplanned analyses, which are performed for the CSR, but not defined in this SAP, will be clearly identified and documented in the CSR as will any changes from the planned analyses as stated in the study protocol.

4. STUDY OBJECTIVES AND ENDPOINTS

4.1. Objectives of Phase 2

The objectives are as follows:

4.1.1. Primary Objective

- To assess the change from baseline in estimated glomerular filtration rate (eGFR) in bardoxolone methyl-treated patients after 12 weeks of treatment.

- To assess the safety of bardoxolone methyl after 12 weeks of treatment.

4.1.2. Secondary Objectives

- To assess the safety and efficacy of bardoxolone methyl after 48 weeks of treatment.
- To assess the safety and efficacy of bardoxolone methyl after 100 weeks of treatment.

4.1.3. Exploratory Objective

- To assess the safety and efficacy of bardoxolone methyl at Week 52 following a 4-week drug treatment withdrawal period.

4.2. Endpoints of Phase 2

4.2.1. Efficacy Endpoints

4.2.2. Primary Efficacy Endpoint

- Change from baseline in eGFR at Week 12.

4.2.2.1. Secondary Efficacy Endpoint

- Change from baseline in eGFR at Week 48.

4.2.2.2. Exploratory Efficacy Endpoint

- Change from baseline in eGFR at Week 52 following a 4-week drug treatment withdrawal period.

4.2.3. Safety Endpoints

Frequency, intensity, and relationship of adverse events (AEs) and serious adverse events (SAEs) to study drug, and change from baseline in the following assessments: vital sign measurements, 12-lead electrocardiograms (ECGs), clinical laboratory measurements, and weight.

5. STUDY DESIGN

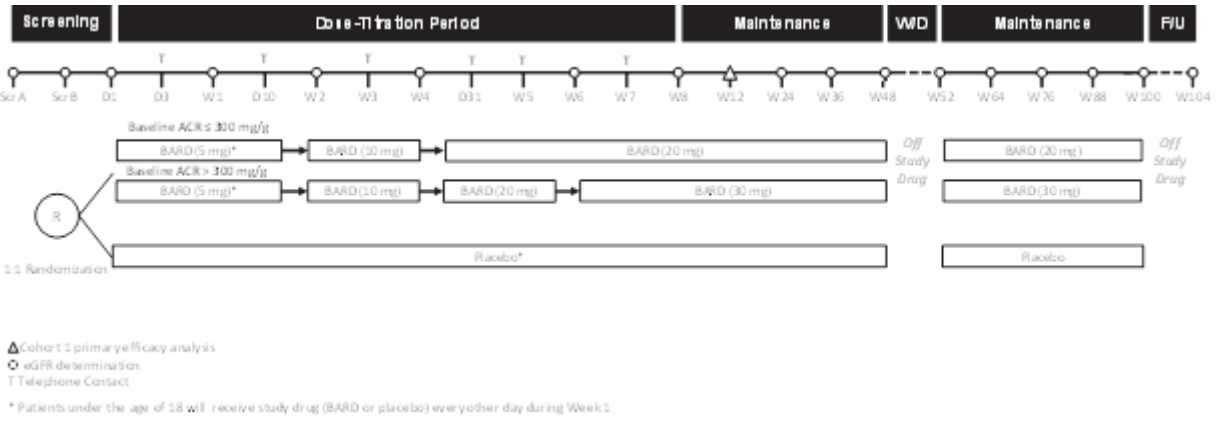
5.1. Overall Study Design

This is a multinational, multi-center, Phase 2/3 trial that will study the safety, tolerability, and efficacy of bardoxolone methyl in patients with Alport syndrome. The Phase 2 portion of the trial will be open-label and enroll approximately 30 patients. The Phase 2 primary efficacy endpoint will be analyzed after all patients in the Phase 2 cohort have completed their Week 12 visit. On the basis of the Phase 2 primary efficacy analyses, the Sponsor may reduce the Phase 3 sample size and/or change the percentage of patients with macroalbuminuria (ACR > 300 mg/g) eligible to enroll in the study.

5.2. Randomization and Dosing

The Phase 2 portion of the study will be open-label without randomization. Patients will receive bardoxolone methyl throughout the study. The maximum bardoxolone methyl dose in Phase 2 cohort will be determined by baseline albumin-to-creatinine ratio (ACR). Patients are stratified by baseline ACR <=300, >300 to 1000, and 1000 to 3500. The diagram below shows dose titration and maintenance schedules according to the baseline (ACR category: ≤300 mg/g or >300 mg/g. All patients will receive study drug from Study Day 1 to Week 48. They will not receive study drug treatment during a 4-week withdrawal period (between Weeks 48 and 52). They will re-start study drug treatment at Week 52 at the same dose level that they received prior to the withdrawal period and will continue study drug treatment through Week 100.

Schema for Phase 2 Portion of the Study
Treatment of Bardoxolone Methyl in Patients with Alport Syndrome



5.3. Assessments

All patients in the study will follow the same visit and assessment schedule. Table 2 lists the overall schedule of assessments for the study. Following the first dose of study drug on Day 1, patients will be scheduled for assessment during treatment at Weeks 1, 2, 4, 6, 8, 12, 24, 36, 48, 52, 64, 76, 88, 100, and 104, as well as by telephone contact on Days 3, 10, 21, 31, 38, and 45. Patients will also be scheduled for assessment at an in person follow-up visit at Week 104, four weeks after the end of treatment.

Table 2: Schedule of Assessments

Assessment	Screen A[a]	Screen B[b]	Day 1[c]	Wk 1 (Phone) Day 3±2	Wk 1 Day 7±3	Wk 2 (Phone) Day 10±2	Wk 2 Day 14±3	Wk 3 (Phone) Day 21±2	Wk 4 Day 28±3	Wk 4 (Phone) Day 31±2	Wk 5 (Phone) Day 38±2	Wk 6 Day 42±3	Wk 7 (Phone) Day 45±2	Wk 8 Day 56±3	Wk 12 Day 84±3
Informed consent	X														
Inclusion/ exclusion	X		X[d]												
Demographics and baseline disease characteristics	X														
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X														
Height	X		X		X		X		X			X		X	X
Weight in clinic	X		X		X		X		X			X		X	X
Weight at home			X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense weight diary			X				X		X			X		X	X
Collect/review weight diary				X	X	X	X	X	X	X	X	X	X	X	X
ECG	X														
Echocardiogram[e]	X														
Vital sign measurements	X		X		X		X		X			X		X	X
Physical exam	X		X		X		X		X			X		X	X
Pregnancy test for WOCBP[f]	X	X	X						X					X	X
Study drug administration			----------X----------												
Dispense study drug			X				X		X			X		X	X
Collect study drug							X		X			X		X	X
Telephone contact				X		X		X		X	X		X		
Adverse event collection			x[g]	X	X	X	X	X	X	X	X	X	X	X	X
Genetic testing[h]	X														
Clinical chemistry (incl. eGFR)	X	X	X		X		X		X			X		X	X
BNP and NT-proBNP	X		X		X		X		X			X		X	X
IGF-1 and serum ketones	X		X		X		X		X			X		X	X
Hemoglobin A1c	X														X
Hematology	X		X				X		X			X		X	X
Urinalysis and microscopy	X		X				X		X			X		X	X
Urine collection for ACR[i]		X							X					X	X
Visual acuity			X												
Audiology assessment			X												
PGIC															
CGI-I															
Virus serology	X														
PK samples[j]															X

