Statistical Analysis Plan
for
402-C-1702

[redacted]

NCT03366337

A PHASE 2 TRIAL OF THE SAFETY AND EFFICACY OF BARDOXOLONE METHYL IN PATIENTS WITH RARE CHRONIC KIDNEY DISEASES

Version: 2.0

Date: July 13, 2018

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
ADPKD	autosomal dominant polycystic kidney disease
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
EC	ethics committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EOT	end of treatment
FDA	Food and Drug Administration (US)
FSGS	focal segmental glomerulosclerosis
GFR	glomerular filtration rate
Hgb	hemoglobin
ICH	International Conference on Harmonization
IgAN	IgA nephropathy
IGF-1	insulin-like growth factor-1

Abbreviation or Specialist Term	Explanation
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
LLD	lower limit of detection
LS	least squares
MCH	mean corpuscular hemoglobin
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
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
T1D	chronic kidney disease associated with type 1 diabetes
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	April 18, 2018	[redacted]	Initial version.
2.0	July 13, 2018	[redacted]	Specified analysis methods for safety analyses in greater detail Added summary of change from baseline in ACR summarized by baseline ACR category (ACR <=300, ACR > 300) Added analysis of covariance calculation of historical change in eGFR Added analysis of covariance calculation of change in eGFR while in PHOENIX Added comparison of eGFR before and after participation in PHOENIX Changed the definition of baseline ACR

The analysis plan is based on the information from the following document:

Protocol Version 1.0, 17 August 2017

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 study 402-C-1702 for the investigational product bardoxolone methyl (BARD). This SAP will be used to analyze the safety, tolerability, and efficacy data collected during the study for four specified types of rare chronic kidney disease (CKD) collected during the study. This SAP complies with the International Conference on Harmonisation (ICH) guidance and relevant Food and Drug Administration (FDA) guidance documents. The analyses described in this plan have been prospectively defined prior to clinical database lock. The planned analyses identified herein may be included in regulatory submissions and/or future manuscripts. Endpoints will be assessed for each rare CKD cohort separately after the data have been locked.

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 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

For patients within each rare CKD cohort enrolled in this study, 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.

4.2. Endpoints

4.2.1. Primary Efficacy Endpoint

- Change from baseline in eGFR at Week 12.

[redacted]

4.2.3. Safety Endpoints

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

5. STUDY DESIGN

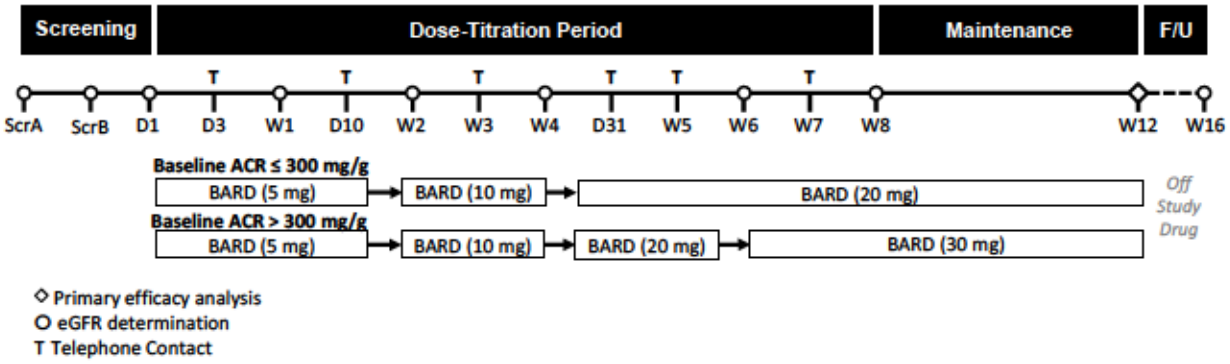
5.1. Overall Study Design

This multi-center, open-label Phase 2 trial will study the safety, tolerability, and efficacy of bardoxolone methyl in qualified patients with the following rare chronic kidney diseases: CKD associated with type 1 diabetes (T1D), IgA nephropathy (IgAN), focal segmental glomerulosclerosis (FSGS), and autosomal dominant polycystic kidney disease (ADPKD). Patients will be enrolled in disease specific cohorts within the trial, and effectiveness of bardoxolone methyl in treating CKD will be assessed separately by cohort for each rare CKD. The trial will be open-label and enroll approximately 25 patients in each cohort of rare CKD etiology.

5.2. Randomization and Dosing

Randomization refers to patients receiving open-label bardoxolone methyl (BARD). All patients will receive BARD throughout the study as described in the protocol with the maximum bardoxolone methyl dose determined by urine albumin-to-creatinine ratio (ACR) at Screen B. The diagram below shows dose titration and maintenance schedules according to the baseline urine albumin-to-creatinine ratio (ACR) ≤ 300 mg/g or >300 mg/g. Patients with macroalbuminuria (300 mg/g < ACR ≤ 2500 mg/g) at the Screen B visit will account for up to approximately 50% of patients enrolled within each cohort. Patients with ACR ≤ 300 mg/g at Screen B will be titrated to a maximum dose of 20 mg BARD, and patients with ACR > 300 mg/g at Screen B will be titrated to a maximum dose of 30 mg BARD. Patients 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 Screen B ACR >300 mg/g) unless contraindicated clinically and approved by the medical monitor.

Schema for Study of Bardoxolone Methyl in Patients with Rare Chronic Kidney Diseases



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 randomization on Day 1, patients will be scheduled for assessments during treatment at Weeks 1, 2, 4, 6, 8, and 12, and by telephone contact on Days 3, 10, 21, 31, 38, and 45. Patients will also be scheduled for an in person follow-up visit at Week 16, 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 or EoT[d] Day 84±3	Wk 16 or F/U Day 112±3
Informed consent	X															
Inclusion/ exclusion	X		X[e]													
Demographics and baseline disease characteristics	X															
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X															
Height	X															
Weight in clinic/BMI	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	
Dispense weight diary			X				X		X			X		X		
Collect/review weight diary				X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X														X	X
Echocardiogram[f]	X															
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[g]	X	X	X						X					X	X	X
Study drug administration			----------X----------													
Dispense study drug			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[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Kidney biopsy[i]	X															
Fasting C-peptide level[j]	X															

Genetic testing[k]	X															
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 or EoT[d] Day 84±3**	**Wk 16 or F/U Day 112±3**
Clinical chemistry (incl. eGFR)	X	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
Hematology	X		X				X		X			X		X	X	X
Urinalysis and microscopy	X		X				X		X			X		X	X	X
Urine collection for ACR[e]		X	X						X					X	X	X
[redacted]															X	X
[redacted]															X	X
Virus serology	X															
PK samples[f]															X	

[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] Patients who terminate from the study prior to the Week 12 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.

[e] 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.

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

[g] 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.

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

[i] Only patients enrolling in the IgA nephropathy cohort or the FSGS cohort are required to have a kidney biopsy. Patients with definitive diagnosis of IgA nephropathy or FSGS from previous biopsy will not have a kidney biopsy as part of the study, but must provide diagnosis documentation from previous kidney biopsy for eligibility.

[j] Only patients enrolling in the T1D cohort are required to have fasting C-peptide levels assessed. Patients should be instructed to fast prior to study visit.

[k] Only patients enrolling in the ADPKD disease cohort are required to have genetic testing. Patients with confirmed PKD1 mutations from previous genetic testing will not have genetic testing performed as part of the study, but must provide documentation of genetic mutation for eligibility.

[l] Albumin to creatinine ratio will be measured by first morning void spot urine collection. Appropriate containers for the collection will be provided to the patient at the visit prior to collection.

[m] 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.

Abbreviations: EoT= end-of-treatment; ECG = electrocardiogram, F/U = follow-up; 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 7.2.1 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 days, prior to study drug dosing (pre-dose; 0 hour), 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 25 patients in each cohort, the study will have approximately 80% power to detect a change from baseline in eGFR relative to zero. [redacted]

[redacted] The primary efficacy endpoint will be analyzed separately for each rare chronic kidney disease cohort. [redacted]

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, a separate set of tables, listings, and figures will be generated for each cohort. Select tables may be generated as appropriate that summarize data for all cohorts pooled. Patient listings will be sorted by patient number first, then 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.