Assessment	Wk 24 Day 168±3	Wk 36 Day 252±3	Wk 48 Day 336±3	Wk 52 Day 364±3	Wk 64 Day 448±5	Wk 76 Day 532±5	Wk 88 Day616±5	Wk 100 or End of Treatment[k] Day 700±3	Wk 104 or Follow-up[k] Day 728±3
Informed consent									
Inclusion/ exclusion									
Demographics and baseline disease characteristics									
Concomitant medications	X	X	X	X	X	X	X	X	X
Medical history									
Height	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	X	X	X	X	X	X	X	
Dispense weight diary	X	X	X	X	X	X	X		
Collect/review weight diary	X	X	X	X	X	X	X	X	
ECG			X	X				X	X
Echocardiogram[e]									
Vital sign measurements	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X	X
Pregnancy test for WOCBP[f]	X	X	X	X	X	X	X	X	X
Study drug administration	----------X----------			----------X----------					
Dispense study drug	X	X		X	X	X	X		
Collect study drug	X	X	X		X	X	X	X	
Telephone contact									
Adverse event collection	X	X	X	X	X	X	X	X	X
Genetic testing[h]									
Clinical chemistry (incl. eGFR)	X	X	X	X	X	X	X	X	X
BNP and NT-proBNP	X	X	X	X	X	X	X	X	X
IGF-1 and serum ketones	X	X	X	X	X	X	X	X	X
Hemoglobin A1c			X					X	
Hematology	X	X	X	X	X	X	X	X	X
Urinalysis and microscopy	X	X	X	X	X	X	X	X	X
Urine collection for ACR[i]	X	X	X	X	X	X	X	X	X
Visual acuity			X					X	
Audiology assessment			X					X	
PGIC	X		X	X		X		X	X
CGI-I	X		X	X		X		X	X
Virus serology									
PK samples[j]									

[a] Total Screening period should not exceed 6 months.
[b] Screen B visit should be no more than 30 days prior to Day 1.

[c] Day 1 is the day of administration of the first dose. **On Day 1, all procedures should 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, and a urine pregnancy test should be performed for WOCBP.

[e] An echocardiogram performed at the Screen A visit or within 6 months prior to Day 1 may be used to determine eligibility.

[f] 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.

[g] AE assessments on Day 1 should be performed following study drug administration.

[h] Patients with definitive diagnosis of Alport syndrome from previous genetic testing will not have genetic testing performed as part of the study but must provide documentation of genetic diagnosis for eligibility.

[i] 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.

[j] Patients must be instructed to not take their study drug prior to coming to the clinic for visits when PK samples will be collected. Patients must administer the study drug dose in the clinic on PK sample collection visits after the 0 hour PK blood sample is collected. Patients will have blood samples for PK analysis drawn just prior to (0 hour) and after (2 and 4 hours) dose administration.

[k] Patients who terminate from the study prior to the Week 100 study visit should be brought back to the clinic as soon as possible for early termination assessments (*i.e.*, end-of- treatment visit) as well as a follow-up visit 4 weeks later.

Abbreviations: ECG = electrocardiogram, PK = pharmacokinetic, WOCBP = women of child-bearing potential

5.3.1. Efficacy Measurement and Variable

Central laboratory reported eGFR values will be used to calculate change from baseline in eGFR, the primary efficacy endpoint for the study. Baseline eGFR value will be calculated as described in Section 7.1.3 below.

5.3.2. Safety Measurements and Variables

Safety will be assessed by repeated clinical evaluation, including AEs, SAEs, vital signs, physical examinations, 12-lead ECGs, clinical laboratory tests (i.e., chemistry, B-type natriuretic peptide [BNP], N-Terminal Pro-Brain Natriuretic Peptide [NT-Pro BNP], Insulin-Like Growth Factor-1 [IGF-1], serum ketones, hematology, ACR, spot urinalysis, and urine microscopy), body weight, visual acuity assessments, audiology assessments, and concomitant medications.

5.3.3. Pharmacokinetics Measurements and Variables

Pharmacokinetic (PK) samples will be collected on Day 84±3 prior to study drug dosing (pre-dose), and at post-dose hours 2 and 4. The PK variables include bardoxolone methyl plasma concentration-time data, and estimated PK parameters.

6. SAMPLE SIZE AND POWER

With 30 patients, the Phase 2 portion of the study will have over 80% power to detect a change from baseline in eGFR relative to zero. The power calculation assumes the following:

- Two-sided type I error rate of 0.05
- 5% of the patients will not complete the full course of study treatment
- A mean change from baseline in eGFR of 4.3 mL/min/1.73 m^2
- A standard deviation of change from baseline in eGFR of 8 mL/min/1.73 m^2.

The primary analysis of efficacy will use a mixed-model for repeated measures (MMRM), which is expected to be at least as powerful as the 2-sided t-test calculations used for the sample size estimation of Phase 2 portion of the study.

7. GENERAL CONSIDERATIONS

The analysis sets, as defined in Section 8, will be used for efficacy, safety, tolerability, and PK analyses. Patient listings of all analysis data that support summary tables and/or figures will be provided along with relevant source data from the electronic case report forms (eCRFs). Measurements from patients excluded from the pre-defined analysis sets or extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables unless specified otherwise, but will be included in the patient listings. Missing data will not be imputed, unless otherwise specified. In general, patient listings will be sorted by patient number and assessment date (time and parameter, as applicable).

Unless otherwise specified, descriptive statistics for continuous variables will include the number of patients with data (N), mean, standard deviation (SD), median, minimum, and maximum. The same number of decimal places as in the observed value will be presented when reporting minimum and maximum; 1 more decimal place than in the observed value will be presented

when reporting mean and median; and 2 more decimal places than in the observed value will be presented when reporting SD. The natural log (ACR)/eGFR will be rounded 3 decimal places.

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

Results of statistical analyses will be reported using summary tables, listings, and figures (TLFs). The ICH numbering convention will be used for all TLFs. The following conventions will be followed:

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

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

7.1. Derived Variables

7.1.1. Age

Age (years) will be calculated as the number of years between date of birth and date of informed consent, expressed as an integer.

7.1.2. Study Day

Study Day will follow the CDISC SDTM standard and is defined as follows:

- assessment date – date of first study drug dosing + 1, where the assessment date is on or after the date of first study drug dosing;
- assessment date – date of first study drug dosing, where the assessment date is before the date of first study drug dosing.

7.1.3. Estimated Glomerular Filtration Rate

Estimated glomerular filtration rate (eGFR) value will be calculated at the central laboratory and used in the data analyses. The equation used to calculate eGFR for each patient will not change throughout the study, and will be based on the patient's age on the date of consent. For patients consented at age 18 years and older, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation will be used:

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

For patients consented at age 12 to 17, the Bedside Schwartz equation will be used:

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

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.

Historical serum creatinine and eGFR values will be treated separately from data collected as part of the trial's central lab assessments. Historical eGFR values will be calculated from historical serum creatinine results.

Missing eGFR values will not be imputed for the primary analysis of efficacy. Values collected after the visit window of the date of last dose for patients who do not complete study treatment will not be included in the analysis.

7.1.4. Urine Albumin and Urine Albumin to Creatinine Ratio

Urine albumin to creatinine ratio (ACR) will be derived using the formula below:

ACR = Urine Albumin (mg/dL) / Urine Creatinine (g/dL)

The central laboratory uses an assay that has a lower limit of detection (LLD) and an upper limit of detection (ULD) for urine albumin. Urine albumin results below LLD will be imputed with LLD/2 in mg/dL. Urine albumin results above ULD will be imputed with the ULD value. Where imputation is necessary, the imputed urine albumin results will be used along with the urine creatinine result provided by the central laboratory for calculating ACR.

7.1.5. Electrocardiogram Fridericia Corrected QT Interval

Electrocardiogram intervals, including the Fridericia corrected QT interval (QTcF), will be assessed locally at each site. In the event that QTcF interval is not provided, it will be calculated from QT and RR intervals using the following formula:

$$QTcF = QT/\sqrt[3]{RR}$$

Where RR = 60 / (Heart Rate).

7.1.6. Log of The Minimum Angle of Resolution

Best-corrected visual acuity (BCVA) assessments will be performed at time points specified in the scheduled assessments Table 2. The Snellen chart values will be used to derive log of the minimum angle of resolution (logMAR) value as below:

logMAR = - log10 (Snellen)

7.1.7. Natural log (ACR)/eGFR

Natural log(ACR)/eGFR is defined as the ratio of the natural log of ACR (defined in Section 7.1.4) divided by eGFR (defined in Section 7.1.3). Values collected after the analysis window of the date of last dose for patients who do not complete study treatment will not be included in the analysis. The natural log (ACR)/eGFR will be rounded 3 decimal places.

7.2. Baseline Values

Baseline values are defined as the last non-missing assessment prior to the first study drug dosing, unless otherwise specified below. Assessments performed after the first dose of study drug will not be used in the baseline calculation.

7.2.1. Estimated Glomerular Filtration Rate

The Screening eGFR value is the average of the last two eGFR measurements collected prior to Day 1, for example (Screen A eGFR + Screen B eGFR) / 2. Unscheduled eGFR values collected prior to Day 1 will be used in the calculation of Screening eGFR if the unscheduled eGFR values are within the last two eGFR measurements collected prior to Day 1. Baseline eGFR will be calculated as a weighted average of the Day 1 measurement and the Screening measurement as shown below:

Baseline eGFR = 0.5 × Day 1 eGFR + 0.5 × Screening eGFR

However, if no Day 1 eGFR value exists or Day 1 study drug administration occurred before Day 1 lab collection, then Baseline eGFR will equal Screening eGFR.

7.2.2. Serum Creatinine

The Screening SCr value is the average of the last two SCr measurements collected prior to Day 1, for example (Screen A eGFR + Screen B eGFR) / 2. Unscheduled SCr values collected prior to Day 1 will be used in the calculation of Screening SCr if the unscheduled SCr values are within the last two SCr measurements collected prior to Day 1. Baseline SCr will be calculated as a weighted average of the Day 1 measurement and the Screening measurement as shown below:

Baseline SCr = 0.5 × Day 1 SCr + 0.5 × Screening SCr

However, if no Day 1 SCr value exists or Day 1 study drug administration occurred before Day 1 lab collection, then Baseline SCr will equal Screening SCr.

7.2.3. Vital Sign Assessments

Baseline vital sign assessments is defined as the average value of measurements (from scheduled and unscheduled visits) collected up through Day 1, prior to first dose of study drug.

7.2.4. Natural log (ACR)/eGFR

Baseline of natural log(ACR)/eGFR is defined as the ratio of the natural log of baseline ACR (as defined as the last non-missing ACR assessment prior to the first dose of study drug) divided by baseline eGFR (defined in Section 7.2.1).

7.3. Analysis Windows

Because clinical visits may occur outside protocol specified windows, instead of relying solely on visit labels in the clinical database, analysis visits and their windows are defined using Study Day (See Section 7.1.2). Analysis visit windows are presented in Table 3 by type of assessments and/or measurements.

If more than one on-treatment assessment and/or measurement exists for a parameter within a visit window, the one that is closest to the protocol scheduled time point (or target Study Day) will be used for the purposes of data analysis and summary. If more than one off-treatment assessment exists, the one closest to the target study day will be used for analysis and summary.

Table 3: Analysis Visit Window

Protocol Scheduled Time Point	Target Study Day	Analysis Visit Windows		
		All Other Assessments	12-lead ECG	Visual Acuity/ Audiology
Screen A	-60	-180 to -31	-180 to 1	-
Screen B	-1	-30 to -1	-	-
Day 1	1	1	-	-30 to 1
Week 1	7	2 to 10	-	-
Week 2	14	11 to 21	-	-
Week 4	28	22 to 35	-	-
Week 6	42	36 to 49	-	-
Week 8	56	50 to 70	-	-
Week 12	84	71 to 126	-	-
Week 24	168	127 to 210	-	-
Week 36	252	211 to 294	-	-
Week 48	336	295 to 350	2 to 350	2 to 490
Week 52	364	351 to 406	351 to 574	-
Week 64	448	407 to 490	-	-
Week 76	532	491 to 574	-	-
Week 88	616	575 to 658	-	-
Week 100	700	659 to 714	575 to 714	> 491
Week 104	728	> 714	> 714	-

Note: Study Day is relative to the first date of study drug administration (Study Day 1). Protocol Scheduled Time Point = Analysis Visit (AVISIT), after applying the analysis windows described above. The Week 52 visit has the additional restriction that assessments must be collected during the off-treatment prior (i.e., after Week 48 dose and on or before Week 52 study drug dispense). For patients who terminated treatment prior to Week 48, use Week 52 as follow-up visit, otherwise Week 104.