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 by rare CKD cohort 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 data analyses. The equation used to calculate eGFR for each patient will be the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation:

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

Where Scr 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 Scr/κ or 1, and max indicates the maximum of Scr/κ or 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. The eGFR values collected after the 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 calculated at the central laboratory using the formula below:

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

Urine creatinine may need to be converted from mg/dL to 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).

7.2. Baseline Values

Baseline values are defined as the last non-missing assessment prior to the first study drug dosing, unless otherwise specified below.

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 are 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. Albumin/Creatinine Ratio (ACR)

Baseline ACR is defined as the average of Screen B and Day 1 ACR values.

7.2.5. Natural log (ACR)/eGFR

Baseline of natural log(ACR)/eGFR is defined as the ratio of the natural log of baseline ACR (defined in Section 7.2.4) 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 assessments and/or measurements 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 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 Windows

Visit Scheduled Time Point	Target Study Day	Analysis Visit Windows	
		All Other Assessments	12-lead ECG
Screen A	-60	-180 to -2	-180 to 1
Screen B[a]	-1	-30 to -1	-
Day 1	1	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 98	2 to 98
Week 16	112	> 98	-

[a]Screen B is after Screen A, and no more than 30 days prior to Day 1

Note: Study Day is relative to the first date of study drug administration (Study Day 1). Visit Scheduled Time Point = Analysis Visit (AVISIT), after applying the analysis windows described above. The Week 16 visit has the additional restriction that assessments must be collected after last dose of study treatment. For patients who terminated treatment prior to Week 12, use Week 16 as follow-up visit.

If more than one measurement is collected equidistant to the target Study Day and on different collection date/time, the first measurement will be flagged 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.

8. ANALYSIS SETS

The analysis sets defined below will be defined for each rare CKD cohort: CKD associated with T1D, IgAN, FSGS, and ADPKD.

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. Off-Treatment Analysis Sets

The Week 16 off-treatment analysis set is defined as all randomized patients who were dosing compliant through Week 12 as defined by:

- Still taking study medication at the Week 12 in-person visit; and
- Had a Week 16 assessment.

The off-treatment analysis sets will be used for evaluation of off-treatment safety at Week 16.

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 by rare CKD cohort. 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 Week 16 off-treatment analysis set
- completed study treatment

- prematurely discontinued study treatment
- completed study visits
- prematurely terminated from the study.

The disposition summary will also include the primary reason for withdrawal from the study.

Patients who completed study treatment are defined as those who received treatment through the Week 12 visit. Patients who completed study visits are defined as those who completed the Week 16 visit. A listing of disposition will be provided for all enrolled patients, including patient source.

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 by rare CKD cohort for the safety analysis set. Demographic characteristics will include age, gender, race, and ethnicity. Baseline ACR will be summarized by baseline ACR values, not the stratification cohort to which a patient was randomized. The baseline characteristics include:

- Baseline weight,
- Height,
- Body mass index (BMI), and BMI category: < 30, ≥ 30,
- Baseline values of eGFR, baseline CKD stage (Stage 3: eGFR 30 to < 60; Stage 2: eGFR ≥ 60 to < 90; Stage 1: eGFR ≥ 90),
- Baseline serum creatinine,
- Baseline ACR,
- Baseline ACR status (ACR ≤ 300 mg/g; 300 mg/g $<$ ACR ≤ 1000 mg/g; ACR > 1000 mg/g),
- Age of the diagnosis (T1D cohort only)
- C-peptide level (T1D cohort only),
- Prescribed a stable dose of insulin (T1D cohort only), and

- 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.

The above information will be listed by patient.

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 14.1). Medical history items will be summarized by MedDRA SOC, cohort, and PT and patient listing will be provided.

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, September 2011, 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 within each rare chronic kidney disease cohort 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. Duration of Study Treatment and Exposure to Study Drug

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 (i.e., drug exposure) 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 doses are expected at Week 12.

All study drug dispensation and accountability data will be listed.

11. EFFICACY ANALYSES

11.1. Primary Efficacy Analysis

A mixed-model for repeated measures (MMRM) will be used to analyze the primary efficacy variable. The MMRM results will be reported by rare CKD cohort. The ITT population will be used for analysis of the primary efficacy objective. All eGFR values collected closest to the target study day (Section 7.3) through the Week 12 visit will contribute to the primary analysis. The primary efficacy variable, the change from baseline in eGFR value, will be calculated for each first post- first dose time point through Week 12 visit (i.e., Weeks 1, 2, 4, 6, 8, and 12). Missing data will not be imputed for the primary analysis. The primary inference will be the test of LS mean at each time point. The primary endpoint is the mean change from baseline in eGFR at Week 12.