If more than one measurement is equidistant to the target Study Day and on different collection date/time, the first measurement will be used for analysis and summary. If more than one measurement is closest to the target Study Day and collected on the same date, the average of those measurements will be used for analysis and summary.

7.4. Missing Data

Missing data will not be imputed for primary analyses of efficacy variables, unless otherwise specified. Lab parameters collected after the visit window of the date of last dose for patients who do not complete study treatment will not be included in the efficacy or safety analysis. Sensitivity analyses may be performed as appropriate to assess the effect of missing data.

8. ANALYSIS SETS

8.1. Safety Analysis Set

Safety analysis set is defined as all patients who received any amount of study drug. The safety analysis set will be used for evaluation of safety variables.

8.2. ITT Analysis Set

The intent-to-treat analysis set is defined as all enrolled patients.

8.3. Per Protocol Analysis Sets

The one-year per protocol analysis set is defined as all enrolled patients who were dosing compliant through Week 48 as defined by:

- No more than 21 consecutive missed doses total through Week 48;
- Received study drug through Week 48; and
- Had a Week 52 visit.

The two-year per protocol analysis set is defined as all enrolled patients who were dosing compliant through Week 100 as defined by:

- No more than 21 consecutive missed doses through Week 48 or from Week 52 to 100;
- Received study drug through Week 100; and
- Had a Week 104 visit.

The off-treatment analysis sets will be used for evaluation of efficacy off-treatment at Week 52 and Week 104, respectively.

8.4. Pharmacokinetics Analysis Set

Pharmacokinetics analysis set is defined as all patients who received any amount of study drug and had at least one bardoxolone methyl plasma concentration measurement. The PK analysis set will be used for evaluation of pharmacokinetics.

9. STUDY POPULATION

9.1. Patient Disposition

Enrollment and disposition will be summarized. A patient will be defined as enrolled if they sign the informed consent form. The patient disposition summary will include the number of patients who:

- enrolled in the study
- are in the safety analysis set
- are in the ITT analysis set

- are in the one-year per protocol analysis set
- are in the two-year per protocol analysis set
- are in the pharmacokinetics analysis set
- completed the Week 12 treatment period
- completed the Week 48 treatment period
- completed the Week 52 treatment period
- completed the Week 100 treatment period
- completed the Week 104 treatment period
- completed the study
- prematurely discontinued from the study.

The disposition summary will also include the primary reason for withdrawal from the study. In addition, a summary of patient source will be provided.

Patients who completed the study are defined as those who completed Week 104 visit. A listing of disposition will be provided for all enrolled patients.

9.2. Protocol Deviations

Where available, protocol deviations will be listed by deviation category (e.g., eligibility criteria, out of window visit, serious adverse event (SAE) reporting, study procedures, treatment procedures). All deviations, including major protocol deviations that could potentially affect the efficacy or safety conclusions of the study, will be identified prior to database lock. Major protocol deviations will be listed in a data listing.

9.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for the safety analysis set. Demographic characteristics will include age, age group (≥ 18 or < 18), gender, race, and ethnicity. Baseline ACR status is based on the baseline ACR value, not the stratification of a patient. The baseline characteristics include:

- Baseline weight;
- Baseline height;
- Body mass index (BMI);
- Baseline values of eGFR;
- Baseline serum creatinine;
- Baseline ACR;
- Baseline ACR status (ACR ≤ 300 mg/g; 300 mg/g < ACR ≤ 1000 mg/g; ACR > 1000 mg/g);
- Alport syndrome related information
    - Age at time of clinical diagnosis

  - Mode of inheritance
- Genotype
  - COL4A3
  - COL4A4
  - COL4A5
  - Unknown
- Mutation type
- Baseline Angiotensin converting enzyme (ACE)-inhibitor and Angiotensin II receptor blocker (ARB) use
  - Only ACEi treatment;
  - Only ARB treatment;
  - ACEi and ARB treatment;
  - No ACEi or ARB treatment and
- Symptoms of Alport.

All of the above information will be listed by patient, including family member information.

9.4. Medical History

Medical history will be mapped to preferred terms (PT) and system organ classes (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA®) Dictionary (version 19.1). Medical history items will be summarized by MedDRA SOC and preferred term (PT) and patient listing will be provided. Medical history will be summarized for each treatment group by MedDRA SOC and preferred term. Patients may have more than one medical history term per MedDRA SOC and preferred term. At each level of patient summarization, a patient is counted once if he/she reported one or more medical history events at that level. Each summary will be ordered by descending order of incidence of MedDRA SOC and preferred term within each MedDRA SOC.

9.4.1. Historical eGFR

Up to 5 years of historical serum creatinine values will be collected for each patient as part of their medical history information. Serum creatinine values will be converted to mg/dL and eGFR will be calculated according to the equations in Section 7.1.3 using the patient age at laboratory collection for adult patients, or patient height at Screening for pediatric patients. Historical serum creatinine values will have been analyzed at various local laboratories (i.e., not collected as part of central lab data). Therefore, historical serum creatinine and eGFR values will be treated separately from data collected as part of the trial's central lab assessments.

Table 4: Comparison of eGFR Slope in CARDINAL vs. Historical eGFR Slope

Analysis Time Point	Study Day Windows
Historical	1825 to 1 days prior to Screen A
Baseline	Screen A to Day 1
On Treatment	Day 2 to Day 714, excluding eGFR measurements collected at Week 52 and Week 104 visits (Study Day 2 to 350 and 407 to 714)

The eGFR values used in the analysis dataset for the baseline label will be the baseline eGFR values for each patient (defined in Section 7.2.1), not the individual Screen A, Screen B, and Day 1 eGFR values. The year will be calculated as a continuous variable as Study Day / 365.25. Historical values will have a negative Study Day value, calculated as Study Day = Date of Historical Lab Collection – Date of Day 1 Study Day. Baseline eGFR values will have a continuous year value of zero. Off-treatment eGFR values collected in CARDINAL (i.e., Week 52 and Week 104) will not be included in the analysis. The general linear model will be run according to the analysis dataset in Table 4 .

A separate dataset will be generated for summary statistics of historical and on-treatment results, for patients with historical eGFR data entered. The second date will separate the historical and on-treatment results by year to calculate summary statistics, but will not be used in the statistical model described in Section 9.4.1.1.

Table 5: Labels for Summary of Historical and On-Treatment Change in eGFR

Analysis Time Point	Study Day Windows
Historical Year 5	1825 to 1461 days prior to Screen A
Historical Year 4	1460 to 1096 days prior to Screen A
Historical Year 3	1095 to 731 days prior to Screen A
Historical Year 2	730 to 366 days prior to Screen A
Historical Year 1	365 to 1 days prior to Screen A
Baseline	Screen A to Day 1
Year 1	Day 2 to Day 350
Year 2	Day 407 to Day 714

The summary statistics will include the average GFR value by patient and analysis time point. For instance, if multiple values are listed in the year 1 results for a given patient, the average of those values will be used to calculate the summary statistics. However, all eGFR values will be used in the statistical model described in Section 9.4.1.1.

9.4.1.1. Statistical Model

Only patients with at least one available historical eGFR value will be included in the analysis.

The table summaries will report the historical change in eGFR vs. baseline (with no post-baseline eGFR values from CARDINAL in the model), and the change in eGFR vs. baseline on bardoxolone methyl treatment for patients who have historical serum creatinine values reported.

The change in eGFR will be analyzed by an analysis of covariance, with baseline eGFR and natural log(Baseline ACR) as covariates:

The LSMeanDiffCL will compare historical eGFR slopes and eGFR slope in CARDINAL along with appropriate confidence intervals, and the Diff results will provide the appropriate p-values.

All historical eGFR data will be listed.

Summary statistics of the datasets listed in Table 5 by analysis time point will also be summarized.

10. STUDY DRUG AND OTHER MEDICATIONS

10.1. Prior and Concomitant Medications

Prior and concomitant medication verbatim terms on eCRFs will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and preferred names using the World Health Organization Drug Dictionary (WHO DD) Enhanced version, March 2016, B2 format.

A prior medication is any medication that is taken and stopped prior to the first dose of study drug. Medications are stopped on the date of first study drug administration are prior medications. 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.

Prior and concomitant medications will be summarized for each treatment group by WHO DD ATC class and preferred name. These summaries will present the number and percentage of patients using each medication. Patients may have more than one medication per ATC class and preferred name. At each level of patient summarization, a patient is counted once if he/she reported one or more medications at that level. Each summary will be ordered by descending order of incidence of ATC class and preferred name within each ATC class.

In addition, patients who take excluded medications (defined in the Protocol Section 9.3.1) during the study will be listed.

10.2. Prior and Concomitant Procedures and Surgeries

Prior and concomitant procedures and surgeries will be listed.

10.3. Duration of Study Treatment

Total number of doses received and total dose (mg) received will be calculated from study drug dispensation and return information. Descriptive summaries for duration of study treatment will include the number of doses received, average daily dose (mg), study drug compliance, and duration (days) of exposure during the study treatment period.

The duration of study treatment is defined as the number of days exposed to treatment, starting with the first dose of study drug through the last dose of study drug

- Duration of study treatment = (last dose – first dose + 1).

If all dispensed kits and bottles are returned, the total number of doses received will be calculated as follows:

- Number of doses received = Total number of doses dispensed – total number of doses returned.

If a dispensed kit or bottle is not returned, the total number of doses received will be calculated as follows:

- Number of doses received = total number of doses dispensed – total number of doses returned – total number of missed doses
- Study drug compliance (%) = 100 × total number of doses received / total number of doses expected in each treatment period.

Adult patients are expected to receive one dose daily, therefore 84, 336, and 700 doses are expected at Weeks 12, 48, and 100 respectively. Pediatric patients (i.e., age < 18 at time of consent) are instructed to dose every other day during the first week, then start with daily dosing in Week 2. Therefore, 81, 333, and 697 doses are expected at Weeks 12, 48, and 100, respectively, for pediatric patients.

All study drug dispensation and accountability data will be listed.

11. EFFICACY ANALYSES

The primary analysis methods for each efficacy objective is described in the following subsections. Additional sensitivity analyses may be performed as appropriate.

11.1. Primary Efficacy Objective

A mixed-model for repeated measures (MMRM) will be used to assess the primary efficacy objective, change from baseline eGFR at Week 12. The ITT population will be used for analysis of the primary efficacy objective. All scheduled eGFR values collected through the Week 12 visit will contribute to the analysis. Change from baseline in eGFR will be calculated for each scheduled visit after Day 1 through Week 12 visit (i.e., Weeks 1, 2, 4, 6, 8, and 12). An inference test of LS mean versus zero will be performed at each time point.

11.1.1. Statistical Hypothesis

For the primary efficacy objective, the null hypothesis is the Week 12 mean (μ_{BARD}) change from baseline in eGFR = 0 mL/min/1.73 m^2. The alternative hypothesis is the Week 12 mean (μ_{BARD}) change from baseline in eGFR ≠ 0 mL/min/1.73 m^2.

11.1.2. Statistical Model

The MMRM model will include the change from baseline in eGFR value as the dependent variable, protocol scheduled time point (analysis visit) as a fixed effect, patient as a random effect, and the baseline eGFR and log-transformed baseline ACR as continuous covariates. Within-patient correlations will be modeled using an unstructured covariance structure. Time ordering is a repeated measure within patients. It is assumed that errors for different patients are independent with an unstructured covariance structure. The estimation method for the model will be restricted maximum likelihood (REML). The SAS pseudo-code is as follows:

```
proc mixed data=efficacy method=reml;
   class usubjid avisitn;
   model chg=avisitn base_egfr lbase_acr;
   repeated avisitn / subject=usubjid type=un rcorr;
   lsmeans avisitn / diff cl alpha=0.05;
run;
```

In the event the MMRM model with an unstructured covariance structure does not converge, the following covariance structures will be as substitution in the following order. Each subsequent covariance structure will be used only if all previous covariance structure(s) is (are) used and the model(s) did not converge.

1. Toeplitz covariance structure (assuming measurements from samples taken closer together in time are more highly correlated than those from samples taken farther apart).
2. First order of auto-regressive [AR(1)] covariance structure (assuming measurements from samples taken closer together in time are more highly correlated than those from samples taken farther apart).
3. Compound symmetry covariance structure (assuming equal correlation for measurements from a patient, regardless of how far apart in time when they were taken).

11.1.3. Reporting Results

The least squares (LS) mean, standard error (SE) of the LS mean, and two-sided 95% confidence interval (CI) of the LS mean and p-value will be reported at each time point. A formal test of mean change from baseline in eGFR ≠ 0 will be conducted at Week 12. The mean change from baseline in eGFR at all other time points will be considered exploratory, so tests at these time points will be performed with no adjustments for multiple comparisons.

A plot of the LS means with 95% CIs of change from baseline in eGFR value over time will be presented.