The eGFR values collected after the study window of study drug discontinuation will be not be used in primary or exploratory efficacy analyses.

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 $\neq$ 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).

A separate MMRM model will be analyzed for each rare CKD cohort.

11.1.3. Reporting Results

The least squares (LS) mean, standard error (SE) of the LS mean, two-sided 95% confidence interval (CI) of the LS mean and p-value will be reported at each time point. Statistical testing will be performed at every time point that eGFR is measured. The change from baseline in

eGFR at Week 12 is the primary endpoint. A formal test of mean change from baseline in eGFR $\neq 0$ 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.

11.2. Additional Efficacy Analyses

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

11.2.2. Historical eGFR Slope Dataset

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 7.1.3 using the patient age at laboratory collection. Historical serum creatinine values will have been analyzed at various local laboratories (i.e., not collected as part of central lab data). Historical serum creatinine values will be converted to mg/dL if not entered in those units. Therefore, historical serum creatinine and eGFR values will be treated separately from data collected as part of the trial's central lab assessments.

One dataset will be generated with the baseline eGFR values, baseline log(ACR) values, the historical eGFR values, and the eGFR results in PHOENIX that were used in the primary efficacy analysis (Section 7.3 and Section 11.1). The analysis time points are defined as follows:

Table 5: Comparison of eGFR Slope in PHOENIX 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 98

The eGFR values used in the analysis datasets for the baseline label will be the baseline eGFR values for each patient (defined in 7.2.1), not the individual Screen A, Screen B, and Day 1

eGFR values. The continuous year will be calculated as a continuous variable as Study Day / 365.25. Historical values will have a negative Study Day value, calculated as Date of Lab Collection – Date of Day 1 Study Day. Week 16 values will not be included in the analysis. Baseline eGFR values will have a continuous year value of zero.

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 11.2.3.

Table 6. Labels for Summary of Historical and On-Treatment Change in eGFR

Label	Study Day Windows
Historical Year 5	Day -1825 Before Screen A to Day -1461 Before Screen A
Historical Year 4	Day -1460 Before Screen A to Day -1096 Before Screen A
Historical Year 3	Day -1095 Before Screen A to Day -731 Before Screen A
Historical Year 2	Day -730 Before Screen A to Day -366 Before Screen A
Historical Year 1	Day -365 Before Screen A to Day -1 Before Screen A
Baseline	Day -60 to Day 1
Year 1	Day 2 to Day 98

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 11.2.3.

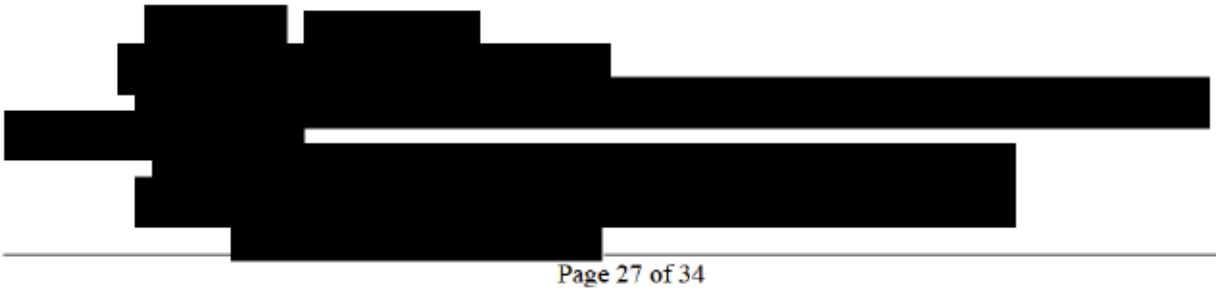
11.2.3. Statistical Model

The general linear model will be run according to the year labels in Table 5.

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

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

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



[redacted]

The LSMeanDiffCL will compare historical eGFR slopes and eGFR slope in PHOENIX along with appropriate confidence intervals, and the Diff results will provide the appropriate p-values. Results will be summarized by cohort.