Descriptive statistics for observed eGFR values and change from baseline in eGFR values will be provided by time point through the end of follow-up. A plot of mean and standard error of eGFR values over time will be presented.

All efficacy data will be listed.

11.2. Additional Efficacy Analyses

Additional efficacy analyses conducted after database lock at Week 52 will not update efficacy tables results for visits at or before Week 52.

11.2.1. Secondary Efficacy Objectives

Additional analyses of on-treatment, continuous eGFR will be evaluated:

- Change from baseline in eGFR at Week 48
- Change from baseline in eGFR at Week 100

Change from baseline in eGFR will be calculated for each scheduled, post-dose time point through the objective specified visit (i.e., Week 48 or Week 100). The ITT population will be used for analysis of the secondary efficacy objectives. An additional sensitivity analysis will be performed using the one-year and two-year per protocol analysis sets to assess the on-treatment effects of eGFR at Weeks 48 and 100, respectively. Using the analysis methods described in below, the above efficacy endpoints will be evaluated in two separate MMRM models:

(1) The first model includes all time points from Week 1 through Week 48;

(2) The second model includes all on-treatment time points from Week 1 through Week 100 (i.e., exclude the off-treatment assessments at Week 52).

The estimation method for the model will be restricted maximum likelihood (REML). The SAS pseudo-code is as follows:

```
proc mixed data=efficacy method=reml;
   class usubjid avisitn;
   model chg=avisitn base_egfr lbase_acr "Baseline BMI>=30 Y/N"n;
   repeated avisitn / subject=usubjid type=un rcorr;
   lsmeans avisitn / diff cl alpha=0.05;
run;
```

In the event the MMRM model with an unstructured covariance structure does not converge, the following covariance structures will be as substitution in the following order. Each subsequent covariance structure will be used only if all previous covariance structure(s) is (are) used and the model(s) did not converge.

1. Toeplitz covariance structure (assuming measurements from samples taken closer together in time are more highly correlated than those from samples taken farther apart).
2. First order of auto-regressive [AR(1)] covariance structure (assuming measurements from samples taken closer together in time are more highly correlated than those from samples taken farther apart).
3. Compound symmetry covariance structure (assuming equal correlation for measurements from a patient, regardless of how far apart in time when they were taken).

Results will be reported as described in Section 11.1.3.

11.2.2. Exploratory Efficacy Objectives

Additional analyses of off-treatment, continuous eGFR will be evaluated:

- Change from baseline in eGFR at Week 52
- Change from baseline in eGFR at Week 104

Change from baseline in eGFR will be calculated for each scheduled, post-dose time point through the objective specified visit (i.e., Week 52 or Week 104). The per protocol analysis sets will be used to analyze the exploratory off-treatment efficacy objectives. Using the analysis methods described in Section 11.1.2, the above efficacy endpoints will be evaluated in two separate MMRM models:

(1) The first model includes all time points from Week 1 through Week 52. The Week 52 off-treatment analysis set will be used to assess efficacy at Week 52;

(2) The second model includes all on-treatment time points from Week 1 through Week 100 (i.e., exclude the off-treatment assessments at Week 52) in addition to the off-treatment values at Week 104. The Week 104 off-treatment analysis set will be used to assess efficacy at Week 104.

The estimation method for the model will be restricted maximum likelihood (REML). The SAS pseudo-code is as follows:

```
proc mixed data=efficacy method=reml;
   class usubjid avisitn;
   model chg=avisitn base_egfr lbase_acr "Baseline BMI>=30 Y/N"n;
   repeated avisitn / subject=usubjid type=un rcorr;
   lsmeans avisitn / diff cl alpha=0.05;
run;
```

In the event the MMRM model with an unstructured covariance structure does not converge, the following covariance structures will be as substitution in the following order. Each subsequent covariance structure will be used only if all previous covariance structure(s) is (are) used and the model(s) did not converge.

1. Toeplitz covariance structure (assuming measurements from samples taken closer together in time are more highly correlated than those from samples taken farther apart).
2. First order of auto-regressive [AR(1)] covariance structure (assuming measurements from samples taken closer together in time are more highly correlated than those from samples taken farther apart).
3. Compound symmetry covariance structure (assuming equal correlation for measurements from a patient, regardless of how far apart in time when they were taken).

Results will be reported as described in Section 11.1.3.

11.2.3. Categorical Analyses of eGFR

11.2.3.1. CKD Stage

Shifts in CKD stage from baseline to Week 48 and baseline to Week 100 will be summarized using frequency counts and percentages based on the following definition of CKD stages:

Table 6: Categorical Analysis of CKD Stage

CKD Stage	eGFR (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

The eGFR values collected after the date of last dose for patients who do not complete study treatment will not be included in the analysis.

11.2.3.2. Categorical Change in eGFR

The percentage of patients with a confirmed increase (i.e., occurring at ≥ 2 visits) from baseline of 30% or more within 48 and 100 weeks of treatment will be summarized using frequency counts and percentages (excluding the Week 52 visit). Similarly, the percentage of patients with a confirmed decrease (i.e., occurring at ≥ 2 visits) from baseline in eGFR of 30% or more within 48 and 100 weeks of treatment will be summarized (excluding the Week 52 visit).

11.2.4. Patient Global Impression of Change

The Patient Global Impression of Change (PGIC) is a 7-point scale that asks the patient to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of an intervention (Guy 1976). The patient global impression of change is assessed by completing the following statement "since I began trial treatment, my overall status is: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7)." PGIC will be summarized by response with frequency counts and percentages at each assessed visit: Weeks 24, 48, 52, 76, 100, and 104.

11.2.5. Clinical Global Impression-Improvement

The Clinical Global Impression-Improvement (CGI-I) is a 7-point scale that asks the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of an intervention (Guy 1976). The clinician global impression of change is assessed by completing the following statement "Compared to the patient's condition at the start of the trial, this patient's overall status is: very much improved (1), much improved (2), minimally improved (3), no change (4), minimally worse (5), much worse (6), very much worse (7)." CGI-I will be summarized by response with frequency counts and percentages at each assessed visit: Weeks 24, 48, 52, 76, 100, and 104.

11.2.6. End Stage Kidney Disease, eGFR decline ≥30%, or eGFR < 15

Time-to-event analyses for a composite renal endpoint consisting of time to end stage kidney disease (dialysis), eGFR decline ≥30%, or eGFR < 15 will be performed. Time-to-event

analyses will only be conducted after all patients have completed Week 104. No off-treatment eGFR values will be included in the analysis.

As a sensitivity analysis, the analyses will be repeated for the time to end stage kidney disease (dialysis), eGFR decline ≥30%, or eGFR < 15, or all-cause death. Confirmation of each eGFR decline event will be based on ≥ 30% decline from baseline in eGFR or eGFR <15 mL/min/1.73 m^2 occurring at 2 or more visits. Hazards ratios and 95% CI will be computed using Cox proportional hazards regression models:

Cases in which a patient has an eGFR value that declined ≥ 30% or fell below 15 mL/min/1.73 m^2 at the last visit, but did not have a second confirmatory visit, will be considered events. Patients who do not experience one of these events will be censored using the following conventions: patients who died from any cause prior to the end of the study will be censored at the date of death for the sensitivity analysis where all-cause death is not included in the composite endpoint; patients who discontinued the study prematurely, withdrew consent, or were lost to follow-up prior to the end of the study will be censored at their last date of contact; patients who are alive and still being followed will be censored on the study termination (for early termination) or study completion date at Week 104.

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

The proportion of patients with, end stage kidney disease (dialysis), eGFR decline ≥30%, or eGFR < 15 will be performed, and the composite of all of these criteria will be evaluated. The frequency analyses will be performed after all patients have completed Week 104. No off-treatment eGFR values will be included in the analysis. Rules for analysis of the composite renal endpoint consisting of time to all-cause death, end stage kidney disease (dialysis), eGFR decline ≥30%, or eGFR < 15 will follow Section 11.2.6. Statistical significance of the proportion of patients with a given event will be evaluated using Fisher's exact test.

As a sensitivity analysis, the analyses will be repeated for the frequency of patients with end stage kidney disease (dialysis), eGFR decline ≥30%, or eGFR < 15, or all-cause death.

11.3. Sensitivity Analyses

The primary analysis method (MMRM) uses all available data, and assumes data are missing at random. A tipping point analysis or other sensitivity analyses may be performed as appropriate for the Phase 2 portion of the study.

11.4. Subgroups Analyses of Efficacy

The efficacy variables will be summarized using descriptive statistics, including 95% CI for change from baseline, will be reported for each subgroup of interest listed below:

- Baseline ACR ≤300, ACR > 300
- Baseline ACR ≤300, 300 < ACR ≤ 1000, ACR > 1000
- Baseline eGFR ≤60, >60
- Male, Female
- Genetic subtype (XLAS vs Non-XLAS)
- Age < 18, Age ≥18.
- Baseline ACEi/ARB use (ACEi and/or ARB vs None)
- Baseline BMI < 30, ≥ 30

For the Phase 2 portion of the study, no statistical testing will be performed for subgroups.

12. SAFETY ANALYSES

Safety and tolerability are evaluated by AEs, SAEs, clinical laboratory test results, body weight, vital signs, 12-lead ECG findings, physical examination, visual acuity, and audiology assessment. All analyses of the safety data will be performed using the safety analysis set and display descriptive statistics (described in Section 7).

12.1. Adverse Events and Serious Adverse Events

All adverse event verbatim terms on eCRFs will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA®) Dictionary (version 19.1).

12.1.1. Treatment Emergent Adverse Events

Treatment-emergent AEs (TEAEs) are defined as any AEs, regardless of relationship to study drug, that have an onset or worsen in severity on or after the first dose of study drug and not more than 30 days after the date of the last dose of study drug. If it cannot be determined whether the AE is treatment-emergent due to a partial onset date, then it will be counted as a TEAE. Adverse events with incomplete start dates will be considered TEAEs, if:

- Onset time is missing but the onset date is on Study Day 1.
- 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.

Related AEs are those with relationship to study drug reported as "possibly related", "probably related", or "definitely related". If severity (relationship) of an AE to study drug is not recorded, the severity (relationship) will be imputed as 'severe' ('definitely related').

All reported AEs (including non-TEAEs), SAE, and deaths will be listed in separate patient listings.

12.1.2. Summary of Treatment-Emergent Adverse Events and Serious Adverse Events

All TEAE and SAE summary tables will include the number and percentages of patients reporting events. A summary of TEAEs by severity, seriousness, and relation to study drug will be tabulated. In addition, TEAEs and SAEs will be summarized by MedDRA system organ class and preferred term. Patients can have more than one TEAE per system organ class and preferred term. These summaries will include the following:

- All TEAEs
- TEAEs by worst severity
- Related TEAEs
- TEAEs leading to study drug interruption (if any)
- TEAEs leading to study drug discontinuation (if any)
- All treatment-emergent SAEs
- Treatment-emergent SAEs by worst severity
- Related treatment-emergent SAEs.

Patients can have more than one TEAE (SAE) per system organ class and preferred term. At each level of patient summarization, a patient is counted once if he/she reported one or more TEAE (SAE) at that level. If a patient reported the same TEAE (SAE) on multiple occasions, the highest severity (severe > moderate > mild) or study drug relationship (related > probable > possible > unlikely > unrelated) recorded for the event will be summarized. Each summary will be ordered by descending order of incidence of system organ class and preferred term within each system organ class.

12.2. Clinical Laboratory Evaluation

Clinical laboratory test (serum chemistry [including NT-Pro BNP, BNP, IGF-1 and serum ketones], hematology [including hematocrit, hemoglobin (Hgb), red blood cell (RBC) count, white blood cell (WBC) count, neutrophils, bands (if detected), lymphocytes, monocytes, basophils (if detected), eosinophils (if detected), absolute platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), and mean corpuscular hemoglobin concentration (MCHC)], spot urine, and urinalysis of pH and specific gravity) results from the central laboratory, where available, will be summarized using descriptive statistics at each scheduled time point. Summaries of ACR will use the geometric mean with 95% confidence intervals instead of the arithmetic mean, and will display ACR results in units of mg/g. Changes from baseline in ACR will be reported as the post-baseline/baseline ratios and will be summarized by geometric means with 95% confidence intervals at each time point. Mean ratios of natural log(ACR)/eGFR will also be summarized at each time point. The ratio of natural

log(ACR)/eGFR by analysis visit will be summarized by arithmetic means. Laboratory assessments below the LLD will be imputed as LLD/2. Laboratory assessments above the ULD will be imputed as the ULD. Changes from baseline will also be summarized by time point. Box plot graphs and line graphs may be generated for selected laboratory tests, such as ACR, ALT, AST, BUN, uric acid, magnesium, and creatinine. Line graphs will include mean ± SE over time for both the observed values and for the change from baseline values.

Two additional summary tables will be provided that include the number and percentage of patients 1) meeting the following pre-specified threshold level at any time during the study (Table 7) and 2) ULN thresholds at any time during the study (Table 8).