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

All historical eGFR data will be listed.

[redacted]

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.

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. Descriptive statistics (described in Section 7) will be presented for the safety analysis set.

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 14.1).

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 to study drug) of an AE to study drug is not recorded, the severity (relationship to study drug) 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

TEAE and SAE presentations will summarize results by rare CKD cohort. All TEAE summary tables will include the number and percentages of patients reporting TEAEs. A summary of TEAEs by severity, seriousness, and relation to study drug will be tabulated. In addition, TEAEs will be summarized by MedDRA 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.

At each level of patient summarization, a patient is counted once if he/she reported one or more TEAE at that level. If a patient reported the same TEAE 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 by rare chronic kidney disease cohort using descriptive statistics at each scheduled time point. Laboratory assessments below 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. 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. 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.

Additional summary tables will be provided that includes that number and percentage of patients meeting the following 1) 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 × ULN)

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			Central lab ULN

Urinalysis results other than pH and specific gravity will not be summarized. Results not summarized include 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. 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 for each rare CKD cohort.

12.4. Body Weight

Descriptive statistics for body weight that are collected on the eCRF and change from baseline values will be summarized by time point for each rare CKD cohort. 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. Summary tables for body weight will be repeated for the following subgroups:

- Weight change will also be summarized by baseline BMI (>30 and ≤30 kg/m2), and
- Baseline age (>18 and ≤18).

12.5. 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 by rare CKD cohort. 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

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

12.6. 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.

12.7. Analyses of Continuous eGFR and ACR

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

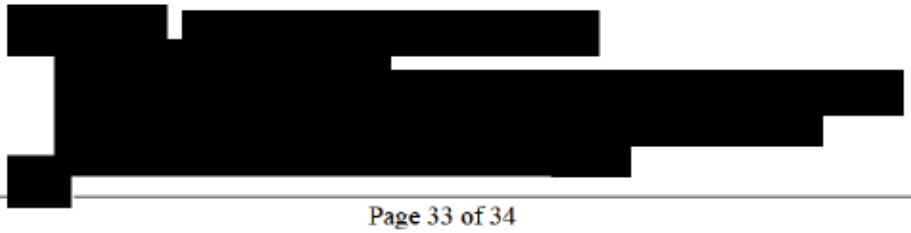
- Change from baseline in eGFR at Week 16 following a 4-week drug treatment withdrawal period
- Ratio of natural log (ACR)/eGFR by analysis visit, for visits at Baseline through Week 16. The ratio of natural log(ACR)/eGFR by analysis visit will be summarized by arithmetic mean and standard deviation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

12.7.1. Change from Baseline in eGFR at Week 16

A mixed-model for repeated measures (MMRM) will be used to analyze the change from baseline eGFR at Week 16. The MMRM results will be reported by rare CKD cohort. The eGFR values collected closest to the target study day (Section 7.3) through the Week 16 visit will contribute to the analysis, and only patients who have completed the study through Week 16 will be included in the analysis. The change from baseline in eGFR value will be calculated for each post first dose time point through Week 16 visit (i.e., Weeks 1, 2, 4, 6, 8, 12, and 16). Missing data will not be imputed. The primary inference will be the test of LS mean at each time point. The MMRM model used will be that in Section 11.1.2.

12.7.2. Ratio of Natural log (ACR)/eGFR

The ratio of natural log(ACR)/eGFR will be analyzed through Week 16. The MMRM results will be reported by rare CKD cohort. 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 16, and the baseline values are described in Section 7.2.5. The change from baseline in natural log(ACR) / eGFR will be calculated for each time point through Week 16 visit (i.e., Weeks 1, 2, 4, 6, 8, 12, and 16). Missing data will not be imputed. The primary 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).

12.7.3. Change from Baseline in ACR

Within each rare CKD cohort, 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.

13. PHARMACOKINETICS ANALYSIS

Blood samples for determination of plasma bardoxolone methyl and potential metabolite concentrations will be drawn as shown in Table 3. 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 Reata or a third party vendor. The bardoxolone methyl plasma concentration data, along with PK parameters, will be listed. The PK parameters will be summarized descriptively by rare CKD cohort. Additional analyses and summaries may be performed, if warranted.