Table 7: Pre-Specified Threshold Levels for Categorical Laboratory Summaries

Lab Parameter	Pre-Specified Level
ACR	> 3500 mg/g
Magnesium	< 1.3 mEq/L (0.65 mmol/L)
BNP	> 200 pg/mL
ALT, AST	> 3 × upper limit of normal (ULN)
ALT, AST	> 8 × ULN
ALT, AST	> 5 × ULN for more than 2 weeks
ALT, AST, TBL, INR	> 3 × ULN and (TBL > 2 × ULN **or** INR > 1.5)

Table 8: Pre-Specified Upper Limit of Normal (ULN) Levels for Laboratory Parameters

Lab Parameter	Sex	Age	ULN
ALT	Female	All	34 U/L
	Male	All	43 U/L
AST	Female	< 18	40 U/L
		≥ 18	34 U/L
	Male	< 18	40 U/L
		≥ 18	36 U/L
TBL			Central lab ULN
INR			1.5

Urinalysis results (other than pH and specific gravity) of ketones, protein, blood, glucose, clarity, color, leukocytes, nitrite, bilirubin, and microscopic examinations (if indicated based on laboratory results), urine microscopic findings, and pregnancy test results will not be summarized.

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

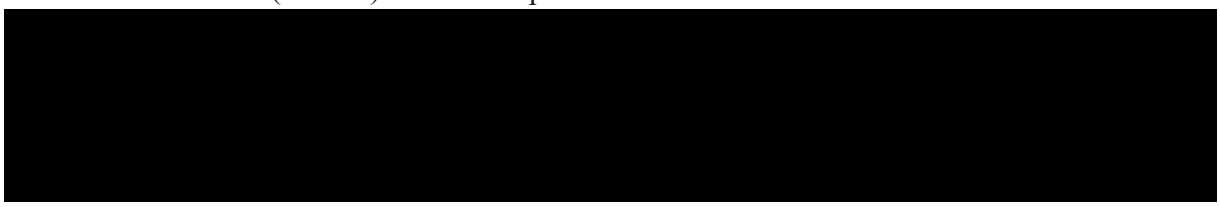
12.3. Analyses of Continuous eGFR and ACR

Additional safety endpoints will be evaluated by rare chronic kidney disease cohort:

- Change from baseline in eGFR at Week 16 following a 4-week drug treatment withdrawal period
- Ratio of natural log (ACR)/eGFR by analysis visit, for visits at Baseline through Week 104. The ratio of natural log(ACR)/eGFR by analysis visit will be summarized by arithmetic mean and standard deviation at each time point.
- Change from baseline in ACR summarized by baseline ACR category (ACR <=300, ACR > 300)

12.3.1. Ratio of Natural log (ACR)/eGFR

The ratio of natural log(ACR)/eGFR will be analyzed through Week 104. The ratio of natural log(ACR) / eGFR will be the natural log (ACR) and eGFR values collected closest to the target study day (Section 7.3) through the Week 104, and the baseline values are described in Section 7.2.4. The change from baseline in natural log(ACR) / eGFR will be calculated for each time point through Week 104 visit. Missing data will not be imputed. The inference will be the test of LS mean at each time point. The estimation method for the model will be restricted maximum likelihood (REML). The SAS pseudo-code is as follows:



In the event the MMRM model with an unstructured covariance structure does not converge, the following covariance structures will be as substitution in the following order. Each subsequent covariance structure will be used only if all previous covariance structure(s) is (are) used and the model(s) did not converge.

1. Toeplitz covariance structure (assuming measurements from samples taken closer together in time are more highly correlated than those from samples taken farther apart).
2. First order of auto-regressive [AR(1)] covariance structure (assuming measurements from samples taken closer together in time are more highly correlated than those from samples taken farther apart).
3. Compound symmetry covariance structure (assuming equal correlation for measurements from a patient, regardless of how far apart in time when they were taken).

12.3.2. Change from Baseline in ACR

The change from baseline ACR will be summarized for all patients, as well as by baseline ACR category (ACR ≤300, ACR > 300). Summaries of ACR will use the geometric mean with 95% confidence intervals instead of the arithmetic mean, and will display ACR results in units of mg/g. Changes from baseline in ACR will be reported as the post-baseline/baseline ratios and will be summarized by geometric means with 95% confidence intervals at each time point.

12.4. Vital Signs

Descriptive statistics for blood pressure, heart rate, respiratory rate, and temperature including baseline values and change from baseline values, will be summarized by time point. All vital signs parameters will be listed.

12.5. Body Weight

Descriptive statistics for body weight that are collected on the eCRF and change from baseline values will be will be summarized and listed by time point. In addition, number and percentage of patients who experience a five-pound (2.3 kilogram) or greater increase in weight will be summarized by time point. Boxplot and line graphs of change from baseline over time for weight will be plotted. Weight change will also be summarized by baseline BMI (>30 and ≤30 kg/m2) and baseline age (>18 and ≤18).

12.6. 12-lead ECG

Electrocardiogram (ECG) data, such as clinical interpretation of ECGs, ventricular rate and interval assessments of PR, QRS, QT, and QTcF, will be collected on the eCRF. Descriptive statistics for observed values and change from baseline at each time point will be 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) will be summarized by time point and overall while on study drug. The pre-specified levels of ECG QTc thresholds are consistent with FDA guidance.

Table 9: Pre-Specified Threshold Levels for ECG Parameters

ECG Parameter	Pre-Specified Level
PR	>200 msec
QTcF	>450, >480 or >500 msec, >30 or >60 msec increase from baseline
Heart rate	<40, >100 beats/min

All ECG parameters will be listed. Any results that exceed the above levels (provided in the above table) will be flagged in the listing.

12.7. Physical Examination

Abnormal clinically significant findings will be reported as Medical History or Adverse Events depending on date of onset. Abnormal non-clinically significant findings from physical examinations will be listed.

12.8. Visual Acuity

Findings from visual acuity examinations will be listed. Observed logMAR value and its associated change from baseline will be summarized descriptively by time point using descriptive statistics.

12.9. Audiology Assessment

Findings from audiology assessments will be listed. The average pure tone audiometry (PTA) values will be summarized by visit. The number and percentage of patients with normal or impaired hearing in at least one ear will be summarized by time point.

13. PHARMACOKINETICS ANALYSIS

Blood samples for determination of plasma bardoxolone methyl and potential metabolite concentrations will be drawn as shown in Table 2. The PK profile of bardoxolone methyl will be evaluated from plasma concentration data from individual patients. The PK parameters, such as C_{max}, T_{max}, and AUC_{0-t} will be determined by a third party vendor. The bardoxolone methyl plasma concentration data, along with PK parameters, will be listed. The PK parameters will be summarized descriptively.

14. REFERENCES

Guy, W. ECDEU Assessment Manual For Psychopharmacology, DHEW Publication No. ADM 76–338, US Government Printing Office, Washington, DC, USA, 1976).